1.0 TITLE PAGE

Forest Research Institute, Inc.*, an affiliate of Actavis, Inc.*
[redacted]

A 52-Week, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Roflumilast 500 µg on Exacerbation Rate in Patients With Chronic Obstructive Pulmonary Disease (COPD) Treated With a Fixed-Dose Combination of Long-Acting Beta Agonist and Inhaled Corticosteroid (LABA/ICS)

ROF-MD-07

IND # 57,883

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Original Protocol Date:	[redacted]
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Amendment # 3:	[redacted]
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Amendment #5	[redacted]

2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: STUDY ROF-MD-07	
Study Number	Study ROF-MD-07
Title of Study	A 52-Week, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Roflumilast 500 µg on Exacerbation Rate in Patients With Chronic Obstructive Pulmonary Disease (COPD) Treated With a Fixed-Dose Combination of Long-Acting Beta Agonist and Inhaled Corticosteroid (LABA/ICS)
Study Centers (Country)	Approximately 400 (International study centers)
Development Phase	4
Objective	To demonstrate the additional benefit of roflumilast added on to fixed-dose combination (FDC) LABA/ICS (Advair 250/50µg 1 puff BID or, Symbicort 160/4.5 µg 2 puffs BID) in the reduction of exacerbations in patients with severe to very severe COPD
Methodology	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, add-on FDC, 52-week double-blind treatment period, stratified by long-acting muscarinic antagonist (LAMA) use
Number of Patients	2300 randomized (1150 per treatment arm)
Diagnosis and Main Criteria for Inclusion	Male and female patients who are ≥ 40 years of age, with diagnosis of severe (stage III) to very severe (stage IV) COPD by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (2013) Forced expiratory volume after 1 second (FEV_1)/forced vital capacity (FVC) ratio (postbronchodilator) < 70% FEV_1 (postbronchodilator) ≤ 50% of predicted At least 2 documented moderate or severe COPD exacerbations within 12 months prior to Screening (Visit 1) Patients must be on FDC LABA/ICS treatment ≥ 3 months prior to Screening
Test Product, Dosage, and Mode of Administration	Roflumilast 500 µg administered orally once daily in the morning
Duration of Treatment	2-week single-blind placebo lead-in period followed by 52-week double-blind treatment with a dosage of 500 µg/day
Reference Therapy, Dosage, and Mode of Administration	Advair 250/50 µg 1 puff BID or Symbicort 160/4.5 µg 2 puffs BID (where available) and placebo oral administration once daily

Criteria for Evaluation	
Pharmacokinetic Analysis	Sparse Pharmacokinetic (PK) Sampling: Population PK samples will be collected in approximately 20% of the patients in the study. One PK sample will be collected at Visit 5, Visit 7, and Visit 8/ Early Termination Visit or Last Visit. Serial PK Sampling: At Visit 7, a sub-group of approximately 40 patients at selected sites will undergo serial PK sampling (PK samples collected at 0 [predose], 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 hours post-dose). Roflumilast and roflumilast N-oxide PK parameters such as C_{max}, AUC, T_{max} and $T_{½}$ will be calculated for patients in the serial PK sub-group. Sparse PK sample data from this study will be added to the existing population PK model for population analysis.
Primary Outcome Measure	Rate of moderate or severe COPD exacerbations per patient per year
Secondary Outcome Measures	***1.*** Change from Randomization (Visit 2) over 52 weeks of treatment in predose FEV_1 (L) ***2. Rate of COPD exacerbations that led to hospitalization or death (i.e., severe COPD exacerbations)*** ***3. Rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics***
Safety Measures	Adverse event (AE) recording, vital signs, physical examinations, body weight, electrocardiograms (ECGs), clinical laboratory measures, and Columbia Suicide Severity Rating Scale (C-SSRS)
Statistical Methods	The primary endpoint of rate of moderate or severe COPD exacerbations will be analyzed using a negative binomial regression model with the number of exacerbations per patient as dependent variable and treatment and stratum (LAMA, no-LAMA) as independent variables. The model will include an offset variable representing patient's treatment duration minus the days that new exacerbations cannot occur. The model will provide point estimates for the rate ratio with the corresponding 95% confidence interval, as well as 2-sided p-value. All safety parameters will be analyzed descriptively. Safety analyses will be based on the Safety Population, defined as all randomized patients who receive at least 1 dose of double-blind investigational product. Efficacy analyses will be based on the Intent-to-Treat (ITT) Population, also defined as all randomized patients who took at least 1 dose of double-blind investigational product.

SCHEDULE OF EVALUATIONS: STUDY ROF-MD-07

	Single-Blind Treatment Period		***Double-blind Treatment Period***													
	Visit 1 (Screening)	*Visit 2 (Randomization)*	*Visit 3*	*Interim TC 3-1*[b]	*Visit 4*	*Interim TC 4-1*[b]	*Visit 5*	*Interim TC 5-1*[b]	*Visit 6*	*Interim TC 6-1*[b]	*Interim TC 6-2*[b]	*Visit 7*	*Interim TC 7-1*[b]	*Interim TC 7-2*[b]	*Visit 8*[a] *(ET/Last Visit)*	*Telephone Contact*[m]
Study Week	**–2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	***V8/EOT + 4 wk***
Visit Window[c]	—	**± 3 d**	**± 3 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 3 d**
Informed Consent[d]	X															
Inclusion/Exclusion Criteria	X	X														
COPD/Exacerbation History	X															
Smoking Status	X	X	X		X		X		X			X			X	
Medical and Surgical History	X															
Prior/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-Ray and CT Scan[e]	X															
Physical Examination[f]	X														X	
Vital Signs[g]	X	X	X		X		X		X			X			X	
Urinalysis	X				X				X						X	
Urine Pregnancy Test[h]	X	X			X		X		X			X			X	
12-lead ECG	X								X						X	
Spirometry Predose[i]	X	X	X		X		X		X			X			X	
Spirometry Postbronchodilator[j]	X															
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

SCHEDULE OF EVALUATIONS: STUDY ROF-MD-07

	Single-Blind Treatment Period		***Double-blind Treatment Period***													
	Visit 1 (Screening)	*Visit 2 (Randomization)*	*Visit 3*	*Interim TC 3-1*[b]	*Visit 4*	*Interim TC 4-1*[b]	*Visit 5*	*Interim TC 5-1*[b]	*Visit 6*	*Interim TC 6-1*[b]	*Interim TC 6-2*[b]	*Visit 7*	*Interim TC 7-1*[b]	*Interim TC 7-2*[b]	*Visit 8*[a] *(ET/Last Visit)*	*Telephone Contact*[m]
Study Week	**–2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	***V8/EOT + 4 wk***
Visit Window[c]	**—**	**± 3 d**	**± 3 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 3 d**
Assess COPD Exacerbations and Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Labs	X				X				X						X	
Pharmacokinetic Sample Collection[k]							X					X			X	
Randomization		X														
COPD Assessment Test (CAT)	X	X	X		X		X		X			X			X	
C-SSRS	X	X	X		X		X		X			X			X	
Dispense EXACT-PRO and Rescue Electronic Diary	X															
EXACT-PRO and Rescue Electronic Diary Assessment		X	X		X		X		X			X			X	
Dispense Investigational Product[l]	X	X	X		X		X		X			X				
Administer Investigational Product	X	X	X		X		X		X			X				
Assess Investigational Product Compliance		X	X		X		X		X			X			X	

SCHEDULE OF EVALUATIONS: STUDY ROF-MD-07

	Single-Blind Treatment Period		***Double-blind Treatment Period***													
	Visit 1 (Screening)	*Visit 2 (Randomization)*	*Visit 3*	*Interim TC 3-1*[b]	*Visit 4*	*Interim TC 4-1*[b]	*Visit 5*	*Interim TC 5-1*[b]	*Visit 6*	*Interim TC 6-1*[b]	*Interim TC 6-2*[b]	*Visit 7*	*Interim TC 7-1*[b]	*Interim TC 7-2*[b]	*Visit 8*[a] *(ET/Last Visit)*	*Telephone Contact*[m]
Study Week	**–2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	***V8/EOT + 4 wk***
Visit Window[c]	**—**	**± 3 d**	**± 3 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 5 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 3 d**
Dispense Rescue Medication	X	X	X		X		X		X			X				

a Assessments described under Visit 8 (ET/Last Visit) are mandatory for all randomized patients. Visit 8 is the Final Visit (Early Termination/Last Visit). In other words, if a patient prematurely discontinues, the procedures listed for Visit 8 and a telephone contact need to be completed. See Section 9.3.3.1 for instructions regarding continued study follow-up for patients who prematurely discontinue the investigational product.

b Follow-up interim telephone contact to access AEs and COPD exacerbations will occur every 4 weeks after Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7.

c Indicates allowable time window, centered on the planned date where the planned date is calculated by number of weeks relative to Visit 2 (see Section 9.5.6).

d May need to occur before Visit 1 in order to accommodate the required washout period for a particular prohibited medication (see Section 9.5.5.1.1).

e Perform chest x-ray if procedure was not completed within 6 months prior to screening; a CT scan should be performed based on the Investigator's clinical judgment and upon agreement with the Sponsor.

f Genitourinary examinations are not required but may be performed at the discretion of the Investigator.

g Height will be measured at Visit 1 (Screening) only. Body weight and vital signs will be collected at each visit.

h For female patients of childbearing potential or less than 1 year postmenopausal, an on-site urine pregnancy test will be administered.

i Forced maneuvers will be completed at 1 hour predose and 10 minutes predose, except at the following visits: Visit 1, where forced maneuvers are conducted before the administration of short-acting bronchodilator; Visit 2, where forced maneuvers are conducted prior to randomization; and Visit 8/ET, where forced maneuvers are performed but patients do not receive double-blind investigational product.

j Administer 4 puffs of Sponsor-provided bronchodilator (albuterol/salbutamol) before testing. Administration of bronchodilator can begin as soon as 10 minutes after the completion of the last predose spirometric effort if the patient is rested and comfortable. Forced maneuvers will be completed within 30 minutes (± 15 minutes) after administration of bronchodilator.

k Applies only to select study centers. Sparse PK samples will be collected at Visit 5, 7, and Visit 8/ET; serial PK samples will be collected only at Visit 7 at 0 hour (predose) and 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose.

l Includes Advair or Symbicort. At Visit 1, single-blind investigational product will be dispensed. At Visits 2-7, double-blind investigational product will be dispensed.

m ***For patients who complete Visit 8, telephone contact should occur 4 weeks after that visit. For patients with ET prior to Visit 8, telephone contact should occur 4 weeks after the ET visit.***

AE = adverse event; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; C–SSRS = Columbia–Suicide Severity Rating Scale; d = day(s); CT = computerized tomography; ECG = electrocardiogram; ET = early termination; PK = pharmacokinetic; TC = telephone contact; ***V = visit; wk = weeks.***

3.1 OVERALL TABLE OF CONTENTS

3.2 LIST OF IN-TEXT TABLES

3.3 LIST OF IN-TEXT FIGURES

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4.0 LIST OF ABBREVIATIONS

AE	adverse event
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	area under the curve
BID	twice daily
BTPS	body temperature and pressure, saturated
CAT	COPD Assessment Test
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
C-SSRS	Columbia–Suicide Severity Rating Scale
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia–Suicide Severity Rating Scale
EDC	electronic data capture
eRT	eResearch Technology, Inc
ET	early termination
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcome
FDA	US Food and Drug Administration
FDC	fixed-dose combination
FEV_1	forced expiratory volume in 1 second
FEV_6	forced expiratory volume in 6 seconds
FR	Federal Register
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
ICS	inhaled corticosteroid(s)
IEC	Independent Ethics Committee

IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	intent to treat
IVRS	interactive voice response system
LABA	long-acting β_2-agonist(s)
LAMA	long-acting muscarinic antagonist(s)
MACE	major adverse cardiac events
MDI	metered-dose inhaler
MMRM	mixed-effects model for repeated measures
NA	not applicable
NNT	number needed to treat
PCS	potentially clinically significant
PDE4	phosphodiesterase-4
PID	patient identification
PK	pharmacokinetic
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
RSM	regional site manager
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
WLW	Wei-Lin-Weissfeld method

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States
Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Forest Research Institute, Inc., ***(Forest) an affiliate of Actavis, Inc.,*** along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with CFR, Title 21, Part 56.

Outside the United States
This study will be carried out in full compliance with the guidelines of the Independent Ethics Committee (IEC) and government agencies of each respective country as well as the European Union Clinical Trial Directive (Directive 2001/20/EC), where applicable. Before the study begins, the study centers will require approval from an IEC and government agency. During the course of the study, the Sponsor or authorized representative will provide timely and accurate reports to the IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IEC of SAEs or other significant safety findings. The study protocol, ICF, information sheet advertisements, and amendments (if any) will be approved by the IEC at the study centers in conformance with CFR, Title 21, Part 56, the European Union Clinical Trial Directive (Directive 2001/20/EC), and local regulations.

5.2 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and Good Clinical Practice (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the CFR.

5.3 PATIENT INFORMATION AND CONSENT

Patients, after being given an explanation of the study, must give voluntary and written informed consent and HIPAA authorization (in compliance with 21 CFR, Parts 50 and 312) or other appropriate forms before participating in any study-related procedures.

Patients unable to give written informed consent must orally assent to the procedures; and written informed consent must be obtained from their parent, legal guardian, or legally authorized representative in accordance with the appropriate local laws, where applicable.

Each patient will read, assent to an understanding of, and sign an instrument of informed consent and the HIPAA and other applicable authorization form after having had an opportunity to discuss them with the study staff before signing; each patient will be made aware that he or she may withdraw from the study at any time without disadvantages for subsequent care.

The informed consent statement contains all the elements of informed consent listed in Appendix I of this protocol; the HIPAA authorization contains all the core elements and mandatory statements as defined in the CFR. Signed copies of the ICF and the HIPAA authorization form will be given to the patient, and both documents will be placed in the Investigator's study files.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 400 globally located study centers.

The Investigator is responsible for ensuring that an investigation is conducted according to the signed Investigator statement, the investigational plan, Good Clinical Practice guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of drugs under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or submitting to any study-related activity.

The Investigator at each study center must meet their obligations to the patients, ethics committee, sponsor and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff; by education, experience and licensure (in accordance with local regulations) and that the Investigator oversight has to be documented and assessment of their capabilities and performance consistent with the study investigational plan.

The Investigator at each study center will be responsible for the management of the study, which will consist of maintaining the study file and the patient records, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

Roflumilast was developed as a novel, once daily oral treatment option for chronic obstructive pulmonary disease (COPD) that targets the underlying inflammatory disease processes. Roflumilast (marketed as Daliresp® in the United States) is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Roflumilast is a novel selective phosphodiesterase-4 (PDE4) inhibitor approved for treatment with a once daily dose of 500-µg tablets. The 500-µg dose was found to be effective and safe in global clinical trials conducted in patients with COPD in 14 placebo-controlled studies in over 12,000 patients treated with roflumilast and placebo. The most frequently reported adverse events ([AEs] ≥ 2% and twice the placebo rate) in patients treated at the 500-µg dose were diarrhea, weight decrease, nausea, and headache. Roflumilast is approved and marketed for treatment in the United States, Canada, European Union, and other countries.

7.1 COPD BACKGROUND

COPD is characterized by a decline in lung function due to small airway fibrosis, mucus hypersecretion and emphysema. The major causative factor is cigarette smoking that drives an inflammatory process resulting in airway fibrosis and loss of alveolar tissue. COPD is complicated by frequent and recurrent acute exacerbations, which are associated with significant morbidity, disability, and also mortality. It is predicted to become the third leading cause of disease burden in terms of disability adjusted life-years and the fifth leading cause of death by 2020 (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2013).

COPD exacerbations are the periodic increases in symptoms (ie, cough, breathlessness, sputum) over baseline that usually necessitate a change in therapy. Data from the literature suggest acute COPD exacerbations have a significant impact on patient health, longevity and decline in lung function. Exacerbations are significant and detrimental clinical events in the natural history of COPD, and the frequency of exacerbations depends on the underlying severity of lung disease and history of prior exacerbations (Miravitlles et al, 2000). Several investigations have suggested that exacerbation frequency increases with disease severity (Burge et al, 2000; Paggiaro et al, 1998). Donaldson and colleagues (2002) have demonstrated exacerbation is a significant risk factor leading to hospitalization and is associated with an accelerated rate of lung function decline. Frequent exacerbations (> 2/year) have been associated with increased dyspnea and reduced exercise capacity (Donaldson et al, 2002; Hodgev et al, 2004), greater decline in health status (Spencer et al, 2001; Spencer et al, 2004), greater likelihood of becoming housebound (Donaldson et al, 2002; Donaldson et al, 2005), and increased mortality.

7.2 CLINICAL PHARMACOLOGY

In humans, after oral administration, roflumilast is rapidly absorbed with high absolute bioavailability of 79%. Roflumilast is metabolized to its major active metabolite, roflumilast N-oxide, mainly by the cytochrome P450 isozymes 1A2 and 3A4. Both roflumilast and roflumilast N-oxide are pharmacologically active, with intrinsic potency of roflumilast N-oxide being 3-fold lower than roflumilast. However, the N-oxide metabolite has a 10- to 12-fold higher plasma area under the plasma concentration versus time curve, and a 3-fold higher free fraction in plasma compared to the parent compound. As the N-oxide contributes about 90% of the overall PDE4 inhibitory activity and is the main moiety contributing to the pharmacodynamics activity of roflumilast, pharmacokinetic (PK) data were evaluated for both roflumilast and its N-oxide metabolite to assess overall PDE4 inhibitory activity.

Absorption following single oral dosing with 500 μg roflumilast was rapid with maximum plasma drug concentration occurring typically about 1 hour and 8 hours post-dose for roflumilast and roflumilast N-oxide, respectively. The absolute bioavailability of roflumilast following a single 500 μg oral dose is approximately 80%.

Use with inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (eg, erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) will increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of roflumilast. Therefore, the use of strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) with roflumilast is not recommended.

Excretion in humans after oral or intravenous administration occurred almost exclusively in the form of roflumilast metabolites and mainly via the kidneys (~70% of the dose). Fecal elimination accounts for approximately 20% of the dose. The total plasma clearance of roflumilast after intravenous administration was 9.6 L/h for a 70-kg person.

7.3 CLINICAL EFFICACY AND SAFETY

The core clinical program comprising Phase 2 and Phase 3 trials included 12,054 COPD patients (5766 treated with roflumilast 500 μg, 5491 with placebo and 797 with roflumilast 250 μg). Both the roflumilast 500 μg once daily and placebo treatment groups had comparable demographics and baseline characteristics in the COPD safety pool. The median age of patients was 64 years, with 45% of the patients being older than 65 years. The majority of patients were male (72%) and white (88%), and 42% of the patients were current smokers. Approximately 56% of the patients had severe COPD.

In two 1-year pivotal trials, M2-124 (1523 COPD patients) and M2-125 (1568 COPD patients) were designed to confirm the effect of roflumilast in reducing exacerbation rates in COPD patients with chronic bronchitis and a history of exacerbations. The COPD patient population enrolled had a postbronchodilator forced expiratory volume in 1 second (FEV_1) of less than 50% predicted, chronic bronchitis, and at least 1 exacerbation within the previous year prior to enrollment.

Both the M2-124 and M2-125 studies confirmed the results from earlier studies (M2-111 and M2-112), that treatment with roflumilast 500 µg once daily significantly reduces the rate of moderate or severe exacerbations. The rate of moderate or severe exacerbations was reduced by 14.9% ($p = 0.0278$) in study M2-124 and by 18.5% ($p = 0.0035$) in Study M2-125 compared to placebo. Predose FEV_1 improvement was also observed when compared to placebo by 39 mL ($p = 0.0003$) in Study M2-124 and by 58 mL ($p < 0.0001$) in Study M2-125. In summary, oral once daily administration of roflumilast 500 µg resulted both in a statistically significant and clinically meaningful reduction of moderate and severe exacerbations and in an improvement of lung function in moderate as well as in severe COPD patients with chronic bronchitis.

In the COPD safety pool, AEs reported more frequently (≥ 2% and twice the placebo rate) in roflumilast-treated patients were diarrhea (10% roflumilast versus 3% placebo), weight decrease (7% roflumilast versus 2% placebo), nausea (5% roflumilast versus 1% placebo) and headache (5% roflumilast versus 2% placebo). Most AEs generally occurred within the first weeks of therapy and resolved during continued treatment.

AEs resulting in study discontinuation occurred in 824 patients (14.3%) with roflumilast and in 503 patients (9.2%) receiving placebo. The difference in discontinuation rate between roflumilast and placebo was mostly due to gastrointestinal events (nausea, diarrhea). Discontinuation due to all other AEs other than GI-related events was similar between roflumilast (9.2%) and placebo (8.4%).

SAEs occurred approximately in equal numbers in patients receiving roflumilast (13.5%) and placebo (14.2%). A total of 177 deaths occurred in the COPD safety pool. Death was reported for 84 patients (1.5%) in the roflumilast 500-µg group, 7 patients (0.9%) in the roflumilast 250-µg group, and for 86 patients (1.6%) in the placebo group.

Treatment with roflumilast is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials, 5.9% (263) of patients treated with roflumilast 500 µg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression, which were reported at higher rates in those treated with roflumilast 500 µg daily (2.4%, 1.4%, and 1.2% for roflumilast versus 1.0%, 0.9%, and 0.9% for placebo, respectively). Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (1 completed suicide and 2 suicide attempts) while receiving roflumilast compared to 1 patient (suicidal ideation) who received placebo.

Roflumilast had no clinically relevant effect on laboratory or electrocardiogram (ECG) values or vital sign measures (with the exception of weight) compared to placebo treatment. On average, roflumilast patients experienced a weight decrease of 2 kg by comparison to placebo patients. The weight loss was greatest (in absolute amounts) in patients who were heaviest at baseline and generally plateaued after 6 months of therapy. Very few patients on roflumilast discontinued due to weight decrease. Most patients did not show further weight loss and many regained weight within 3 months from cessation of treatment.

No clinically relevant PK interactions were observed with drugs that are used in the clinical management of patients, including inhaled albuterol/salbutamol, formoterol, budesonide, oral theophylline, montelukast, digoxin, warfarin, sildenafil, oral or intravenous midazolam, Maalox®, oral contraceptives containing gestodene and ethinyl estradiol, fluvoxamine, cimetidine, enoxacin, erythromycin and ketoconazole.

Overall roflumilast has demonstrated benefit independent of other concomitant COPD treatments. When administered at a dose of 500 μg once daily to COPD patients, beneficial effects of roflumilast with respect to lung function and exacerbation frequency were statistically significant and clinically relevant. These improvements were accompanied by improvements in breathlessness and reductions in rescue medication. While some patients may experience gastrointestinal complaints or headache upon initiation of treatment, there is no evidence to suggest that roflumilast is associated with an increased risk of serious sequelae. Weight decrease has not been associated with increased morbidity and can be easily monitored by both patient and physician.

Roflumilast offers a once daily oral therapy that reduces exacerbations when taken with both long- and short-acting beta agonists. In patients with chronic bronchitis, roflumilast, taken as a 500-μg tablet once daily, is expected to improve and support patient treatment compliance in patients already challenged by concomitant diseases and multiple inhalation delivery devices.

7.4 STUDY RATIONALE

Roflumilast has been shown to be effective and safe when combined with either long-acting bronchodilators or inhaled corticosteroids (ICS). As a result, this trial is designed to provide additional clinical trial efficacy and safety results to demonstrate the benefits of roflumilast when added on to fixed-dose combinations (FDC) of long-acting β_2-agonists (LABA) and ICS.

Because exacerbations are linked to inflammation, ICS are often added in advanced disease to improve lung function and lessen the frequency of exacerbations. For example, salmeterol alone versus placebo reduced exacerbations by 15%; adding fluticasone to salmeterol in a fixed combination demonstrated an additional reduction in exacerbations by 12% versus salmeterol alone (Calverley et al, 2007). The use of fixed combinations of LABA and ICS as maintenance therapy is recognized as a standard of care by international COPD treatment guidelines in symptomatic patients with severe to very severe COPD with a history of recurrent exacerbations (Global Initiative for Chronic Obstructive Lung Disease, 2010).

This study is designed to evaluate the effect of roflumilast on the frequency of exacerbations in patients with COPD treated with fixed combinations of LABA and ICS. Approximately 2300 patients will be randomized into a 52-week, double-blind, placebo-controlled trial to evaluate the effects of roflumilast 500 µg versus placebo added on to patients with ongoing FDC LABA/ICS therapy. Approximately 400 global study centers in the United States and internationally will participate.

7.4.1 Target Population

The patient population will be male and female patients with severe to very severe COPD who are ≥ 40 years of age and have a history of at least 2 moderate or severe exacerbations within 12 months prior to Screening. Patients will have chronic bronchitis and will have been receiving an FDC LABA/ICS daily for a minimum of 3 months before Screening. Patients may have switched from one FDC LABA/ICS to another during this time if clinically indicated. Up to 60% of patients are allowed to be on a stable treatment regimen with a long-acting muscarinic antagonist (LAMA) for a minimum of 3 months prior to Screening in addition to the FDC LABA/ICS.

7.4.2 Treatment

The trial consists of 2 periods. The single-blind lead-in period begins at Visit 1, Week-2 (relative to Visit 2, randomization). All patients who qualify for entry into the study at Visit 1 will enter the lead-in period and will receive placebo as well as the appropriate FDC LABA/ICS as selected by the Investigator.

The second period is a double-blind treatment period of 52 weeks duration. At the start of this period (Visit 2), patients will be randomized to receive blinded roflumilast or placebo tablets at Week 4 (Visit 3), 12 (Visit 4), 20 (Visit 5), 28 (Visit 6), and 40 (Visit 7). All patients will be maintained on their study-prescribed FDC LABA/ICS until Visit 8/ET. Patients who are on stable LAMA treatment at Screening should also remain on that dose throughout the study. Upon completion of the double-blind treatment period, patients will discontinue investigational product and receive a phone call (approximately 4 weeks after Visit 8/ET) to further monitor and assess patient AEs and exacerbation events.

7.4.3 Duration

The study duration will be 58 weeks and will include a 2-week, single-blind, lead-in (placebo) period, 52-week treatment (roflumilast 500 µg or placebo tablets, randomized 1:1) period, followed by a phone contact approximately 4 weeks after completion of the study.

7.4.4 Efficacy Endpoints

7.4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the rate of moderate or severe COPD exacerbations per patient per year. Moderate exacerbations are defined as a worsening of COPD symptoms necessitating oral or parenteral glucocorticosteroids. Severe exacerbations are defined as worsening of COPD resulting in hospitalization and/or leading to death (see Section 9.5.1.1.2).

7.4.4.2 Secondary Efficacy Endpoints

- ***C***hange from Randomization (Visit 2) over 52 weeks of treatment in predose FEV_1.
- ***Rate of COPD exacerbations that led to hospitalization or death (i.e., severe COPD exacerbations)***
- ***Rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics***

7.4.4.3 Additional Efficacy Endpoints

- COPD exacerbation parameters
    - Rate of exacerbations in the following categories: mild; moderate; treated with systemic steroids and/or antibiotics; treated with antibiotic therapy only***; mild, moderate, or severe; mild, moderate, severe***, ***or treated with antibiotics;*** exacerbations that led to COPD-related emergency room visit or hospitalization or death, exacerbations derived from the Exacerbations Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT-PRO) questionnaire, and exacerbations as reported on the eCRF (see Section 9.5.1.1.4)
    - Proportion of patients with at least 1 exacerbation for all categories including moderate or severe exacerbation***s***
    - Time to first, second, and third moderate or severe exacerbations

- Number needed to treat (NNT) to avoid 1 moderate or severe COPD exacerbation per patient per year***, NNT to avoid 1 severe COPD exacerbation per patient per year, and NNT to avoid 1 moderate or severe exacerbation or exacerbation treated with antibiotics***
- Number of COPD exacerbation days (all categories)
- Duration of COPD exacerbations (all categories)

Note: The algorithm for deriving COPD exacerbations from the EXACT-PRO questionnaire will be described in the Statistical Analysis Plan (SAP).

- Spirometry parameters, mean change from baseline over post-randomization visits during treatment period in
  - FVC: Forced vital capacity (expiratory)
  - FEV_1/FVC: Ratio of forced expiratory volume after 1 second to forced vital capacity
  - FEV_6: Forced expiratory volume in the first 6 seconds
- Diary parameters, mean change from baseline over post-randomization visits during treatment period in
  - Rescue medication use (puffs/day)
  - EXACT-PRO total score, and scores from the Breathlessness, Cough & Sputum, and Chest symptom domains (daily score derived from EXACT-PRO questionnaire)
- COPD Assessment Test (CAT) (Appendix VI)
- All-cause hospitalizations
- COPD-related hospitalizations
- Major adverse cardiac events (MACE)

8.0 STUDY OBJECTIVES

The primary objective of this study is to investigate the effect of roflumilast 500-µg tablets once daily versus placebo on the exacerbation rate in COPD patients concomitantly treated with FDC LABA/ICS. An anticipated benefit when adding roflumilast to FDC LABA/ICS therapy is expected in the reduction of exacerbation in COPD patients, based upon prior data demonstrating an additive effect of roflumilast to LABA and ICS in separate studies.

The key secondary objectives will evaluate the effects of roflumilast on lung function (spirometry), COPD symptoms (as collected in diaries), and the safety and tolerability of roflumilast in COPD patients concomitantly treated with FDC LABA/ICS.

9.0 INVESTIGATIONAL PLAN

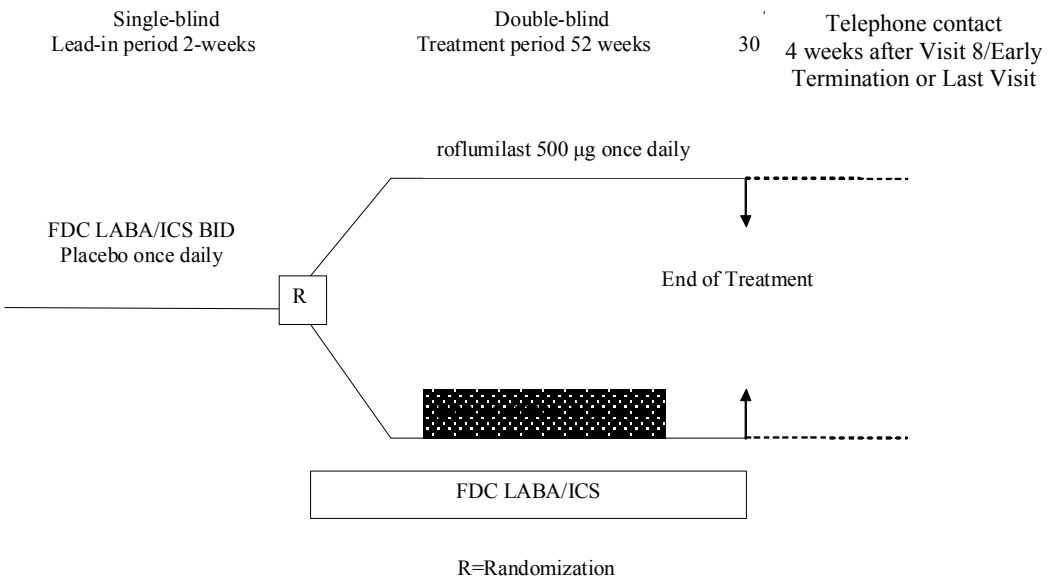
9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing roflumilast to placebo in patients with a diagnosis of severe to very severe COPD (GOLD 2010 stage III-IV). The study will consist of 2 weeks of single-blind placebo lead-in with FDC LABA/ICS treatment followed by 52 weeks of double-blind treatment in addition to maintenance FDC LABA/ICS. Patients will be stratified to 2 strata based on their background LAMA use (LAMA, no LAMA). At the end of the single-blind period, patients meeting the entry criteria for this study will be randomized (1:1) to 1 of 2 double-blind treatment groups (roflumilast or placebo) within the appropriate stratum. The LAMA stratum will not enroll more than 60% of the total planned number of patients. All patients randomized into the study will be contacted by phone approximately 4 weeks after study completion to assess exacerbations and AEs.

Figure 9.1-1 provides a schematic of the study design. The Schedule of Evaluations is presented in Section 2.0. Detailed descriptions of each study visit can be found in Section 9.5.5.

Figure 9.1-1. Study Design

ROF-MD-07 Study Design



9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This is a randomized, double-blind, placebo-controlled study. The placebo arm is included to investigate the efficacy and safety of roflumilast when added on to FDC LABA/ICS. All patients will continue to receive their established standard therapy (FDC LABA/ICS) while treated with placebo. Patients who are on stable LAMA treatment will continue that treatment. The placebo treatment will not add any additional risk and is therefore ethically justified. Rescue medication use will be allowed during the entire study. To monitor lung function throughout the study, spirometry for pulmonary function will be performed using centralized testing (Appendix III). All patients will be required to record their COPD symptoms (via EXACT-PRO) and frequency of rescue medication use in an electronic diary provided by the sponsor.

The study design includes a 2-week, single-blind, lead-in period to assess study medication compliance, baseline disease severity, and frequency of rescue medication use.

The 52-week treatment period is considered appropriate to investigate the primary endpoint, reduction of exacerbation rate, taking into account the seasonal variation of COPD exacerbations during the year (Donaldson et al, 1999).

It has been demonstrated that a treatment regimen with a once daily dose of roflumilast 500 µg in a period of 52 weeks was effective and safe in several clinical trials. A follow-up phone call, which will occur approximately 4 weeks after treatment end, is included to identify any AEs or exacerbations following study completion.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

9.3.1.1 Inclusion Criteria at Screening (Visit 1)

To be eligible to participate in the study, patients must meet the following criteria at Screening (Visit 1):

1. Male or female patients at least 40 years of age

2. History of COPD according to GOLD 2010 for at least 12 months prior to Screening (Visit 1) associated with chronic productive cough for 3 months in each of 2 consecutive years (with other causes of productive cough excluded). Only patients with chronic bronchitis will be included (concomitant emphysema is permitted)

3. Forced expiratory volume after 1 second (FEV_1)/forced vital capacity (FVC) ratio (postbronchodilator) < 70% at Screening (Visit 1)

4. FEV_1 (postbronchodilator) ≤ 50% of predicted at Screening (Visit 1)

5. At least 2 documented moderate or severe COPD exacerbations within 12 months prior to Screening (Visit 1) (See Section 9.5.1.1.2, Definition of Exacerbation) Listed below are the only acceptable forms of documentation for COPD exacerbations used to qualify patients for the study. An interview of the patient is not an acceptable form of documentation.

Acceptable Forms of Documentation for Qualifying COPD Exacerbation

The following types of documentation of previous COPD exacerbations are considered acceptable to qualify the patient for the study.

1) Physician Note: A note from primary care or other treating or referring physician is acceptable documentation of an exacerbation if signed/stamped and dated by the physician. The note should either be written on the physician's official letter head or be stamped by the physician.

The note must describe the occurrence of a moderate or severe COPD exacerbations 12 months prior to screening and indicate diagnosis/therapy start date and end date. If the note is intended to document 2 previous exacerbations, these must be described separately, as follows:

- COPD exacerbation # 1 - diagnosis and treatment (start and end dates of oral/parenteral steroid treatment and hospitalization dates if applicable)

- COPD exacerbation # 2 - diagnosis and treatment (start and end dates of oral/parenteral steroid and treatment and hospitalization dates if applicable)

The documents need to be confirmed for their clinical validity and signed/stamped and dated by the primary care or referring physician and then signed/stamped and dated by the Investigator.

2) Outpatient or hospital records indicate diagnosis of COPD exacerbation and therapy start and end dates:

- Oral or parenteral steroid treatment history (dose/duration)

- Oral or parenteral steroid treatment /hospital admission with diagnosis and treatment for exacerbation and discharge note(s), if applicable

3) Pharmacy Records indicating dispensing of the following therapy/date:

- Oral or parenteral steroid (dose/duration/indication) and any other medications used to treat the exacerbation (dose/duration/indication).

4) Investigator contact with the treating physician(s) to confirm history of previous COPD exacerbation, and treatment.

- Treating physician should check the medical records to verify history of exacerbations and respective treatment.
- An additional option is for the Investigator or treating physician to query the pharmacy to ask for the drug(s) dispensed (steroids) for exacerbation.
- The Investigator must document the details of the contact with the treating physician and/or pharmacy in the patient's source documentation.

Note: The Investigator is responsible for verifying the patient had two (2) moderate or severe COPD exacerbations in the 12 months prior to the screening visit, as well as the respective treatments as defined in Section 9.5.1.1.2.

6. Patients must be receiving an FDC LABA/ICS daily ≥ 3 months prior to Screening (Visit 1)

7. Patients who were previously treated with LAMA must have been on a stable dose for ≥ 3 months before Screening (Visit 1)

8. Former smokers (defined as smoking cessation at least 1 year ago) or current smokers (including patients who ceased smoking within the past year) both with a smoking history of at least 20 pack-years

   Note: Total pack-years of cigarette smoking (number of pack-years) is defined as the number of cigarettes smoked each day divided by 20 (the number of cigarettes in a pack) and the result multiplied by the number of years the person has been smoking.

   Pack-years = (number of cigarettes smoked per day/20) ×
   (number of years the patient has been a smoker)

9. Patients must be able to perform repeatable pulmonary function testing for FEV_1 according to the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (Miller et al, 2005)

10. Women of childbearing potential with a negative urine pregnancy test at Screening (Visit 1) with ongoing use of birth control from study start (Screening) to Visit 8/ET

11. Patients judged by the Investigator to be physically capable of participating in a year-long study based on medical history, physical examination, ECG, and routine laboratory data evaluations

12. Patients who understand the study procedures and are willing to participate in the study as indicated by signing the informed consent

9.3.1.2 Inclusion Criteria at Randomization (Visit 2)

Patients must meet the following additional criteria at Randomization (Visit 2) to be eligible to enter the double-blind treatment period:

13. No moderate or severe COPD exacerbations between Screening (Visit 1) and Randomization (Visit 2)

14. Single-blind investigational product compliance ≥ 80% and ≤ 125%

15. Advair or Symbicort compliance of ≥ 80% and ≤ 125%

16. Patients must have remained on the same COPD maintenance therapy between Screening (Visit 1) and Randomization (Visit 2) (ie, FDC LABA/ICS or LAMA added onto FDC LABA/ICS)

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria will <u>not</u> be eligible to participate in the study**:**

1. Moderate or severe COPD exacerbation and/or COPD exacerbations treated with antibiotics or systemic glucocorticosteroids within 4 weeks of Screening (Visit 1) (ie, patients must be clinically stable)

2. Lower respiratory tract infection within 4 weeks of Screening (Visit 1)

3. Diagnosis of significant lung disease other than COPD (eg, history of primary bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease [eg, fibrosis, silicosis, sarcoidosis], active tuberculosis, pulmonary thromboembolic disease, lung volume surgery, Kartagener syndrome), post organ transplantation, or patients who are expected to require thoracotomy or other lung surgery during the study

4. Known alpha-1-antitrypsin deficiency

5. Current diagnosis of asthma (either controlled or uncontrolled) (Note: History of childhood asthma is not exclusionary.)

6. Liver impairment Child-Pugh B or C and/or active viral hepatitis

7. Body mass index (BMI) $\geq$ 45 kg/m^2

8. Patients who have participated in an acute pulmonary rehabilitation program within the previous 3 months. (Note: Patients on a stable pulmonary rehabilitation exercise regimen for at least 6 weeks are not excluded)

9. Suicidal risk, as determined by meeting any of the following criteria:

    a. History of suicidal ideation $\leq$ 3 months prior to Screening (Visit 1) with a score of 4 (intent to act) or 5 (specific plan and intent) on the electronic Columbia–Suicide Severity Rating Scale (eC-SSRS)

    b. History of suicidal behavior (actual attempt, interrupted attempt, aborted attempt, and/or preparatory acts/behavior on the eC-SSRS) $\leq$ 1 year prior to Screening (Visit 1)

    c. Significant risk, as judged by the Investigator (or psychiatric referral), based upon the patient's medical (and/or psychiatric) history

10. Patients with clinically significant cardiovascular conditions, including myocardial infarction within the previous 6 months; newly diagnosed arrhythmia within the previous 3 months; unstable angina; unstable arrhythmia that has required changes in pharmacological therapy or other intervention (eg, use of an automated implantable cardioverter-defibrillator); hospitalization within the previous 12 months for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity, and presence of symptoms at rest) (New York Heart Association criteria [NYHA])

11. Patients with a QTcB, as determined by the ECG over-reader at the central laboratory, $\geq$ 470 milliseconds in the resting ECGs performed at Screening (Visit 1)

12. Patients with clinically relevant abnormalities (as judged by the Investigator or Study Physician) in the results of the clinical laboratory tests, in ECG parameters other than QTc, or in the physical examination or vital signs at Screening (Visit 1) except for those related to COPD

13. Patients who are HIV positive or have active viral hepatitis or other chronic systemic infection

14. Patients with a history of drug or alcohol abuse or dependence within the previous 5 years

15. Patients with any other serious or uncontrolled physical or mental condition/disease that, as judged by the Investigator, could place the patient at higher risk derived from his/her participation in the study, could confound the results of the study, or would be likely to prevent the patient from complying with the requirements of the study or completing the study. If there is a history of such disease but the condition has been stable for more than 1 year and is judged by the Investigator not to interfere with the patient's participation in the study, the patient may be included, with the documented approval of the Study Physician

16. Clinically relevant abnormal vital signs or laboratory values suggesting an undiagnosed disease requiring further clinical evaluation as determined by the Investigator

17. Patients who have used theophylline (including long-acting theophylline) or add-on theophylline derivatives (eg, aminophylline) within 2 weeks before Screening (Visit 1)

18. Patients who have received any investigational drugs within 30 days (or 6 half-lives, whichever is longer) or who have received treatments employing an investigational device within 30 days before Screening (Visit 1)

19. Women who are pregnant or breastfeeding

20. Patients with a history (within 5 years) or current diagnosis of cancer other than basal or squamous cell skin cancer (Note: per Exclusion Criterion No. 3, patients with any history of lung cancer are not eligible)

21. Patients who intend to use any concomitant medication not permitted by this protocol or who have not undergone the required washout period for a particular prohibited medication (Section 9.4.8 and Appendix II)

22. Patients who are unlikely to be compliant with study requirements (eg, take their medication, complete their electronic diaries, attend clinic at the required times)

23. Employee or immediate relative of an employee of Forest Laboratories, ***LLC***., ***an affiliate of Actavis, Inc.,*** any of its affiliates or partners, or the study center or its affiliates

9.3.2.1 Treatment Considerations

It is the responsibility of the Investigator to fully assess each patient's overall clinical and COPD status at baseline to determine that the patient's maintenance COPD treatment is adequate, prior to initiation into this study. Patients will be assigned to 1 of 2 strata: LAMA or no LAMA.

Every effort should be made to keep the patient on the assigned maintenance treatment (LAMA or no LAMA) throughout the duration of the study treatment period. Any change to maintenance treatment during the study can confound the interpretation of the study results. Examples are as follows: the addition of a LAMA to a patient in the LABA/ICS arm, discontinuation of either LABA/ICS or LAMA from the patient's maintenance treatment, or the addition of maintenance oral steroids for any patient.

Sponsor-provided albuterol/salbutamol is permitted as rescue medication in both groups for transient worsening of COPD symptoms. In addition, patients in the LABA/ICS stratum may be treated with short-acting muscarinic antagonists, but those in the LABA/ICS/LAMA stratum may not.

Should a patient's clinical status (worsening of COPD symptoms) deteriorate during the study, and rescue treatment is inadequate to control the patient's symptoms, the Investigator should consider additional COPD medications (eg, LAMA in the ICS/LABA group). The Investigator must contact the Sponsor (Study Physician) for notification and discussion of the change prior to implementation (when non-emergent).

The date of the change in maintenance medication must be clearly documented in the source document and in the concomitant medication eCRF.

9.3.3 Removal of Patients from Therapy or Assessment

Premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study. Patients can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria (only for screen failures)
- Adverse event (AE)
- Insufficient therapeutic response
- Protocol deviation/violation
- Withdrawal of consent (a clear reason must be documented)
- Lost to follow-up. (Every effort must be made to contact the patient; a certified letter [or equivalent] must be sent)
- Study or site prematurely terminated by the Sponsor for any reason
- A deterioration in pulmonary function that, in the judgment of the Investigator compromises a patient's health
- Other reasons, such as administrative reasons or pregnancy

All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment. A final assessment is defined as completion of the evaluations scheduled for Visit 8 (Early Termination Visit or Last Visit) at the end of Week 52. Patients who do not complete all scheduled visits/procedures must be requested to come in for an ET Visit and to return any used and unused investigational product. Even if the patient is not able to attend, the eCRF must be completed with all available data. The Drug Accountability Form must be filled in as well. The reasons for premature discontinuation from the study will be reflected on the Study Termination Record of the eCRF.

In case of patients lost to follow-up, every reasonable effort should be made to contact the patient to encourage continued trial participation as scheduled. Sites are required to provide documentation of due diligence before considering a patient "lost to follow-up." Every effort should be made by the Investigator to ascertain the reason for discontinuation and to encourage the patient to return to the clinic as soon as possible to complete study activities. If the patients cannot be reached by telephone, a certified letter must be sent by the Investigator. Documentation of these efforts is to be noted in the source documents that are held at the site. If the letter is sent back to the site as a result of failed delivery, the patient is considered "lost to follow-up." If the letter is successfully delivered, the site is to contact the patient again and, if unsuccessful, wait for a response from the patient to attempt to schedule a study visit. If the patient still cannot be contacted, the investigative site may, at their discretion, send a second letter to the patient further reinforcing the importance that the patient responds to the letter. If the patient has not responded to any of these attempts within a reasonable timeframe, the investigative site and Forest Research Institute, ***Inc., an affiliate of Actavis, Inc.,*** consider the patient "lost to follow-up," assuming no reason can be ascertained for the premature discontinuation.

All randomized and prematurely discontinued patients will be followed up for exacerbations and AEs by a phone call approximately 4 weeks following withdrawal from the study or sooner if clinically indicated (Section 9.5.5.4).

Patients who discontinue double-blind investigational product will no longer be provided with LABA/ICS or rescue medication by the Sponsor.

If the patient discontinues the investigational product for any reason, every effort should be made to continue following the patient according to the schedule described in Section 9.3.3.1. If the patient is unable or unwilling to follow this schedule, the reason for this must be documented in the source records and as a form-level comment in the Study Termination eCRF.

9.3.3.1 Assessments for Patients Who Discontinue Investigational Product After Randomization

Randomized patients who have received at least 1 dose of double-blind treatment during the study will be asked to participate in post-treatment follow-up assessments upon discontinuation. Once investigational product is discontinued, the Investigator should institute appropriate treatment for these patients according to the Investigator's clinical judgment and standard of care. The follow-up period will include 1 or 2 on-site visits (depending on the time of discontinuation) as well as interim telephone contacts to collect information regarding exacerbations, concomitant medication use, and AEs experienced from the time of the patient's last contact with the site. At the on-site visits, assessments are to be performed as described in Section 9.5.5.3. Visits and telephone contacts will occur according to the schedule in Table 9.3.3.1–1 based on the time of investigational product discontinuation.

The ET Visit will be conducted according to the instructions provided in Section 9.5.5.2.7.

Table 9.3.3.1–1. Schedule of Visits and Telephone Contacts for Patients Who Discontinue Randomized Treatment and Continue in the Study

Patient Visit Discontinued	*Visit*							
	Visit 1 Screening	*Visit 2 Randomization*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Last Visit*
Study Week	–2	0	4	12	20	28	40	52
At Visit 3	—	—	ET	TC[a]	TC[a]	X[b]	TC[a]	X[b]
At Visit 4	—	—	—	ET	TC[a]	X[b]	TC[a]	X[b]
At Visit 5	—	—	—	—	ET	X[b]	TC[a]	X[b]
At Visit 6	—	—	—	—	—	ET	TC[a]	X[b]
At Visit 7	—	—	—	—	—	—	ET	X[b]

a Patient telephone contact to occur at designated time points to collect the following: exacerbations, concomitant medication use, and adverse events since last visit or telephone contact.
b On-site patient visit to be completed as indicated (Visit 6 and/or Visit 8/Last Visit), to conduct the assessments described in Section 9.5.5.3; a 4-week follow-up call will be conducted after this visit.
ET = early termination, TC = telephone contact; X = on-site visit.

9.3.3.2 Rescreening

Rescreening of patients is allowed only with written permission of the Sponsor. Patients may be rescreened a minimum of 4 weeks after resolution of a moderate to severe exacerbation and completion of exacerbation medication. For example, patients who were withdrawn at Visit 2, prior to randomization due to an exacerbation (moderate and/or severe exacerbation, and/or treated with antibiotics [see Section 9.3.1.2 and Section 9.5.1.1.2]) between Visit 1 and Visit 2) may be rescreened after resolution of the exacerbation (4 weeks). If, during the second screening, the patient again experiences such an exacerbation, the patient must be withdrawn and no further rescreening is allowed.

For rescreened patients, a new eCRF has to be filled in starting at Visit 1.

9.3.3.3 Replacement Procedures

Patients withdrawn early after randomization will not be replaced.

9.4 TREATMENTS

During the study, all investigational products, including roflumilast and matching placebo, Advair, Symbicort, and rescue medication will be supplied by the Sponsor.

9.4.1 Treatments Administered

- Roflumilast, 500-µg tablet
- Placebo tablet
- Advair (fluticasone/salmeterol) 250/50 µg 1 puff twice daily (BID*)* or Symbicort (budesonide/formoterol)160/4.5 µg 2 puffs BID
- Albuterol/salbutamol for rescue

Investigational product in the form of tablets (roflumilast and matching placebo) will be provided by Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.*** For the single-blind, lead-in period, patients will be supplied with placebo tablets and FDC LABA/ICS treatment. For the double-blind treatment period, patients will be supplied with identically appearing tablets containing either 500 µg of roflumilast or placebo along with FDC LABA/ICS treatment. All investigational products supplied by the Sponsor for this trial will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines.

Investigational products for this study will be dispensed at each visit except at Visit 8/ET. During the single-blind, lead-in period, patients will receive placebo, plus either FDC Advair or Symbicort, and rescue medication dispensed at Visit 1. The Investigator will determine whether a given patient is to be provided with Advair or Symbicort, based on prior FDC LABA/ICS treatment. Patients meeting randomization criteria will receive double-blind investigational product (roflumilast or placebo), FDC Advair (250/50 µg 1 puff BID) or Symbicort (160/4.5 µg 2 puffs BID), and rescue medication at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7. Patients who sign informed consent before Visit 1 (ie, patients who are prescreened and return to the site for Visit 1 procedures at a later time) will receive only rescue medications until Visit 1.

FDC LABA/ICS and rescue medication will be supplied individually as indicated in Table 9.4.1–1. Each study center will be provided with drug supplies corresponding to a sequence of medication numbers.

Table 9.4.1–1. Dispensing Frequency of FDC LABA/ICS and Rescue Medication

Visit	*No. of Weeks Since Randomization*	*No. of Weeks to Next Treatment Visit*	*No. Advair or Symbicort Inhalers*	*No. Rescue Inhalers*
ICF Visit	n/a	n/a	n/a	1
Screening (Visit 1)[a]	–2	2	1	1
Randomization (Visit 2)	0	4	1	2[b]
Visit 3	4	8	2	3[b]
Visit 4	12	8	2	3[b]
Visit 5	20	8	2	3[b]
Visit 6	28	12	3	4[b]
Visit 7	40	12	3	4[b]
Visit ET/Last Visit	52	—	—	—

a If 30 days or more lapse between the time of Informed Consent and Visit 1, the patient must be re-consented. Rescue medication is to be provided at the time of informed consent if this occurs prior to Screening (Visit 1).
b The Investigator will distribute additional rescue medication as needed according to use.
ET = early termination; FDC = fixed-dose combination; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist.

If additional units of Advair, Symbicort and/or Ventolin are needed from Visits 2-7, use the “emergency resupply” visit in IXRS. Keep in mind that each Advair and Symbicort kit/unit has 30 days of dosing, and with visits being 8 weeks (or 56 days) and 12 weeks (or 84 days) apart, there is enough drug to last 60 days. So as not to encounter situations where a patient may run out of drug, it’s very important that you instruct patients to monitor the counter on each device to ensure they have enough Advair or Symbicort to carry them until their next scheduled visit.

Rescue Medication Use
Albuterol (known as salbutamol outside of the United States) will be provided by the Sponsor to be used according to the product labeling and the individual needs of a patient. Marketed albuterol/salbutamol provided by the Sponsor will be the only permitted rescue medication during participation in the trial. Rescue medication is to be provided by the Investigator to the patient at the time of informed consent and subsequent study visits, as necessary according to consumption. When administered for the reversibility test at the study center (Screening [Visit 1]), albuterol/salbutamol should be given through a spacer device (AeroChamber) to be certain it has been inhaled properly. During the study, the use of spacers for the albuterol/salbutamol administration will be permitted, provided they were used routinely by the patient prior to study entry.

When administered as rescue medication, albuterol/salbutamol should be discontinued at least 4 hours prior to any visit until after completion of the last spirometry measurement at the visit, unless the use is absolutely necessary. If more than 3 hours have passed since the last use of rescue medication, the patient may wait until 4 hours (an additional hour) have elapsed to begin the visit, provided that investigational product would be administered by 11 AM. Otherwise, the visit should be rescheduled for the next possible day. If rescue medication is taken during the visit, the visit will be stopped and no additional assessments will be made. The patient will then return for the next scheduled visit.

Administration should be on “as needed” basis, as per the Investigator’s instructions in accordance with the product labeling and clinical status of the patient. Patients will record the number of puffs of albuterol/salbutamol used in the patient electronic diary, which will be checked by the Investigator at each visit.

9.4.2 Identity of Investigational Products

The investigational product labels will be country specific and include the protocol number, medication number, expiration date, storage information, warning language (eg, “Caution: New Drug—Limited by Federal Law to Investigational Use”), and instructions to take the tablets once daily in the morning as directed. Immediately before dispensing the investigational product, the Investigator will write the patient’s 8-digit patient identification (PID) number, patient’s initials, study center number, and date on the label.

All investigational products, including maintenance FDC LABA/ICS and rescue medication, will be provided by Forest Research Institute, Inc***., an affiliate of Actavis, Inc***. All study drug products must be stored in an appropriate secure area (eg, a locked cabinet in a locked room) and must be protected from heat and moisture. All study drug products, with the exception of Ventolin, (albuterol or salbutamol), must be stored at 2***0***°C ***to 25°C (68°F to 77°F)***, with a permitted range of 15°C to 30°C ***(***59°F to 86°F). Ventolin (albuterol or salbutamol) ***must*** be stored ***at*** **15°*C to*** *25°C* ***(***59°***F*** **to** 77°F***), with a permitted range of 15°C to 30°C (59°F to 86°F).*** Formulation information for the investigational products is provided in Table 9.4.2–1.

Table 9.4.2–1. Investigational Product Formulation

Investigational Product	***Dosage***		***Active Substance***	
	Form	***Route***	***Compound***	***Amount***
Roflumilast	Tablet	Oral	Roflumilast	40 tablets (500 µg/tablet)
Placebo	Tablet	Oral	—	40 tablets (—)

Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** will prepare the double-blind investigational product according to the randomization list. Each manufacturing process will be performed and documented in conformity with Good Manufacturing Practices. Forest ***Research Insitute, Inc., an affiliate of Actavis, Inc.,*** will provide a certificate of release and analysis.

Manufacturing of roflumilast and placebo will be performed at:

Takeda GmbH
[redacted]

Clinical packaging and labeling of all double-blind investigational products and labeling of marketed products (Advair, Symbicort, and albuterol/salbutamol) will be performed at the following locations:

Packaging of Double-Blind Investigational Products for North America and Rest of World:
[redacted]

Labeling of Double-Blind Investigational Products for North America and Rest of World and Marketed Products for North America:
Forest Research Institute, Inc***., an affiliate of Actavis, Inc.***
[redacted].

Release testing of the roflumilast and placebo clinical supplies and stability testing will be performed at:

Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.***
[redacted].

The Investigator is responsible for recording the receipt and use of all investigational products supplied and for ensuring the supervision of the storage and allocation of these supplies. Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** or a designated drug depot, will provide drug delivery, drug dispensing, and drug return forms to facilitate inventory control at the study center.

Study centers are immediately to return any malfunctioning or damaged FDC LABA/ICS and rescue medication devices (as identified by the patient or Investigator) to Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** or a designee along with the malfunctioning study medication inhaler form for further analysis. A log will be kept at each study center to identify and track any malfunctioning devices. Unopened FDC LABA/ICS and rescue medication may be re-dispensed to the patient at the next visit. Please make sure the expiration of the unopened rescue medication is beyond the date at which the patient is expected to come back for their next visit. If it is not, then don't re-dispense it; rather have IVRS dispense a new one.

All unused investigational products will be returned and unit counts will be performed. All investigational products must be accounted for. At the end of the study, all used and unused drug supplies and empty drug packages will be returned to the following depots:

North America
Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.***
[redacted]

Europe
[redacted]

Asia Pacific

[redacted]

Russia

[redacted]

Ukraine

[redacted]

Latin America

Argentina

[redacted]

Mexico

[redacted]

Chile

[redacted]

Colombia

[redacted]

Peru

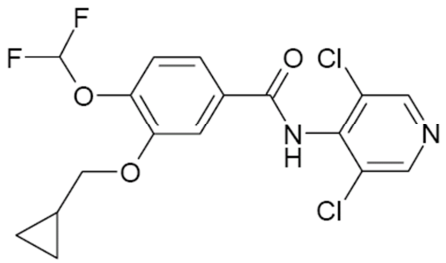
[redacted]

9.4.2.1 *Description of Investigational Products*

9.4.2.1.1 Roflumilast

The active ingredient in Daliresp tablets is roflumilast. Roflumilast and its active metabolite (roflumilast n-oxide) are potent and selective PDE4 inhibitors. The chemical name of roflumilast is n-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22.

The chemical structure is:



The drug substance is a white to off-white non-hygroscopic powder with a melting point of 160°C. It is practically insoluble in water and hexane, sparingly soluble in ethanol, and freely soluble in acetone. Daliresp/roflumilast is marketed as white to off-white, round tablets, embossed with "d" on one side and "500" on the other side. Each tablet contains 500 µg of roflumilast.

Each tablet of Daliresp/roflumilast for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, povidone, and magnesium stearate. Please see package insert (Appendix VII) for additional details.

9.4.2.1.2 Placebo

Placebo investigational product will appear identical to roflumilast 500-µg tablet. Ingredients: microcrystalline cellulose, methylcellulose, stearic acid, magnesium stearate, and silicon dioxide. Placebo investigational product contains no sugar, starch, yeast, preservatives, or artificial colors and flavors.

9.4.2.1.3 Advair Diskus (250/50 µg)

The dosage of Advair is 1 puff BID orally. Advair Diskus 250/50 µg is an FDC LABA/ICS consisting of fluticasone propionate 250 µg and salmeterol xinafoate 50 µg and is manufactured by GlaxoSmithKline.

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile. Please see package insert (Appendix VIII) for additional details.

9.4.2.1.4 Symbicort

The dosage of Symbicort (160 µg budesonide/4.5 µg formoterol fumarate dihydrate) is 2 puffs orally BID. Each Symbicort 160/4.5-µg canister is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered-dose inhaler (MDI) containing 120 actuations. Please see the Symbicort package insert (Appendix IX) for additional details.

9.4.2.1.5 Ventolin HFA

The dosage of Ventolin HFA is 2 puffs every 4 to 6 hours as needed. Each puff contains 108 µg albuterol sulfate (90 µg albuterol base). It is supplied in an 18-g canister containing 200 puffs.

9.4.3 Method of Assigning Patients to Treatment Groups

Patients in each stratum (LAMA, no LAMA) will be randomized to roflumilast 500 µg or placebo in a 1:1 ratio. However, the LAMA stratum should not have more than 60% of the planned total sample size of 2300 randomized patients. Therefore, when the LAMA stratum reaches 1380 patients, the stratum will be closed for enrollment.

Patients will be assigned a PID number via the interactive voice response system (IVRS) upon signing the ICF. This PID will consist of 2 parts as follows:

- 3-digit study center number
- 5-digit patient screening number consisting of the 2-digit protocol number (07) and a 3-digit sequential patient number unique to the site

For example, for a study center with Investigator number 005, the first consented patient (001) would have the following PID number: 005-07001.

9.4.3.1 IVRS Procedures

After a patient signs the ICF at the Screening Visit, study personnel will register the patient in the IVRS, and the system will assign the patient a sequential PID number. The first patient to sign the ICF at each site will be assigned the first number in the sequence by the system.

The IVRS will monitor the number of patients enrolled in each stratum. Once the cap for a stratum is reached, that stratum will be closed for enrollment.

The PID number will be used to identify the patient throughout the study and will be recorded on the eCRF. This number must not be reused. Patients who are rescreened will receive the next available PID number to avoid confusion with data from previous screenings. The IVRS service provider will supply the study centers with the appropriate materials (including the Investigator's manual) and ensure appropriate training. The contact address of the IVRS provider is as follows:

The study center must contact the IVRS at the time informed consent is provided, and at all subsequent study visits in order to obtain the instructions on the study medication to be dispensed to the patient at that visit.

Confirmation of the study medication and the single-blind and double-blind study medication number will be faxed or e-mailed (per the study center's preference) to the study center following each assignment. A detailed description of IVRS procedures is contained in the IVRS Manual in the Study Reference Binder.

9.4.4 Selection of Dosages in the Study

Roflumilast dosages chosen for this study are based on earlier dose-finding studies and the approved dose of roflumilast. The 500-µg dose was selected for this study as it was determined to be safe and effective in reducing exacerbations in patients with severe COPD (chronic bronchitis) with a history of exacerbations.

All single-blind and double-blind investigational products will be administered orally as a once daily dosing.

9.4.5 Selection and Timing of Dose for Each Patient

At each visit, the Investigator will review the tablets taken, used inhalers for FDC LABA/ICS, and rescue medication. The electronic diary will be used to establish rescue medication use and returned by the patient to assess treatment compliance. Used investigational product will not be re-dispensed; however, unopened rescue medication and FDC LABA/ICS may be re-dispensed to the patient at the visit. Please make sure the expiration of the unopened rescue medication is beyond the date at which the patient is expected to come back for their next visit. If it is not, then don't re-dispense it; rather have IVRS dispense a new one.

Patients will be asked to self-administer the study medication according to the following regimen (Table 9.4.5–1):

Table 9.4.5–1. Investigational Product (Roflumilast and Placebo) Dosing Schedule

Treatment Group	*Time*[a]	*Week*							
		Single-blind Lead-in Period	*Double-blind Treatment Period*						
		–2	*0*	*4*	*12*	*20*	*28*	*40*	*52*
Roflumilast	7 to 11 AM	Placebo	500 µg	500 µg	500 µg	500 µg	500 µg	500 µg	—
Placebo	7 to 11 AM	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	—

a Dosing should occur at approximately the same time each day, including days of study visits (administered on-site).

Patients who meet all eligibility criteria at Screening (Visit 1) will be dispensed 1 bottle containing placebo (40 tablets) for the 2-week, single-blind, lead-in period and will be instructed to take 1 tablet. Patients will begin dosing with 500 µg roflumilast or placebo on the day of the randomization visit (Visit 2) (see Section 9.5.5.2.1).

- Single-blind, lead-in period (Visit 1): 1 tablet containing placebo
- Double-blind treatment period (Visit 2 Randomization through ET/Last Visit): 1 tablet containing placebo or roflumilast 500 µg once daily

The tablets must be taken in the morning by mouth after breakfast with water. Patients will be instructed not to take tablets in the morning on clinic visit days before arrival at the site. Administration of the investigational product will occur after the pulmonary function test has been conducted.

During the entire study, albuterol/salbutamol will be used as rescue medication on an as-needed basis. The FDC LABA/ICS must be used at the labeled dose BID as prescribed for the individual patient throughout the entire trial.

Before Visit 2 (randomization), the use of rescue medication should be withheld for at least 4 hours if possible, and FDC LABA/ICS for 10 hours before the visit. See Section 9.4.1 for instructions on conducting visits when patients are unable to withhold rescue medication use.

9.4.6 Blind

During the single-blind, lead-in period, the Sponsor and Investigator will know that the patient is receiving placebo. Care should be taken to avoid informing the patient of the placebo treatment during the lead-in period. During the double-blind treatment period, all parties involved in the study (eg, patients, Investigators, site personnel, regional site managers [RSMs], clinical research assistants [CRAs], and the Sponsor) will be blinded.

9.4.7 Unblinding

Any unblinding should be done only in an emergency that requires that the investigational product be identified for the welfare of the patient. Forest ***Research, Inc., an affiliate of Actavis, Inc.,*** will be notified immediately (see Section 9.4.11), and a full, written explanation will be provided if the blind is broken. Before investigational product is unblinded, every attempt should be made to discuss the case with the Study Physician. Breaking the code at the study center will immediately disqualify the patient from further participation in the study.

Such emergency unblinding should be recorded in the eCRF.

Treatment codes may be broken by Global Drug Safety at Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** for regulatory reporting purposes. In such cases, the study staff will be kept blinded, and the patient will not need to be disqualified from the study.

9.4.7.1 For IVRS Blinding

A list of patient randomization codes will be generated by Statistical Programming at Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** and implemented by the IVRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

Randomization numbers and their corresponding treatment assignments will be assigned to patients per the randomization list by sequential ascending block number. Randomization will utilize a sequential assignment of block to each country.

9.4.7.2 For IVRS Unblinding

In an emergency, the Investigator can obtain the treatment assignment of any patient at his or her study center through the IVRS. In an emergency, the Investigator will access the IVRS to break the blind.

9.4.8 Prior and Concomitant Therapy

A complete list of drugs that are allowed and not allowed as concomitant medications for either episodic or chronic use, including washout requirements, is provided in Appendix II. All medications the patient is taking at the time of Screening (Visit 1) and has taken within the previous 30 days must be recorded on the concomitant medication page in the eCRF. Medications taken for COPD within the previous 12 months are also to be recorded. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

Rescue medication (albuterol/salbutamol) provided by the Sponsor is permitted as needed throughout the study duration for all participants and is to be dispensed once the patient signs the ICF.

9.4.9 Monitoring Treatment Compliance

Patient compliance with the investigational product dosing regimen should be monitored closely. During the single-blind period, patients who are noncompliant (defined as < 80% or > 125% of the expected number of doses over a given time frame) are to be screen failed, according to Section 9.3.1.2.

During the double-blind period, patients who are noncompliant may be discontinued or may be reinstructed on tablet and inhaler use accordingly by the Investigator or a designee. Treatment compliance, according to the dose counter, will be recorded in the eCRF.

Compliance for roflumilast will be calculated as follows:

$$\% \text{ compliance} = \frac{\text{Number of tablets taken}}{\text{Number of days in period}} \times 100$$

Dosing compliance for FDC LABA/ICS (Advair or Symbicort) is defined in a similar manner with number of puffs replacing the number of tablets.

9.4.10 Medication, Dietary, and Activity Restrictions Before Study Visits

The following are prohibited within the times indicated before any study visit:

- Vigorous physical activity should be avoided for at least 20 minutes before each visit. Alcohol consumption should be avoided for at least 4 hours before each visit. The intake of caffeinated products (coffee, tea, soda) will not be permitted for at least 12 hours before each visit up to the last procedure on that day

- Smoking should be avoided for at least 1 hour before each visit until the completion of all study procedures. Exposure to cold air, dust, or polluted air should be limited to the extent possible for at least 8 hours before each visit until the completion of all study procedures. For patients having difficulty not smoking, nicotine gums or patches may be used

- Large meals for at least 2 hours before the visit

- Albuterol/salbutamol must be discontinued at least 4 hours before the visit. If more than 3 hours have passed since the last use of albuterol/salbutamol, the patient may wait until 4 hours have passed to begin the visit provided that investigational product would still be administered by 11 AM; otherwise, the visit should be rescheduled for the next day

- FDC LABA/ICS must be withheld for at least 10 hours before the visit; otherwise, the visit should be rescheduled for the next day

- LAMA must be withheld for at least 22 hours before the visit; otherwise, the visit should be rescheduled for the next day

- Other COPD medications (Appendix II contains additional restrictions on concomitant medication use during the study)

Any event likely to interfere with the objectives of the trial will be communicated to the Investigator and reported without delay to the Sponsor

9.4.11 Study Management

Study management in the United States and Canada will be conducted by Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.***

Program Director: [redacted]

Study ***Physician***: [redacted]

A complete contact list of Forest personnel will be provided separately.

Study management outside of the United States and Canada will be conducted by [redacted], under the supervision of Forest Research Institute***, Inc., an affiliate of Actavis, Inc.,*** Contact information for [redacted] personnel will be provided separately.

During off hours, study sites may contact the on-call physician, who can be reached by pager at [redacted] (US sites only). For other countries, a separate toll-free number will be provided.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy Assessments

9.5.1.1 Primary Efficacy Assessment

9.5.1.1.1 Exacerbation

A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management (Celli and MacNee et al, 2004). These symptoms may be accompanied by increased wheeze, chest tightness, purulent sputum, and symptoms of cold and/or fatigue (Hurst and Wedzicha et al, 2004). Systemic glucocorticosteroids form the cornerstone in the treatment of COPD exacerbations (Hurst and Wedzicha et al, 2004).

The primary efficacy variable is the rate of moderate or severe COPD exacerbations per patient per year. Exacerbations will be reported in a COPD Exacerbation eCRF, according to the severity definitions provided in Section 9.5.1.1.2.

9.5.1.1.2 Definition of Exacerbation

In order to differentiate between severity grades of exacerbations, the following categories will be used:

- Mild: Increase in rescue medication of 3 or more puffs/day on at least 2 consecutive days during the double-blind treatment period
- Moderate: Requiring oral or parenteral glucocorticosteroid therapy
- Severe: Requiring hospitalization and/or leading to death

9.5.1.1.2.1 Additional Exacerbation Information

For analysis purposes, the Sponsor will further evaluate exacerbations according to the following criteria:

- Treated with systemic glucocorticosteroids and/or antibiotics
- Treated with antibiotic therapy only
- Moderate or severe and/or treated with antibiotics

In addition, exacerbations within 10 days of each other will be combined by the Sponsor for analysis and counted as a single exacerbation. Treatments administered during exacerbations should be recorded in the eCRF.

9.5.1.1.3 Identification and Treatment of Exacerbations

COPD symptoms (EXACT-PRO) and use of rescue medication will be recorded on a daily basis in the patient electronic diary to increase the patient's awareness for worsening of COPD symptoms. To ensure that all exacerbations are captured, patients will be encouraged to contact the Investigator in case of a deterioration of COPD symptoms. If, according to the Investigator, an exacerbation requires additional treatment, the following is recommended and allowed:

- Up to 40 mg prednisone per day over 7 to 14 days (tapering will be accepted according to the Investigator's decision)
- Additional therapy with antibiotics should be considered in case of purulent sputum or suspected bacterial infection
- In case an exacerbation is already treated with systemic glucocorticosteroids and/or antibiotics, the Investigator should contact the Study Physician to discuss additional treatment options (eg, administering a LAMA to a patient in the no-LAMA stratum)

All patients should make every effort to notify the Investigator at the time of an exacerbation (of any severity) at the earliest possible time. The patient will be requested to come in for an unscheduled visit for evaluation and treatment as soon as possible after notification of the exacerbation. Every effort should be made to maintain the patient in the trial, unless the patient is considered by the Investigator to be at an excessive risk by doing so. Patients experiencing a moderate or severe COPD exacerbation and/or COPD exacerbation treated with antibiotics during the lead-in period cannot enter the double-blind treatment period (see Section 9.3.1.2). However, they may be rescreened with written Sponsor approval after the exacerbation has resolved (post 4 weeks).

Patient Contact between Visits:

From the time a patient is consented until his or her completion of the study, it is essential that the site maintain regular contact with the patient to assess for any adverse events and COPD exacerbations. If COPD exacerbations occur, the duration, severity, and treatment must be obtained and recorded in the eCRF as soon as possible. Due to the long periods between visits of 8 or 12 weeks, the site must contact the patient at least monthly between visits to assess for AEs and COPD exacerbations. Therefore, the schedule of evaluations has been modified to add telephone calls to the patient at weeks 8, 16, 24, 32, 36, 44, and 48, with this purpose (please refer to the Schedule of Evaluations in Section 2.0).

9.5.1.1.4 Documentation of Exacerbation

All COPD exacerbations must be entered into the exacerbation section of the eCRF as soon as possible after learning of their occurrence. The additional treatment required for the exacerbation and whether the patient was withdrawn due to this exacerbation must be specified. Additionally, start and end dates of the exacerbation must be documented. The end of an exacerbation is defined as the time point when the patient's COPD symptoms or lung function have clinically improved, as determined by the Investigator; to warrant stopping treatment with additional medications.

*9.5.1.1.5 **COPD Exacerbations During the Study***

If an exacerbation is worsening, the patient should be clinically stabilized first before any study related procedure.

Patients should remain on the protocol-defined visit schedule and study visits should not be skipped (if preventable). If a study visit is conducted outside of the scheduled visit window, subsequent visits must be scheduled and performed as indicated in the protocol with respect to Randomization (Visit 2). If a patient presents with a COPD exacerbation at a scheduled study visit:

- If the patient is treated with a steroid, wait 2 weeks after the steroid treatment is completed before any further scheduled study visits are conducted
- If it is confirmed the patient has not received steroid treatment in the past 2 weeks, then complete the following:
    - Complete study procedures as tolerated by the patient, except for spirometry
    - Contact IVRS and dispense investigational product per visit schedule
    - Capture data in EDC under scheduled visit and COPD exacerbation pages
    - Ask the patient to come in for an unscheduled visit for evaluation to determine resolution of the exacerbation before the next scheduled visit. If the unscheduled visit date falls within 1 week or less from the following per protocol visit, then the next scheduled visit will be conducted.

If the patient notifies the site of an exacerbation between scheduled visits:

- Ask the patient to come in for an unscheduled visit for evaluation and treatment as soon as possible
- Capture data in EDC under the COPD exacerbation page and the Unscheduled Visit page

- Contact IVRS and dispense an emergency re-supply of investigational product, if needed

- If the patient is treated with a steroid, wait 2 weeks after the steroid treatment is completed before any further study visits are conducted

- If the patient notified the Investigator that they are already being treated for a COPD exacerbation, continue with study visits per protocol. In case of a treatment with a steroid for a COPD exacerbation, the next study visit must be postponed until 2 weeks after the steroid treatment is completed.

9.5.1.2 Secondary Efficacy Assessments

9.5.1.2.1 Spirometry

Pulmonary Function Tests
Spirometry for pulmonary function testing will be performed using a centralized spirometry provider. Spirometers will be provided by the Sponsor and will be customized and programmed according to the trial protocol-specific requirements. It is mandatory that the supplied device will be used for all measurements during the trial. Proper training of the trial personnel regarding the use of the device will be reinforced by a face-to-face training session. An instruction manual specifying all relevant details (handling of the spirometry equipment, data processing, quality assurance) will be provided.

Printouts of pulmonary function measurements have to be stored in the source document. Furthermore, electronic data transfer of the obtained spirometry data has to be done as specified by the provider (see Section 9.5.1.2.8 and Appendix III).

Calibration will be performed and documented as specified by the provider (see Appendix III). All spirometry measurements will be done at trough values. Values will be corrected to BTPS (body temperature and pressure, saturated) conditions.

Predicted values will be calculated according to the reference values of Crapo (Crapo et al, 1981) and Knudson (Knudson et al, 1976; Knudson et al, 1983). For African Americans, predicted values for FEV_1 and FVC will be obtained by multiplying values by a factor of 0.88.

The following parameters will be recorded:

- FEV_1: Forced expiratory volume in the first second

- FVC: Forced vital capacity (expiratory)

- FEV_1/FVC: Ratio of forced expiratory volume after 1 second to forced vital capacity
- FEV_6: Forced expiratory volume in the first 6 seconds

At Visit 1, the predose and postbronchodilator assessment to calculate reversibility will be completed.

FEV_1, FVC, and FEV_6 will be chosen as the largest value from the different efforts. These values may come from different test curves. FEV_1/FVC will be calculated from the largest FEV_1 and largest FEV_6.

9.5.1.2.2 Conduct of Spirometry Test

A minimum of 3 and a maximum of 8 spirometric efforts (if required) may be made, in order to produce repeatable results. The patients must withhold the investigational product tablet until after spirometry testing on clinic visit days.

- For all measurements at all study visits, patients should withhold rescue medication (albuterol/salbutamol) at least 4 hours, if possible, and FDC LABA/ICS for at least 10 hours prior to the measurement (see Section 9.4.10)
- The pulmonary function tests must always be performed in the morning hours between 7 AM and 11 AM
- The patient should have been at rest 15 to 30 minutes prior to each pulmonary function test
- All measurements are to be made with the patients seated upright
- Measurements are to be made with nose clips
- The predose measurements at Screening (Visit 1) must be performed prior to inhalation of bronchodilator, and the postbronchodilator measurements must be performed 30 minutes (± 15 minutes) after 4 inhalations of Sponsor-provided albuterol/salbutamol from an MDI with a spacer
- The same equipment will be used throughout the trial, and every reasonable effort should be made to have the same person perform the measurements at each visit

After the tests, patients will be asked to take their investigational product and FDC LABA/ICS.

Additional information on spirometry testing is provided in Appendix III.

9.5.1.2.3 Reversibility

Calculation of reversibility at Visit 1 will be done as follows:

$$FEV_1 \text{ reversibility (\% initial)} = \frac{\text{highest post-value} - \text{highest pre-value}}{\text{highest pre-value}} \times 100$$

FEV_1 = forced expiratory volume in 1 second; Pre = predose; post = postdose

9.5.1.2.4 Morning Predose (Trough) Forced Expiratory Volume in 1 Second

Trough FEV_1 is calculated as the mean of the 2 greatest FEV_1 readings obtained at 1 hour and 10 minutes predose at Visits 2 through 8.

Patients should withhold rescue medication, albuterol/salbutamol, at least 4 hours, if possible, and FDC LABA/ICS for at least 10 hours prior to the measurement.

9.5.1.2.5 Standardization of Pulmonary Function Tests

Spirometry will be performed according to recommendations of the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus guidelines on pulmonary function testing (Miller et al, 2005). According to these standardization criteria, individual efforts from the patients will be classified for acceptability (within-effort criteria) and repeatability (between-effort criteria).

9.5.1.2.6 Within-effort Criteria

For the evaluation of acceptability criteria within each forced expiratory maneuver, the Investigator should check whether the individual efforts are free from artifacts (cough during the first second of exhalation, glottis closure that influences the measurement, early termination or cut-off, effort is not maximal throughout, leak, obstructed mouthpiece). The Investigator will be informed by the computer-based spirometric system if the following within-effort criteria have been met for individual efforts:

- They have good starts (extrapolated volume < 5% of FVC or 0.15 L, whichever is greater)

- They show satisfactory exhalation (duration of > 6 seconds or a plateau in the volume time curve or if the patient cannot or should not continue to exhale). COPD patients with severe airflow obstruction, as included in this trial, may not always be able to fulfill all of the above defined acceptability criteria due to their underlying clinical condition. In this case, the following 2 conditions have to be met in order to categorize these efforts as usable:

    - No unsatisfactory start of expiration (extrapolated volume < 5% of FVC or 0.15 L, whichever is greater) and,

    - No coughing during the first second of the maneuver, thereby affecting the measured

FEV_1 value, or any other cough that, in the technician's judgment, interferes with the measurement of accurate results.

9.5.1.2.7 Between-effort Criteria

A minimum of three and a maximum of eight spirometric efforts (if required) may be made, in order to produce repeatable results. Acceptable repeatability is achieved when the difference between the largest and the next largest FEV_1 is ≤ 150 mL. For those patients with an FVC of < 1.0 L, both of these values are ≤ 100 mL. The repeatability criteria are used to determine in which case more than 3 efforts are needed. These criteria are not to be used to deselect efforts. If a patient performs less than 3 usable efforts, this should not prevent the determination of the best test result, since this may be the best performance from this patient at this visit.

9.5.1.2.8 Quality Control of Spirometry Data

A 3-level quality review process for pulmonary function test data will be performed, which is briefly described below. Further details will be defined in the spirometry instruction manual. During the Level 1 quality review, the spirometer device automatically provides information on acceptability and repeatability of the efforts during the pulmonary function test. This information immediately advises the Investigator on how to improve data quality. In line with the recommendations of the ATS/ERS consensus statement, it is at the discretion of the Investigator to perform additional forced expiratory maneuvers, beyond the minimum 3 maneuvers, especially considering the disease status of the individual COPD patient.

During the Level 2 quality review, the Investigator compares all efforts recorded. The Investigator is requested to check if misperformed efforts (eg, poor efforts as well as reversed pneumotach or other obvious technical flaws) should be deselected. It is in the judgment of the Investigator to accept or deselect any effort based on the within-effort criteria. All performed pulmonary function tests and associated efforts that are accepted and confirmed by the Investigator after the active measurement phase with the patient on site are processed for level 3 review. Deselected efforts will not be used in determining the best values for FVC and FEV1.

All spirometry recordings performed at the investigational site are transferred electronically to:

During the Level 3 quality review, a central overreader (spirometry specialist) at eRT checks the quality and adherence to ATS/ERS and study specific criteria of all spirometry data. Level 3 codes are assigned to the data, which are used by the Sponsor to determine the quality of the data submitted by the investigational sites. The purpose of this centralized spirometry Level 3 review is to systematically monitor the quality of spirometry testing and to help determine if sites need retraining. This type of quality improvement measure is recommended by the ATS/ERS Consensus guideline on standardization of spirometry (Miller et al, 2005). The Level 3 review does not change or deselect any data without documented approval from the Investigator.

Handling of pulmonary function data is described in Appendix III.

9.5.1.3 Additional Efficacy Assessments

9.5.1.3.1 Rescue Medication Use

Patients will record twice daily in the patient electronic diary the number of puffs of Sponsor-provided albuterol/salbutamol taken during the day time and during the night time. Administration and use of the rescue medication should be on an “as needed” basis, according to the Investigator’s instructions in accordance with the clinical status of the patient. Patients will record the number of puffs of Sponsor-provided albuterol/salbutamol used during each 24-hour period (differentiating between morning and evening use) in the patient electronic diary. The electronic diary will be checked by the Investigator for compliance at each visit.

All electronic diary assessments performed by the patient are transferred electronically to:

[redacted]

9.5.1.3.2 COPD Assessment Test

The CAT is a short, validated, patient-completed questionnaire to assess the impact of COPD on health status. It comprises 8 questions that cover a broad range of effects of COPD on patients' health.

Each question is scored in a range between 0 and 5, with the higher end indicating a higher impact of COPD on the patient's well-being. The CAT scoring ranges from 0 to 40 for the total score of all 8 questions. The CAT will be evaluated at all visits (Visit 1 through Visit 8/ET).

9.5.1.3.3 Exacerbations Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT-PRO)

The EXACT-PRO instrument is designed to collect data to capture the frequency, severity, and duration of acute exacerbations in patients with COPD including patients with chronic bronchitis. The instrument assesses the severity of respiratory and systemic manifestations of exacerbations identified by patients and confirmed by clinical experts.

For this study, each patient will complete the instrument daily, in order to capture the underlying day-to-day variability of the patient’s symptoms.

Daily symptoms will be assessed electronically by the patients each day in the evening, before bed, through the EXACT-PRO tool, which is validated in several different languages.

The EXACT-PRO captures the cardinal symptoms of COPD (dyspnea, cough, sputum production) since exacerbations represent a sustained worsening in the patient’s condition and also includes additional items capturing dyspnea with activity and several systemic manifestations of COPD (eg, tired/weak). It can be used to measure changes in an exacerbation over time, to show changes in the patient’s health state prior to an exacerbation, during a clinician-confirmed exacerbation and recovery and return to a stable state.

The EXACT-PRO tool is designed as a daily diary to be completed nightly before bed through an electronic diary. The recall period is “today.” Patients are instructed to select the answer that best describes their experience for that day.

At each visit, the Investigator is responsible for reviewing the patient's entries in the EXACT-PRO tool and the CAT to look for potential changes in patient reported outcome parameters which may be indicative of an exacerbation, and if one is detected, then record it in the EDC.

9.5.1.3.3.1 Scoring the EXACT-PRO Tool

Scoring for EXACT-PRO is calculated by using raw-to-scale score conversion tables. There is an EXACT-PRO overall scale score and 3 EXACT-PRO sub-scale scores.

Raw score values are assigned to each item response option. There are 4 different scores to be obtained from the EXACT-PRO. The EXACT-PRO overall scale is converted from the sum of the raw scores of the 14 items. The 3 sub-scale scores are converted from the following: chest symptoms (sum of items 1, 5 and 6), cough and sputum (sum of items 2 and 3), and breathlessness (sum of items from 7 to 11).

9.5.1.3.4 Major Adverse Cardiac Events

Due to the prevalence of cardiovascular diseases in patients with COPD, MACE will be evaluated according to pre-defined criteria by a MACE Adjudication Committee composed of independent cardiologists who are not participating in the ROF-MD-07 study. The MACE Adjudication Committee is charged with the development of specific criteria used for the classification of specific cardiovascular events that are to be adjudicated by this committee in this trial.

Criteria will be established for the following events:

- Death (cardiovascular, non-cardiovascular, or undetermined cause)
- Myocardial infarction
- Stroke (ischemic, hemorrhagic, or unknown)
- Transient ischemic attack
- Hospitalization for unstable angina
- Hospitalization for heart failure
- Cardiac arrhythmias (any atrial or ventricular arrhythmia documented by electrocardiography not associated with an acute or ongoing cardiac ischemic event)
- Venous and peripheral arterial thromboembolic events (deep vein thrombosis, pulmonary embolism, peripheral arterial events)

- Other (eg, coronary revascularization [elective], peripheral arterial events such as mesenteric ischemia, aortic dissection/rupture)
- Insufficient documentation for confirmation
- Non-fatal, non-cardiovascular event (does not meet the event definition and likely represents an alternative or nonevent diagnosis)
- Not considered a separate event (in cases where patients have multiple cardiovascular events occurring at the same time the primary cardiovascular event will be adjudicated)

The events above are defined as outlined by the FDA guidance paper titled Standardized Definitions for End Point Events in Cardiovascular Trials (Hicks et al, 2010).

At the onset of the trial, the MACE Adjudication Committee will establish the criteria required to classify a pre-defined cardiovascular event. All members of the MACE Adjudication Committee will be blinded to the patient treatment assignment in the study.

The Sponsor or designee will compile global cardiovascular event dossiers when the necessary data are available from the trial sites and will provide this information to the MACE Adjudication Committee for their adjudication. A charter will be established to govern these processes.

9.5.1.3.5 Appropriateness of Measurements

All assessments are standard measurements in COPD.

9.5.2 Safety Assessments

Patients must be seen by the Investigator at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of data collection for this study, any untoward events that were reported from the time the patient signed the ICF until 30 days after the last dose of treatment are to be considered AEs and SAEs will be collected for patients who discontinued investigational product but participate in the follow-up assessments through the ET visit.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or other study center personnel
- All diseases that occur after signing inform consent, including any worsening in severity or frequency of preexisting disease
- All clinically relevant abnormalities, in the judgment of the Investigator or Study Physician, in laboratory values or clinically relevant physical findings that occur during the study schedule

9.5.2.2 Causality Assessment

For all AEs, the Investigator must provide an assessment of causal relationship to the investigational product. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the investigation product caused the event?

Yes: There is evidence to suggest a causal relationship between the investigational product and AE; ie:

- There is a reasonable temporal relationship between the investigational product and the event, and
- The event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors, and/or
- Positive de-challenge and/or re-challenge exist

No: There is no evidence to suggest a causal relationship between the investigational product and AE; ie:

- There is no reasonable temporal relationship between the investigational product and the event, or

- The patient did not take the investigational product, or
- The event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, or
- The event is commonly occurring in the (study) population independent of drug exposure

9.5.2.3 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. The term severe AE is not synonymous with the term serious AE, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4). Severity will be assessed according to the following scale:

Mild: Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention

Moderate: Discomfort that interferes with usual activities and may require minimal intervention

Severe: Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention.

9.5.2.4 *Serious Adverse Events*

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.5.2.5 Reporting Adverse Events and Serious Adverse Events

Any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment, in treatment, or post treatment period are to be considered AEs and/or SAEs, and will be consequently recorded and reported as such.

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a non-leading question such as, “How do you feel since your last visit?” Study center personnel will then record all pertinent information in the patient’s eCRF. Any AEs reported in diaries will also be reported on the relevant eCRF page.

All AEs and SAEs reported by the patient (or patient representative) or observed or otherwise identified by the Investigator (or other study center personnel) during any communication with the patient (or patient representative) occurring from the time the ICF is signed to within 30 days after the last dose of investigational product must be documented by the investigational site and provided to the Sponsor.

All AEs must be recorded on the appropriate AE reporting page of the patient’s eCRF whether or not they are considered causally related to the investigational product.

For every AE, the Investigator must:

- Provide an assessment of the severity, causal relationship to the investigational product, and seriousness of the event (eg, SAE)
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE

Additional information regarding the immediate reporting required for SAEs is provided in Section 9.5.2.6.

COPD exacerbations are captured as efficacy endpoints and are anticipated to occur in the study population independent of drug exposure. COPD exacerbations must be entered into the COPD exacerbation section of the eCRF as soon as possible, instead of on the AE section of the eCRF. COPD exacerbations are subject to on-going safety monitoring and evaluation by the Sponsor. Therefore, the following events that meet the criteria of an SAE are not to be recorded on the SAE form:

- COPD exacerbation
- Signs and symptoms associated with COPD exacerbation
- COPD exacerbation resulting in hospitalization and/or death

9.5.2.6 Immediate Reporting of Serious Adverse Events

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE (except for COPD exacerbations as described in Section 9.5.2.5 above), the study center personnel must report the event to Forest Global Drug Safety on the SAE Form for Clinical Trials. The Sponsor's Study Physician should also be notified by telephone or e-mail.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE Form for Clinical Trials to the SAE fax number: [redacted]. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details, even if very limited, must still be faxed within 24 hours of knowledge of the event at the study center.

Supplemental information shall be submitted as soon as available within 24 hours of receipt and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. The Sponsor may contact the study center to solicit additional information or follow up on the event. Although pregnancy is not considered an AE, it is nevertheless handled as an SAE.

Fax the SAE Form for Clinical Trial Pregnancy Form to Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.***

SAE/Clinical Trial Pregnancy Form fax number: [redacted]

Medical Emergency phone number: [redacted] **(US and Canadian sites only). For other countries, a separate toll-free number will be provided.**

9.5.2.7 Exposure to Investigational Product During Pregnancy

Study center personnel must report every pregnancy on a Clinical Trial Pregnancy Form as soon as possible (within 24 hours of learning of the pregnancy) to the pregnancy fax number, [redacted], even if no AE has occurred. The pregnancy must be followed to term and the outcome reported by completing the Clinical Trial Pregnancy Form. If, however, the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), in addition to the Pregnancy Form, a separate SAE Form for Clinical Trials must be filed as described in Section 9.5.2.6 with the appropriate serious criterion (eg, hospitalization) indicated.

9.5.2.8 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at all visits except at Visit 2, Visit 3, Visit 5, and Visit 7. At Screening (Visit 1), the Investigator will assess the clinical significance of any values outside the reference ranges provided by the central laboratory; patients with abnormalities at Screening judged to be clinically significant will be excluded from the study. Any clinically significant laboratory abnormalities, as determined by the Investigator, will be recorded as an AE or SAE, if applicable. The patient may be continued in the study at the discretion of the Investigator and/or Study Physician.

Patients do not need to be fasting; however, the patient's fasting condition should be consistent at all visits. Women of childbearing potential will be required to have an on-site urine pregnancy test at Screening (Visit 1), Visit 2, Visit 4, Visit 5, Visit 6, Visit 7, and ET/last visit.

The following clinical laboratory tests will be performed:

Hematology: Absolute and differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), white blood cell count, erythrocyte count, platelets, hemoglobin, and hematocrit

Chemistry: Sodium, potassium, calcium, chloride, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase, creatine kinase, inorganic phosphorus, serum bicarbonate, alanine aminotransferase, total cholesterol, and triglycerides, uric acid

Urinalysis: Dipstick analysis will be performed at the center and will include: pH, blood, leukocytes, protein, glucose, bilirubin, ketones and pregnancy. The assessment will be recorded on the corresponding eCRF page. If clinically relevant abnormalities are detected, a urine sample will be sent to the central laboratory for analysis of the sediment

Laboratory reports and alert reports will be faxed to the Investigator when any laboratory result is outside of reference ranges. The Investigator should review and assess all laboratory reports and sign and date the reports. Any new clinically significant abnormality or an AE that has worsened significantly should be recorded on the AE eCRF page.

In the event of a technical problem or if the Investigator considers a laboratory abnormality to be clinically relevant, additional samples for repeat analysis or additional analysis may be collected, as deemed appropriate, and sent to the central laboratory for analysis. A comment should be added on the eCRF, indicating the need for follow-up assessments. These laboratory samples should be identified as repeated samples.

A central laboratory will be used to evaluate all urine and blood sample other than the urine pregnancy tests; these will be collected, processed, and stored according to instructions provided by the laboratory. The address of this laboratory is as follows:

Central Laboratory:
[redacted]

The Hy's Law criteria will be assessed. Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase or aspartate aminotransferase ≥ 3 × ULN, along with total bilirubin ≥ 2 × ULN and a non-elevated alkaline phosphatase < 2 × ULN, all based on blood draws collected within a 24-hour period.

9.5.2.9 Vital Signs

Vital sign measurements and body weight will be documented at every visit before administration of investigational product throughout the study. At Screening (Visit 1), vital signs, body weight, and height will be measured at the same time the physical examination is completed. Vital sign parameters will include sitting pulse rate, sitting systolic and diastolic blood pressure, respiratory rate, and body temperature. Pulse rate, blood pressure, and respiratory rate readings will be taken after the patient has been sitting for approximately 5 minutes; the same arm should be consistently used for the pulse rate and blood pressure measurements.

The Investigator will assess the clinical significance of any abnormal values. A comment should be entered into the comment eCRF for abnormal vital signs.

9.5.2.10 Electrocardiograms

A 12-lead ECG is performed at Screening (Visit 1), Visit 6, and ET/Last Visit and repeated during treatment, if the Investigator considers it necessary. The patient should rest for at least 15 minutes prior to the recording and should be in a resting position during the recording. Resting ECG should be performed before any pulmonary function testing.

The Investigator will be responsible for interpretation of the ECG to ensure patient safety. All ECGs will also be read by the ECG over-reader at the central laboratory. In case of a discrepancy between the Investigator's interpretation and the central laboratory's, the central laboratory reading will be used to qualify patients for randomization at Visit 2. The ECG printout will be reviewed, interpretation should be noted, and the printout will be signed and dated by the Investigator and will be filed at the investigational site as source data. All abnormal findings must also be recorded in the eCRF. Any clinically relevant findings compared to Visit 1 must be documented as AEs.

The central ECG interpretation laboratory will supply the study centers with materials (including the Investigator's manual) and ensure appropriate training. The address of this laboratory is as follows:

[redacted]

A specialized cardiac safety technician and a cardiologist at eRT will read and interpret the ECG tracings according to the company's internal processes. For each ECG, eRT will send a report to the study center once the manual reading is completed.

Following any investigational product administration, or upon a patient's ET, any new clinically significant abnormalities on the ECG or those that have worsened compared with abnormalities observed at Screening (Visit 1) and are judged clinically relevant by the investigator should be recorded on the AE eCRF form.

If a patient experiences a significant increase in QT interval or any other clinically significant abnormality while being treated with investigational product, additional ECGs should be recorded using the same equipment within a reasonable time, as deemed appropriate by the Investigator.

9.5.2.11 Other Safety Assessments

9.5.2.11.1 Physical Examination

A physical examination will be performed at Screening (Visit 1) and the ET/Last Visit by a physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations. The physical examination will include an examination of general appearance; eyes, ears, nose, and throat; the abdomen; the skin/mucosa; and the lymphatic, cardiovascular, respiratory, neurological, and musculoskeletal systems. A genitourinary examination is not required unless judged to be necessary by the Investigator. Height should be recorded only at Screening (Visit 1) to calculate body mass index and predicted values for pulmonary function studies. Weight should also be measured and recorded at every patient visit.

9.5.2.11.2 Columbia Suicide Severity Rating Scale

The Columbia–Suicide Severity Rating Scale (C-SSRS) is a 2-page questionnaire that prospectively assesses suicidal ideation and behavior using a structured interview via IVRS for patient responses. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). The C-SSRS questionnaire is presented in Appendix V.

A validated, self-rated, electronic version of the C-SSRS, the eC-SSRS, will be used to capture these data via IVRS (Mundt et al, 2010). The eC-SSRS will be performed during each evaluation visit according to the assessment schedule (see Section 2.0, Schedule of Evaluations). During a visit, patients will be directed to a private, quiet place with a telephone to complete the assessment. Patients who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in approximately 3 minutes. Patients with significant suicidal ideation and/or behavior may require up to 10 minutes to answer all relevant questions. This assessment should be conducted early during the study site visit to provide sufficient time for the report to be received and reviewed at the study site prior to patient departure.

At the conclusion of each assessment, the study site will receive an eC-SSRS Findings Report. These reports will be available by accessing the eC-SSRS vendor (ERT) My Study Portal account. The report presents the findings for suicidal ideation, intensity of ideation, suicidal behavior, and lethality/medical damage (for actual suicide attempts only).

Negative suicidality indication reports are generated when there are no indications of the above. The patient should not be released from the evaluation site until it is confirmed that the call is complete, the report is reviewed, and the patient is not considered to be at any suicidal risk.

Positive reports are generated for any of the following findings:

- Suicidal ideation with intention to act (score of "4")
- Suicidal ideation with specific plan and intent (score of "5")
- Made suicide attempt
- Interrupted suicide attempt
- Aborted suicide attempt
- Preparatory behaviors for making a suicide attempt

At Screening (Visit 1), the eC-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior. At all other visits, the eC-SSRS will be completed for ideation and behavior since the previous visit. The patient's findings report should remain negative throughout the entire trial. Should the system report that the patient has a positive suicidal indication, the site will be immediately notified by fax/email and a telephone call from the eC-SSRS vendor (ERT). If a possible exclusion alert is triggered by a positive response at Screening (Visit 1), 2 additional questions at the bottom of the report will need to be asked to determine whether exclusion criteria 9a and/or 9b have been met. The follow-up questions will need to be asked by qualified site personnel - a certified healthcare professional as designated on the site delegation log. A response of "Yes" to either one or both of the follow-up questions will exclude the patient from the trial and necessitate immediate psychiatric referral of the patient on the same date as the site visit. For all subsequent visits after Screening (Visit 1), if the patient's response generates a change in the findings report from negative to positive, the patient should be referred for immediate psychiatric evaluation on the same date as the site visit and the Sponsor should be contacted. Positive suicidality indication findings reports after the Screening Visit (Visit 1), if confirmed by the Investigator, should be considered to be an SAE. SAEs must be reported as outlined in Section 9.5.2.5. Ultimately, the determination of suicidality and risk is up to the Investigator's clinical judgment.

The eC-SSRS Findings Report will remain at the sites as source data, and the data will be sent by the eC-SSRS vendor electronically for inclusion in the database. This system was developed in close collaboration with the Scale authors and psychiatrists (Mundt et al, 2010). The eC-SSRS will be provided by:

[redacted]

In the event that the eC-SSRS cannot be administered via IVRS due to unavailability of the ERT system (ie, emergency/planned maintenance or system outage) and not user error or user technical inability, the C-SSRS will be administered by the Investigator or trained designee on paper, submitted to the Sponsor for review, and captured in the eCRF as an unscheduled assessment. All appropriate procedures for administration of paper assessment are to be followed.

The C-SSRS is to be reviewed in the same manner as the eC-SSRS to determine if a positive suicidal indication has been reported by the patient at any visit. If a possible exclusion is triggered by the patient's positive response at Screening (Visit 1), it is the sole responsibility of the person administering the C-SSRS to necessitate and write-in the follow-up questions and respective patient responses on the paper assessment to determine whether exclusion criteria 9a and/or 9b have been met. Unlike the eC-SSRS, where the system will automatically generate 2 additional questions at the bottom of the report for a triggered possible exclusion alert, this will need to be manually populated on the paper C-SSRS by the administrator for any possible exclusion on the C-SSRS at Screening (Visit 1). Any required follow-up actions based on the responses to the follow-up questions (ie, exclusion from trial and necessitating immediate psychiatric referral, etc.) will be the same for eC-SSRS and C-SSRS. To mirror the functionality of the automated system, when administration of the paper C-SSRS is required, the site will also be responsible for providing a copy of the completed paper assessment to the Sponsor via fax or email immediately following completion of the assessment with the patient.

9.5.3 Pharmacokinetic Sample Collection

9.5.3.1 Serial Pharmacokinetic Sample Collection

For determination of roflumilast and roflumilast N-oxide plasma concentration-time profiles, PK blood samples will be collected in approximately 40 patients at selected sites (serial PK sites). Blood samples will be collected according to the following time schedule at Visit 7: 0 (predose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing (10 blood samples).

Actual clock times of PK sample collection and actual dosing time will be documented in the eCRF. PK blood samples should be drawn at the nominal times specified above, relative to the dosing time. Samples taken > 5 minutes outside the nominal time will be noted as protocol deviations, and the reason for deviation must be documented in the source documents and the Clinical Trial Management System (CTMS).

Consenting patients at these selected sites will be encouraged to participate in the serial PK substudy. However, those who are unwilling may still participate in the main study and sparse PK substudy (see Section 9.5.3.2).

9.5.3.2 Sparse Pharmacokinetic Collection

Sparse (population) PK samples will be collected in ~ 20% of the patients in the study. One PK sample will be collected at Visit 5, Visit 7, and Visit 8/ET. Reminder: Once the blood sample is obtained for PK analysis, collect the date and time for the last three doses taken by the patient prior to the PK sample collection date/time. Sparse PK samples are to be collected before investigational product dosing and pulmonary function tests.

9.5.3.3 Pharmacokinetic Blood Withdrawal and Sample Handling Methods

A total of 6 mL of blood will be taken using prechilled lithium-heparin–containing Vacutainers at each sample collection time point for the determination of roflumilast and roflumilast N-oxide. Blood samples will be stored on ice and centrifuged within 20 to 30 minutes (start of centrifugation) after collection in a refrigerated centrifuge for 15 minutes at 1600*g* and approximately + 4°C to obtain plasma. The plasma will be transferred into 3 polypropylene tubes (1 primary sample with at least 0.75 mL plasma 1 back up sample with 0.75 mL plasma, and a second back up sample with the residual plasma) and immediately deep-frozen below –20°C. The tubes will be labeled with study code, study center, Visit number, PID number, and relative time of sampling (time post-dose) by using freezer-proof labels or freezer-proof pens. Two of the 3 aliquots will be labeled as "backup."

The handling of blood samples and shipping instructions are provided in Appendix IV.

9.5.3.4 Amount of Blood Withdrawals for Serial and Sparse PK Collection

A total amount of approximately 60 mL (10 samples of 6 mL each) of blood will be collected for serial PK assessment per patient. A total amount of up to 18 mL (1 sample of 6 mL each at Visit 5, Visit 7, and Visit 8/Last Visit of blood will be collected for sparse PK assessment per patient.

See Appendix IV for instructions on packing and shipping of PK plasma samples.

9.5.4 Health Economics and Outcomes Research Assessments

Not applicable.

9.5.5 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.0. The descriptions of the procedures to be performed at each visit are provided below.

Excluding any unscheduled study visits deemed necessary by the Investigator, all patients participating in this study may have a maximum of 8 scheduled visits throughout a treatment period of 52 weeks.

If necessary for scheduling or other purposes, a visit may take place within ± 3 days of the protocol-defined visit week for Visit 2 (Randomization) and Visit 3; within ± 5 day window for Visit 4, Visit 5, Visit 6, and within ± 7 day window for Visit 7, ET Visit or Last Visit.

Study procedures should generally be carried out in the order indicated, unless there are unexpected logistical constraints that require changes according to the Investigator's judgment. In particular, on-site questionnaires should always be administered and completed before spirometry is performed.

All visits are to be scheduled in the morning to accommodate the spirometry measurement and investigational product dosing time requirements (see Section 9.4.5). Maintenance FDC LABA/ICS will be dispensed at each visit. Training on the proper use of all investigational product provided for the trial should be performed at Screening (Visit 1) and subsequent visits as needed. Patients should be advised to bring the investigational product, FDC LABA/ICS, and rescue medication (including tablet bottles, MDI, and cartons), electronic diary, and, if applicable, a reading aid (eg, glasses for completing the questionnaires) to every study visit. The Investigator or his/her designated representative will check the electronic diaries for completeness at each visit.

The patient will rest quietly for at least 15 minutes before a pulmonary function test (see Section 9.5.1.2.2) or ECG is performed and for at least 5 minutes before vital signs are assessed.

At each visit (except Visit 8/ET), patients should be advised of the following:

- Patients should take 1 tablet of single or double-blind investigational product once daily in the morning
- Patients should take FDC LABA/ICS twice daily, except 10 hours prior to the study visit
- Patients should take rescue medication (Sponsor-provided albuterol/salbutamol) as needed, except that rescue medication must be withheld for at least 4 hours prior to each study visit
- Patients should not take their single or double-blind investigational product (tablet) on the morning of their study visit prior to arriving at the site

At all study visits, administration of the investigational product and FDC LABA/ICS should occur at the site between 7 AM and 11 AM after the pulmonary function measurement.

At each visit the patients will be asked to return to the investigational site for the following study visit according to the schedule of assessments listed in Section 2.0. However, the patients should also be instructed to contact the investigational site at any time during the entire trial if they experience a COPD exacerbation, a pronounced deterioration of their disease, or other adverse effects. The Investigator will be required to provide suitable instructions and site contact information to the patient for use in case of emergency.

9.5.5.1 Single-Blind Treatment Period

9.5.5.1.1 Visit 1 (Screening)

To better assure Visit 1 goes smoothly, prior to the actual screening visit, you should call the patient who is scheduled for screening and prepare them for what they can expect to take place as well as direct them to bring with them their records of medical and surgical histories (including X-rays) and a list of all prior and concomitant medications including the dosages. This is most pertinent when the patient is not from the Investigator's clinic, but rather has been referred by another physician or is responding to an advertisement about the study.

At Screening (Visit 1), a review of inclusion/exclusion criteria will be conducted to determine the patient's eligibility for enrollment. Study procedures will be reviewed with the patient, and documentation of informed consent will be obtained.

After signing the ICF, patients must be registered in the IVRS system which will then generate a unique PID.

If a patient is taking any prohibited medication, the patient must sign the ICF before any medications are discontinued and return to the site for Visit 1 after the appropriate washout period has been completed. After the patient signs the ICF, IVRS automatically dispenses albuterol once the PID is assigned and Sponsor provided albuterol is used for Visit 1 PFTs. Rescue medication (Sponsor-provided albuterol/salbutamol) will be dispensed to the patient and should be used as needed during the washout period. The patient will use Sponsor-provided rescue medication (albuterol/salbutamol) as needed and Sponsor-provided FDC LABA/ICS as an add-on treatment during the single-blind (Visit 1 through Visit 2) and double-blind (Visit 2 through Visit 8/ET) treatment periods.

The following procedures will be performed at Screening (Visit 1):

- Obtain informed consent (for patients not requiring wash-out of prohibited concomitant medications)
    - Patients participating in the serial or sparse PK substudy will give additional informed consent
- Register patient with IVRS and assign PID number
- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been withheld for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA has been withheld for at least 22 hours before the visit
- Review prior treatment with FDC LABA/ICS for ≥ 3 months prior to Screening (Visit 1)
- Collect COPD history including phenotype (ie, chronic bronchitis, emphysema, or both), smoking history, date of COPD diagnosis, minimum number of 2 moderate or severe COPD exacerbations documented during the last year, and start and stop date of all COPD exacerbation available). Only patients with chronic bronchitis should be included (indicated population). See Section 9.3.1.1 for examples of acceptable documentation for COPD exacerbations used to qualify patients for the study.
- Exclude patients with a reported exacerbation within ≤ 1 month prior to Screening (Visit 1)
- Assess smoking status
- Collect medical and surgical history (including concurrent illnesses at this visit)
- Collect prior and concomitant medication history (see prohibited and allowed medication list in Appendix II)
- Perform chest X-ray if procedure was not completed within 6 months prior to Screening; a computerized tomography scan may be performed based on the Investigator's clinical judgment and upon agreement with the Sponsor (Study Physician)
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)

- Administer and assess the electronic C-SSRS. A patient with a C-SSRS score of 4 or 5 indicating "suicidal ideation and or suicidal behavior" should be excluded from the trial as defined in Exclusion Criterion No. 9 (see Sections 9.3.2 and 9.5.2.11.2 and Appendix V)

- Perform physical examination, measure body weight and height, and assess vital signs (pulse rate, blood pressure, respiratory rate, and body temperature [see Section 9.5.2.9]); body mass index will be calculated automatically by the eCRF

- Obtain urine samples, including an on-site urine pregnancy test for women of childbearing potential

- Perform a 12-lead ECG with the patient in the supine position

- Perform predose spirometry (forced maneuvers) with the patient in the seated position. A minimum of 3 measurements will be performed according to the acceptability and repeatability criteria in Appendix III.

- Administer 4 puffs of Sponsor-provided albuterol/salbutamol through a spacer device (to ensure proper inhalation). Bronchodilator administration can begin as soon as 10 minutes after the completion of the last predose spirometric effort if the patient is rested and comfortable

- Forced spirometry repeatability for FEV1 will be calculated according to ATS/ERS 2005 guidelines. Perform postdose spirometry to assess reversibility (ATS/ERS Criteria [Miller et al, 2005]). Assessment should be performed with patients in the seated position. A minimum of 3 measurements will be performed according to the acceptability and repeatability criteria in Appendix III

For patients who meet all eligibility criteria to this point:

- Obtain blood samples for clinical laboratory determinations

- Dispense electronic diary (see Section 9.5.1.3.1). Patients will be trained to use the electronic diary and instructions for completing the electronic diary will be provided inside the cover page of the electronic diary

- Call IVRS again to obtain assigned FDC LABA/ICS, single-blind investigational product and if needed, albuterol/salbutamol.

- Dispense rescue medication (Sponsor-provided albuterol/salbutamol) and Sponsor-provided FDC LABA/ICS. Provide training to the patient on the proper use of the inhalation devices

- Dispense single-blind investigational product and instruct the patient on proper dosing. Reminder: Site personnel should not inform patients of the contents of the single-blind investigational product

- In the patient record, document doses taken of investigational product.

- Administer the first dose of single-blind investigational product after the performance of the pulmonary function test before 11 am.

At the end of the visit, eligible patients will be dispensed a bottle containing single-blind investigational product (placebo) to be administered at a dose of 1 tablet taken once daily in the morning over the 2 weeks prior to Visit 2. The first dose from this bottle will be administered before the patient leaves the study site after the Screening Visit; the patient will take the last dose on the morning of the day before Visit 2.

Schedule the patient to return to the investigational site for Visit 2 in 2 weeks. Remind the patient to bring the single-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications

- Remind patients not to take single-blind investigational product on the morning of the next study visit, Randomization (Visit 2)

- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the single-blind treatment period

- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible

- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit

- Remind patients to withhold LAMA for at least 22 hours before the next study visit

- The study staff will call all patients the day before Visit 2 to remind them of the above

Only patients who meet all inclusion/exclusion criteria at the end of this visit will be allowed to continue to Randomization (Visit 2). On a case-by-case basis and upon the approval of the Sponsor, patients who do not meet all inclusion/exclusion criteria may repeat the full visit; however, whenever a patient is rescreened, a new PID number is to be assigned.

9.5.5.2 Double-Blind Treatment Period

9.5.5.2.1 Visit 2 (Randomization)

After Visit 1, the patient will return to the investigational site 2 weeks later (± 3 days) for Visit 2. The randomization visit (Visit 2) will determine whether patients are eligible to continue into the double-blind treatment period of the study. Patients must have remained on the same COPD maintenance therapy between Screening (Visit 1) and Randomization (Visit 2) (ie, FDC LABA/ICS or LAMA added onto FDC LABA/ICS) in order to be randomized into the study. At Randomization (Visit 2), the randomization criteria will be reviewed (see Section 9.3.1.2); if the patient is eligible to enter the study, the patient will be randomized. Study procedures will then be reviewed with the patient.

The patient will return all used and unused investigational product for a compliance check. The following assessments or procedures will be performed:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit
- Question the patient about any AEs that have occurred since the previous visit
- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4). Patients who have had an exacerbation during the 2-week, lead-in period will be screen failed
- Assess smoking status
- Assess concomitant medications
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)
- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)
- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)
- Perform weight assessment; body mass index will be calculated automatically by the eCRF
- Obtain an on-site urine pregnancy test for women of childbearing potential

- Perform 2 sets of spirometry assessments before administering double-blind investigational product, at the following time points: approximately 1 hour predose and 10 minutes predose. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III

- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visit.

- Review electronic diary for completeness. Set the threshold at 80% for electronic diary entry compliance. Expected entry compliance is ≥ 80%

- Re-confirm that all eligibility criteria for the study have been met

For patients who still meet eligibility criteria:

- Randomize the patient via IVRS

- Dispense double-blind investigational product, including FDC LABA/ICS and rescue medication (if needed). Do not re-dispense used investigational products.

- Administer the first dose of double-blind investigational product 10 minutes after the performance of the second set of pulmonary function tests

Patients not fulfilling all randomization criteria after the 2-week lead-in period must be excluded from the trial.

Further Procedures
Schedule the patient to return to the investigational site for Visit 3 in 4 weeks. Remind the patient to bring the double-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications.

- Remind patients not to take double-blind investigational product on the morning of the next study visit

- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the double-blind treatment period

- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible

- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit

- Remind patients to withhold LAMA for at least 22 hours before the next study visit
- The study staff will call all patients the day before Visit 3 to remind them of the above

9.5.5.2.2 Visit 3 (4 Weeks After Randomization)

The following assessments or procedures will be performed at Visit 3:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit
- Question the patient about any AEs that have occurred since the previous visit
- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)
- Assess smoking status
- Assess concomitant medications
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)
- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)
- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)
- Perform weight assessment; body mass index will be calculated automatically by the eCRF
- Perform 2 sets of spirometry assessments before administering double-blind investigational product, at the following time points: approximately 1 hour predose and 10 minutes predose. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III
- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visits. Please note: Patient noncompliance with dosing after randomization should not be recorded as a deviation; however, compliance should be monitored closely.

- Review electronic diary for completeness

- Dispense investigational product, including FDC LABA/ICS and rescue medication (if needed). Do not re-dispense used investigational products.

- Administer double-blind investigational product 10 minutes after the performance of the second set of pulmonary function tests, before 11 am.

Further procedures
Schedule the patient to return to the investigational site for Visit 4 in 8 weeks. Remind the patient to bring the double-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications.

- Remind patients not to take double-blind investigational product on the morning of the next study visit

- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the double-blind treatment period

- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible

- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit

- Remind patients to withhold LAMA for at least 22 hours before the next study visit

- The study staff will call all patients the day before Visit 4 to remind them of the above

- During the follow-up telephone contact at Week 8 (interim TC 3-1), the following should be assessed and recorded in the eCRF: concomitant medications, AEs, COPD exacerbations duration and treatment.

9.5.5.2.3 Visit 4 (12 Weeks After Randomization)

The following assessments or procedures will be performed at Visit 4:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit
- Question the patient about any AEs that have occurred since the previous visit
- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)
- Assess smoking status
- Assess concomitant medications
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)
- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)
- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)
- Perform weight assessment; body mass index will be calculated automatically by the eCRF
- Obtain blood and urine samples for clinical laboratory determinations, including an on-site urine pregnancy test for women of childbearing potential
- Perform 2 sets of spirometry assessments before administering double-blind investigational product, at the following time points: approximately 1 hour predose and 10 minutes predose. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III
- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visits. Please note: Patient noncompliance with dosing after randomization should not be recorded as a deviation; however, compliance should be monitored closely.
- Review electronic diary for completeness

- Dispense investigational product, including FDC LABA/ICS and rescue medication (if needed). Do not re-dispense used investigational products.

- Administer double-blind investigational product 10 minutes after the performance of the second set of pulmonary function tests, before 11 am.

Further procedures
Schedule the patient to return to the investigational site for Visit 5 in 8 weeks. Remind the patient to bring the double-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications.

- Remind patients not to take double-blind investigational product on the morning of the next study visit

- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the double-blind treatment period

- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible

- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit

- Remind patients to withhold LAMA for at least 22 hours before the next study visit

- The study staff will call all patients the day before Visit 5 to remind them of the above

- During the follow-up telephone contact at Week 16 (interim TC 4-1), the following should be assessed and recorded in the eCRF: concomitant medications, AEs, COPD exacerbations duration and treatment.

9.5.5.2.4 Visit 5 (20 Weeks After Randomization)

The following assessments or procedures will be performed at Visit 5:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit

- Question the patient about any AEs that have occurred since the previous visit

- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)
- Assess smoking status
- Assess concomitant medications
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)
- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)
- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)
- Perform weight assessment; body mass index will be calculated automatically by the eCRF
- Obtain an on-site urine pregnancy test for women of childbearing potential
- For patients in the sparse PK substudy only: Obtain blood sample for PK analysis (see Section 9.5.3.2)
- Perform 2 sets of spirometry assessments before administering double-blind investigational product, at the following time points: approximately 1 hour predose and 10 minutes predose. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III
- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visits.
- Review electronic diary for completeness
- Dispense investigational product, including FDC LABA/ICS and rescue medication (if needed). Do not re-dispense used investigational products.
- Administer double-blind investigational product 10 minutes after the performance of the second set of pulmonary function tests, before 11 am.

Further Procedures
Schedule the patient to return to the investigational site for Visit 6 in 8 weeks. Remind the patient to bring the double-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications.

- Remind patients not to take double-blind investigational product on the morning of the next study visit
- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the double-blind treatment period
- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible
- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit
- Remind patients to withhold LAMA for at least 22 hours before the next study visit
- The study staff will call all patients the day before Visit 6 to remind them of the above
- During the follow-up telephone contact at Week 24 (interim TC 5-1), the following should be assessed and recorded in the eCRF: concomitant medications, AEs, COPD exacerbations duration and treatment.

*9.5.5.2.5 **Visit 6 (28 Weeks After Randomization)***

The following assessments or procedures will be performed at Visit 6:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit
- Question the patient about any AEs that have occurred since the previous visit
- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)
- Assess smoking status
- Assess concomitant medications
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)
- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)
- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)

- Perform weight assessment; body mass index will be calculated automatically by the eCRF
- Perform a 12-lead ECG with the patient in the supine position
- Obtain blood and urine samples for clinical laboratory determinations, including an on-site urine pregnancy test for women of childbearing potential
- Perform 2 sets of spirometry assessments before administering double-blind investigational product, at the following time points: approximately 1 hour predose and 10 minutes predose. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III
- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visits.
- Review electronic diary for completeness
- Dispense investigational product, including FDC LABA/ICS and rescue medication (if needed). Do not re-dispense used investigational products.
- Administer double-blind investigational product 10 minutes after the performance of the second set of pulmonary function tests, before 11 am.

Further procedures
Schedule the patient to return to the investigational site for Visit 7 in 12 weeks. Remind the patient to bring the double-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications.

- Remind patients not to take double-blind investigational product on the morning of the next study visit
- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the double-blind treatment period
- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible
- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit
- Remind patients to withhold LAMA for at least 22 hours before the next study visit

- The study staff will call all patients the day before Visit 7 to remind them of the above

- During the follow-up telephone contact at Weeks 32 and 36 (interim TC 6-1 and interim TC 6-2, respectively), the following should be assessed and recorded in the eCRF: concomitant medications, AEs, COPD exacerbations duration and treatment.

9.5.5.2.6 Visit 7 (40 Weeks After Randomization)

The following assessments or procedures will be performed at Visit 7:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit

- Question the patient about any AEs that have occurred since the previous visit

- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)

- Assess smoking status

- Assess concomitant medications

- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)

- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)

- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)

- Perform weight assessment; body mass index will be calculated automatically by the eCRF

- Obtain an on-site urine pregnancy test for women of childbearing potential

- For patients in the sparse PK substudy only: Obtain blood sample for PK analysis (see Section 9.5.3.2).

- For patients in the serial PK substudy only: Obtain blood samples according to the following time schedule: 0 (predose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 hours after dosing (10 blood samples [see Section 9.5.3.1])

- Perform 2 sets of spirometry assessments before administering double-blind investigational product, at the following time points: approximately 1 hour predose and 10 minutes predose. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III

- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visits.

- Review electronic diary for completeness

- Dispense investigational product, including FDC LABA/ICS and rescue medication (if needed). Do not re-dispense used investigational products.

- Administer double-blind investigational product 10 minutes after the performance of the second set of pulmonary function tests, before 11 am.

Further Procedures
Schedule the patient to return to the investigational site for ET/Last Visit in 12 weeks. Remind the patient to bring the double-blind investigational product, albuterol/salbutamol, and FDC LABA/ICS to the next visit and to avoid prohibited medications.

- Remind patients not to take double-blind investigational product on the morning of the next study visit

- Remind patients to record daily COPD symptoms via EXACT-PRO and use of rescue medication in the electronic diary during the double-blind treatment period

- Remind patients to withhold rescue medication for at least 4 hours before the next study visit, if possible

- Remind patients to withhold FDC LABA/ICS for at least 10 hours before the next study visit

- Remind patients to withhold LAMA for at least 22 hours before the next study visit

- The study staff will call all patients the day before Visit 8/ET to remind them of the above

- During the follow-up telephone contact at Weeks 44 and 48 (interim TC 7-1 and interim TC 7-2, respectively), the following should be assessed and recorded in the eCRF: concomitant medications, AEs, COPD exacerbations duration and treatment.

9.5.5.2.7 Visit 8 /ET/Last Visit - (52 Weeks after Randomization) or Early Termination Visit

The following assessments or procedures will be performed at Visit 8/ET:

- Confirm with the patient that no prohibited medications (see Appendix II) have been taken and that albuterol/salbutamol has been discontinued for at least 4 hours before the visit, that FDC LABA/ICS has been withheld for at least 10 hours before the visit, and that LAMA (if applicable) have been withheld for at least 22 hours before the visit
- Question the patient about any AEs that have occurred since the previous visit
- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)
- Assess smoking status
- Assess concomitant medications
- Administer and assess CAT (see Section 9.5.1.3.2 and Appendix VI)
- Administer and assess electronic C-SSRS (see Section 9.5.2.11.2 and Appendix V)
- Perform physical examination, measure body weight, and assess vital signs (pulse rate, blood pressure, respiratory rate, and body temperature; see Section 9.5.2.9); body mass index will be calculated automatically by the eCRF
- Perform a 12-lead ECG with the patient in the supine position
- Obtain blood and urine samples for clinical laboratory determinations, including an on-site urine pregnancy test for women of childbearing potential
- For patients in the sparse PK substudy only: Obtain blood sample for PK analysis (see Section 9.5.3.2)
- Perform 2 sets of spirometry assessments approximately 50 minutes apart by 11 AM. For each set of assessments, three technically adequate measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III
- Collect albuterol/salbutamol and FDC LABA/ICS and check the dose counter; record compliance of FDC LABA/ICS and double-blind investigational product in the source and eCRF at all visits.
- Review electronic diary for completeness

Further Procedures
Patients should be advised a follow-up telephone contact will be made 4 weeks after ***Visit 8 or*** ET Visit to assess exacerbations and AEs.

Ensure that the patient returns all investigational product (including albuterol/salbutamol and FDC LABA/ICS) at Visit 8/ET.

Any clinical findings obtained during the last visit or early termination visit for any reason, including clinically significant laboratory abnormalities, will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to investigational product. A follow-up visit, if one should be necessary, will take place within 30 days of investigational product termination.

9.5.5.3 Follow-up Visits for Patients Who Discontinue Investigational Product

As described in Section 9.3.3.1, patients who discontinue double-blind investigational product will be asked to return for 1 or 2 on-site follow-up visits, depending on the time of discontinuation (potentially Visit 6 and ET/Last Visit). (These follow-up visits will not apply to patients who are screen failed.) The following assessments are to be performed at these visits:

- Question the patient about any AEs that have occurred since the previous visit
- Monitor for exacerbations (see Section 9.5.1.1.1 through Section 9.5.1.1.4)
- Assess concomitant medications
- Record vital signs: pulse rate, blood pressure, respiratory rate, and body temperature (see Section 9.5.2.9)
- Perform weight assessment; body mass index will be calculated automatically by the eCRF
- Perform 2 sets of spirometry assessments. A minimum of 3 measurements will be performed with the patient in the seated position according to the acceptability and repeatability criteria in Appendix III

9.5.5.4 4-Week Follow-Up Telephone Contact (4 Weeks after Visit 8 or ET Visit)

For all randomized patients who completed or early terminated from the study, 1 follow-up telephone contact will be performed 4 weeks after the ET or Last Visit. All parties involved in the study will remain blinded between the ET/Last Visit and the follow-up contact.

During the follow-up telephone contact, the following should be assessed and recorded in the eCRF:

- Report of moderate or severe exacerbations
- Status of new or ongoing AEs
- Concomitant medications

9.5.6 Time Windows

The time windows allowed for the scheduled visits will be as follows:

Table 9.5.6–1 Visit Time Windows

Visit	*Scheduled Visit Day*[a]	*Window*
Baseline (Visit 2)	Day 1	Days ≤ 1
Visit 3	Day 29	± 3 days
Visit 4	Day 85	± 5 days
Visit 5	Day 141	± 5 days
Visit 6	Day 197	± 5 days
Visit 7	Day 281	± 7 days
Visit 8	Day 365	± 7 days

a Relative to the date of the first dose of double-blind investigational product. Day 1 = the date of the first dose of double-blind investigational product. There is no Day 0 or Week 0.

b Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

Before any patient enters the study, a representative of Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** will meet with the Investigator and the study center staff to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train PIs and authorized designees on recording the data in the eCRFs using the electronic data capture EDC system. After the first patient is enrolled, the ***Actavis*** representative, a Regional Site Manager (RSM) or designee, will periodically monitor the progress of the study by conducting on-site visits. This RSM or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the Investigator and the study center staff. The Investigator will make available to the RSM or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study center staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording and Documentation

Data collection will involve the use of the ***Actavis*** EDC system, to which only authorized personnel will have access. Patients' data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring and reviews, queries may be electronically issued to the study centers and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date, and time) to assist ***Actavis*** and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator prior to final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** its authorized representatives, and the FDA or other health authorities.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Patient Populations

Four populations will be considered in the statistical analysis of the study.

9.7.1.1 Screened Population

The Screened Population will consist of all patients who underwent the Screening Visit (Visit 1) and received a PID number.

9.7.1.2 Randomized Population

The Randomized Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

9.7.1.3 Safety Population

The Safety Population will consist of all randomized patients who took at least 1 dose of double-blind investigational product. For the Safety Population, patients will be assigned to the treatment they actually received.

9.7.1.4 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all randomized patients who took at least 1 dose of double-blind investigational product. For ITT Population, patients will be assigned to the treatment group based on the treatment to which they were randomized.

9.7.2 Patient Disposition

The number of patients in 3 of the study populations (ie, Randomized, Safety, and ITT) will be summarized by treatment group and study center; the Screened Population will only be summarized overall by study center.

Screen failures (ie, patients screened but not randomized) and the associated reasons for failure will be tabulated overall. The number and percentage of patients who complete the double-blind treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the Randomized Population. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the eCRFs will be summarized (number and percentage) by treatment group for all randomized patients.

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, sex, weight, height, body mass index) and other baseline characteristics will be summarized by treatment group and pooled across treatment groups for the Safety and ITT populations.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Investigational Product

Exposure to double-blind investigational product for the Safety Population during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind investigational product taken to the date of the last dose taken, inclusive. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

9.7.4.2 Prior and Concomitant Medication

Prior medication is defined as any medication taken before the date of the first dose of double-blind investigational product. Concomitant medication is defined as any medication taken during the double-blind study treatment period between the date of the first dose of investigational product and the date of the last dose of investigational product. Any medications started after the date of the last dose of investigational product will not be considered concomitant medications.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple uses of each medication by a patient will be counted only once.

9.7.4.3 Measurement of Treatment Compliance

Dosing compliance for roflumilast in a specific period is defined as the total number of tablets actually taken by a patient during that period divided by the number of tablets that were expected to be taken during the same period multiplied by 100. The total number of tablets actually taken will be obtained from the investigational product record of the patient's eCRF. The number of tablets expected to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of tablets to be taken per day. Descriptive statistics for investigational product compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the whole double-blind treatment period of the study for the Safety Population.

Dosing compliance for FDC LABA/ICS (Advair or Symbicort) is defined in a similar manner with number of puffs replacing the number of tablets.

9.7.5 Efficacy Analyses

Efficacy analyses will be based on the ITT Population. For the efficacy analysis, patients will be assigned to the treatment group based on the treatment to which they were randomized. Baseline for efficacy is defined as the last measurement prior to the first dose of double-blinded investigational product, unless specified otherwise. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter will be the rate of moderate or severe COPD exacerbations, defined as requiring oral or parenteral glucocorticosteroids (moderate) or requiring hospitalization and/or leading to death (severe).

The rate of moderate or severe COPD exacerbations will be analyzed using a negative binomial regression model with treatment and stratum (LAMA, no LAMA) as fixed factors. In order to adjust for the exposure for each patient, the natural logarithm of the exposure time will be used as an offset variable. For each patient, the exposure time will be expressed in years and calculated as the number of days a patient spent in the double-blinded treatment period but exclude the days during which new exacerbations cannot occur (i.e. the days when the patient is experiencing existing moderate or severe exacerbations and 10 days after each moderate or severe exacerbation)**,** divided by 365.25.

The negative binomial regression model will make the assumption of a negative binomial distribution of the outcome of events. The analysis of events will be done using SAS PROC GENMOD, specifying negative binomial as distribution and the logarithm (log) as link function. The model will provide point estimates for the rate ratio with the corresponding 95% confidence interval, as well as 2-sided p-value.

In addition to the primary analysis, a sensitivity analysis will be used to assess the potential impact of missing data (resulting from patients after investigational product discontinuation) on the primary endpoint, moderate or severe exacerbations. Data on moderate or severe exacerbations will be collected by phone contacts and visits (up to 1 year from randomization) for patients discontinuing the investigational product prematurely. For this sensitivity analysis of moderate or severe exacerbations combining pre- and post-discontinuation data, a negative binomial regression model analogous to the primary analysis will be applied. For patients who discontinued investigational product, the exposure time will be re-calculated based on the last data collection (visit or phone contact). For all other patients, the exposure time that was already calculated for the primary analysis will be used.

In addition, another sensitivity analysis will be conducted to assess the potential impact of patients in the no-LAMA stratum who start to take LAMA treatment after randomization. This sensitivity analysis will be similar to the primary analysis except that, for patients in the no-LAMA stratum who start to take LAMA treatment after randomization, the exacerbation data collected after starting LAMA will not be included, and the number of days before starting LAMA treatment will be used to calculate the exposure time.

If the negative binomial regression does not converge for primary or sensitivity analyses, the Poisson regression model with robust variance estimate using the sandwich method will be applied.

9.7.5.2 Secondary Efficacy Parameters

The secondary efficacy parameter***s*** will be***:***

- ***M***ean change from Randomization (Visit 2) over 52 weeks of treatment in predose FEV_1
- ***Rate of COPD exacerbations that led to hospitalization or death (i.e., severe COPD exacerbations)***
- ***Rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics***

The secondary efficacy parameter***s*** will be tested in a confirmatory manner 2-sided at a significance level of 5% ***using Hochberg testing procedure*** if the primary efficacy parameter shows a statistically significant difference between 500 µg roflumilast and placebo. In the case that the test for the secondary efficacy parameter***s*** cannot be performed on a confirmatory basis because the test of the primary efficacy parameter***s*** has failed, the test of the secondary efficacy parameter***s*** will be performed in an exploratory manner.

A mixed model for repeated measurements (MMRM) will be used for ***mean change from randomization (Visit 2) over 52 weeks of treatment in predose FEV_1***. The dependent variable will be the change from Randomization (Visit 2) to each scheduled post-randomization visit (encompassing all available measurements in a patient) during the treatment period. The model will include treatment, stratum (LAMA, no LAMA), and time as factors, baseline value as covariates, and baseline-by-time and treatment-by-time interactions. Time will be used as a categorical variable and will represent the scheduled number of weeks since Randomization (Visit 2).

The repeated correlation structure in the visit time-points will be specified to be unstructured, allowing for the maximum flexibility in estimation. The restricted maximum likelihood (REML) method will be used for estimation, and the Kenward Roger method will be used for calculating the degree of freedom. Least square means for each treatment, averaging over all post-randomization visits during the treatment period, and the estimate of the between treatment difference together with the corresponding 95% confidence interval, as well as 2-sided p-values will be presented.

In addition, a sensitivity analysis will be used to assess the potential impact of missing data (resulting from patients after premature investigational product discontinuation) on the secondary endpoint, predose FEV_1. FEV_1 data will be collected at selected visits (up to 1 year from randomization) for patients discontinuing the investigational product prematurely. For this sensitivity analysis of predose FEV_1 combining pre- and post-discontinuation data, an MMRM analogous to the primary analysis for the secondary endpoint will be applied. The results similar to those from the primary analysis will be presented.

Another sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions (Kenward et al, 2003) will be performed to assess the robustness of the primary MMRM results to the possible violation of the missing at-random assumption. In this sensitivity analysis, the observed FEV_1 at a visit is assumed to have a linear relationship with the patient's prior measurements. The missing values will be imputed under the assumption that the distribution of the missing observations differs from that of the observed only by a shift parameter value. The dataset with observed and imputed missing values will be analyzed using the same model as the primary analysis for between-treatment group comparisons. The imputation of missing values and the analysis will be performed multiple times (n = 20), and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. Three values for the shift parameter (-0.025, -0.05 and –0.1 L) will be explored based on experience with historical data. More details of the sensitivity analysis using pattern-mixture model approach will be provided in the SAP.

A sensitivity analysis will also be conducted to assess the potential impact of patients in the no-LAMA stratum who start to take LAMA treatment after randomization. This sensitivity analysis will be similar to the primary analysis except that, for patients in the no-LAMA stratum who start to take LAMA treatment after randomization, the FEV_1 data collected after starting LAMA will not be included.

For the rate of COPD exacerbations that led to hospitalization or death (i.e., severe COPD exacerbations) and for the rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics, the primary analysis method specified for the primary efficacy parameter will be used.

9.7.5.3 Additional Efficacy Parameters

The additional efficacy parameters are:

- COPD exacerbation parameters
    - Rate of exacerbations in the following categories: mild; moderate; treated with systemic steroids and/or antibiotics; treated with antibiotic therapy only; mild, moderate, ***or*** severe; ***mild, moderate, severe*** or treated with antibiotics; exacerbations that lead to COPD related emergency room visit or hospitalization or death; exacerbations derived from EXACT-PRO questionnaire; and exacerbations as reported on the eCRF (see Section 9.5.1.1.4)
    - Proportion of patients with at least 1 exacerbation for all categories including moderate or severe exacerbations

- Time to first, second, and third moderate or severe exacerbations
- NNT to avoid 1 moderate or severe COPD exacerbation per patient per year***, NNT to avoid 1 severe COPD exacerbation per patient per year,*** and NNT to avoid 1 moderate or severe exacerbation or exacerbation treated with antibiotics
- Number of COPD exacerbation days (all categories)
- Duration of COPD exacerbations (all categories)

The algorithm for deriving COPD exacerbations from EXACT-PRO questionnaire will be described in the SAP.

- Spirometry parameters, mean change from baseline over post-randomization visits during treatment period in
  - FVC: Forced vital capacity (expiratory)
  - FEV1/FVC: Ratio of forced expiratory volume after 1 second to forced vital capacity
  - FEV6: Forced expiratory volume in the first 6 seconds
- Diary parameters, mean change from baseline over post-randomization visits during treatment period in
  - Rescue medication use (puffs/day)
  - EXACT-PRO total score, and scores from the Breathlessness, Cough & Sputum, and Chest symptom domains (daily score derived from EXACT-PRO questionnaire)
- CAT, change from baseline over post-randomization visits during treatment period in CAT score
- Rate of all-cause hospitalization
- Rate of COPD-related hospitalization
- Major adverse cardiac events (MACE)

COPD Exacerbations

The rate of COPD exacerbations will be analyzed using negative binomial regression model similar to the primary analysis of the primary efficacy parameter. For categories that negative binomial regression does not converge, the Poisson regression model with robust variance estimate using sandwich method will be applied.

The proportion of patients with at least 1 COPD exacerbation will be analyzed using stratified Miettinen and Nurminen (M&N; Miettinen and Nurminen, 1985) method, stratified by LAMA use. Between-treatment difference, 95% confidence interval and p-value will be provided.

Time to moderate or severe exacerbation (time to first, second, and third exacerbation in 1 analysis) will be analyzed using the method of Wei-Lin-Weissfeld (WLW) method (Wei et al, 1989). This multiple time-to-event analysis will be used for the first 3 exacerbations. The WLW method with equal weights for the 3 exacerbations will be used since the second and the third exacerbations are of equal interest as much as the first exacerbation. Results from the WLW method will be used as supportive analysis for the primary analysis based on rate of exacerbations.

In addition, time to first, time to second, and time to third moderate or severe exacerbation will be analyzed separately using Cox-proportional hazards regression. Time in terms of the number of days will serve as response, where this will represent the time to event in case the event occurred or otherwise time in trial in case the patient has not experienced an event (ie, event time is censored). This model will provide point estimates for the hazards ratio of instantaneous event (the ratio will be presented as roflumilast 500 µg over placebo), as well as corresponding 95% confidence intervals and 2-sided p-values. Kaplan-Meier estimates of the median time to first, second and third exacerbations will also be provided when estimable.

The NNT to avoid 1 moderate or severe COPD exacerbation per patient per year will be calculated as the reciprocal of the estimated difference between placebo and roflumilast 500 µg in the rate of moderate or severe COPD exacerbations per patient per year (based on the negative binomial or Poisson regression models). The NNT to avoid 1 moderate or severe exacerbation or exacerbation treated with antibiotics will be calculated similarly**.**

Frequency of COPD exacerbations will be provided for all categories.

The number of COPD exacerbation days and the duration of COPD exacerbations (all categories of exacerbations) will be analyzed using descriptive statistics.

Spirometry
The additional spirometry parameters (predose FVC, FEV_1/FVC, and FEV_6) will be analyzed using an MMRM model including independent factors and covariates analogous to the model specified for the secondary efficacy parameter.

Furthermore, all lung function variables will be summarized in a descriptive manner. In addition to the analysis in terms of absolute values, percent predicted values for predose FEV_1 and FVC will be summarized in a descriptive manner.

Rescue Medication Use and EXACT-PRO Score
Rescue medication use and EXACT-PRO scores (EXACT-PRO total score and scores from the Breathlessness, Cough & Sputum, and Chest symptom domains) will be recorded by patients using the electronic diary, or derived from EXACT-PRO questionnaire. Prior to analyses the daily values will be aggregated to averages of 1 week.

An MMRM model as specified for the analysis of the secondary efficacy parameter, but specifying compound symmetry as correlation structure, will be used to evaluate within- and between-treatment differences for the use of rescue medication and EXACT-PRO scores. The dependent variable will be the change from baseline (average value of the week prior to the first dose of double-blind investigational product) to each scheduled post-randomization week (encompassing all available measurements in a patient) during the treatment period. Analyses will be presented only for scheduled visits. For this analysis, data from all weeks will be included in the model.

Additionally, use of rescue medication and EXACT-PRO scores will be summarized in a descriptive manner.

The number (in terms of percentages) of rescue medication-free days will be analyzed using descriptive statistics.

COPD Assessment Test
The change from baseline of CAT score will be analyzed with MMRM models in analogy to analysis of the secondary efficacy parameter. Descriptive statistics will also be provided.

In addition, changes from baseline in the CAT score will be evaluated in a responder analysis.

Further details for CAT calculation and analysis will be given in the SAP.

All-Cause Hospitalization and COPD-Related Hospitalization
The rate of all-cause hospitalization and COPD-related hospitalization will be analyzed using negative binomial regression model similar to the primary analysis of the primary efficacy parameter. If the negative binomial regression does not converge, the Poisson regression ***with robust variance estimate using the sandwich method*** will be used.

The proportion of patients with at least 1 hospitalization will be analyzed using M&N method. Descriptive statistics will also be provided.

Major Adverse Cardiac Events (MACE)
The MACE Adjudication Committee will classify pre-defined adverse events into the following categories of cardiovascular events:

- Death (cardiovascular, non-cardiovascular, or undetermined cause)
- Non-fatal myocardial infarction
- Non-fatal stroke (ischemic, hemorrhagic, or unknown)
- Hospitalization for unstable angina
- Non-fatal Transient ischaemic attack
- Hospitalization for heart failure
- Arrhythmia
- Venous and peripheral arterial thromboembolic events
- Other cardiovascular events
- Insufficient documentation for confirmation of an event

Adjudicated MACE will include the following 3 categories: cardiovascular death (including death with undetermined cause), non-fatal myocardial infarction, and non-fatal stroke.

The number and percentage of patients with adjudicated composite MACE, defined as a cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, will be presented by treatment group. The number and percentage of patients with each subcategory of MACE (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) will also be presented by treatment group.

Time to first composite MACE will be analyzed using Cox-proportional hazards regression model with treatment and LAMA use as factors. This model will provide a point estimate for the hazards ratio (roflumilast 500 μg over placebo), as well as corresponding 95% confidence interval and two-sided p-value. The same model will also be applied to each subcategory of MACE: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

The number and percentage of patients with other cardiovascular events (hospitalization for unstable angina, urgent coronary revascularization, hospitalization for heart failure, arrhythmia, venous and peripheral arterial thromboembolic events, and other cardiovascular events) will also be presented by treatment group. Supportive listings will be provided for all adjudicated cardiovascular events with adjudication conclusions.

9.7.5.4 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy parameter (rate of moderate or severe exacerbations) and the secondary efficacy parameter (predose FEV_1) based on the negative binomial regression and MMRM analysis, respectively, to assess the consistency of analysis results among subgroups. For subgroups for which the negative binomial regression does not converge, the Poisson regression model with robust variance estimate using sandwich method will be applied.

The following subgroups will be analyzed:

- Age group (≤ 65 years, > 65 years)
- Sex (female, male)
- Race (white, other)
- Smoking status (ex-smoker, current smoker)
- LABA/ICS therapy (Advair, Symbicort)
- LAMA use (yes, no)
- COPD severity (severe, very severe)

Details of the analysis models for subgroup analysis will be described in the SAP.

9.7.6 Safety Analyses

The safety analysis will be performed using the Safety Population. For the safety analysis, patients will be assigned to the treatment they actually received. The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, ECG parameters, and C-SSRS. For each safety parameter, the last assessment made before the first dose of double-blind investigational product will be used as the baseline for all analyses of that safety parameter.

9.7.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the double-blind treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present before the date of the first dose of double-blind investigational product or was present before the date of the first dose of double-blind investigational product and increased in severity during the double-blind treatment period. If more than 1 AE is reported before the date of the first dose of double-blind investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the double-blind treatment period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of double-blind investigational product will not be counted as a TEAE, but a listing of those AEs will be provided.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the investigational product.

The distribution of TEAEs by severity and relationship to the investigational product will be summarized by treatment group.

The incidence of common (≥ 2% of patients in any treatment group) TEAEs, on-therapy SAEs, and AEs leading to premature discontinuation of the investigational product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the test treatment. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of double-blind investigational product and within 30 days of the date of the last dose of double-blind investigational product.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

9.7.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 post-baseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS post-baseline value. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, study center number, and baseline and post-baseline values. A listing of all AEs for patients with PCS laboratory values will also be provided.

Patients who meet the potential Hy's Law criteria from the first dose of double-blind investigational product to within 30 days after the last dose of double-blind investigational product will be summarized for the Double-blind Safety Population. Supportive tabular displays will also be provided.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) and body weight and changes from baseline values at each visit and at end of study will be presented by treatment group.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline–value criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with baseline values and at least 1 post-baseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS post-baseline value. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, study center number, and baseline and post-baseline values. A listing of all AEs for patients with PCS vital sign values will also be provided.

9.7.6.4 Electrocardiogram

Descriptive statistics for ECG parameters (ie, pulse rate, PR interval, QRS interval, QT interval, and QTc interval) and changes from baseline values at each assessment time point will be presented by treatment group.

The number and percentage of patients with PCS post-baseline ECG values will be tabulated by treatment group. The criteria for PCS ECG values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 post-baseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS post-baseline value. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, study center number, and baseline and post-baseline values. A listing of all AEs for patients with PCS ECG values will also be provided.

9.7.6.5 Columbia Suicide Severity Rating Scale (C-SSRS)

For the C-SSRS, the number and percentage of patients with suicidal ideation or suicidal behavior will be presented by treatment group for the Safety Population. Supportive listings will be provided that include the PID number, treatment group, visit number, lifetime history, and post-baseline values for each patient. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings.

9.7.7 Health Outcomes Analyses

No health outcome assessment is planned for this study.

9.7.8 Pharmacokinetic Analysis

Roflumilast and roflumilast N-oxide PK parameters such as C_{max}, AUC, T_{max} and $T_{½}$ will be calculated for patients in the serial PK sub-group. Sparse PK sample data from this study will be added to the existing population PK model for population analysis.

9.7.9 Determination of Sample Size

The primary endpoint of this trial is the rate of moderate or severe COPD exacerbations. For a 2-sided test at significance level of 0.05, a sample size of 1150 patients per treatment group, or 2300 in total, will have a power of 90% to detect an 18% reduction in the exacerbation rate in the roflumilast group relative to the placebo group.

For sample size estimation the following assumptions were made: a rate of 1.35 moderate or severe exacerbations per patient per year in the placebo group (resulting in a rate of 1.11 exacerbations per patient per year for an 18% reduction with roflumilast 500 μg), and a mean exposure time of 287 days. The mean exposure time are estimated from data of previous trials (BY217/M2-124 and BY217/M2-125) with roflumilast in a comparable setting.

9.7.10 Computer Methods

Statistical analyses will be performed using version 9.2 (or newer) of SAS on a UNIX operating system.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** or its representative. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/EC and the signature page, signed by the Investigator, has been received by Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** or its representative. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/EC review and approval. However, the IRB/EC must be informed in writing of such an amendment, and approval must be obtained within a reasonable time limit.

9.9 PROTOCOL DEVIATIONS AND VIOLATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of treatment, failure to perform the required assessments at specified time points, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to Forest Research Institute, Inc***., an affiliate of Actavis, Inc.***

Protocol deviations must be reported to the Sponsor either verbally or electronically within 5 working days from the day of discovery.

A *protocol violation* is a form of protocol deviation that has a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data.

Protocol violations must be reported to the Sponsor immediately, if possible. The IRB/IEC must be notified within the time period dictated by the IRB/IEC associated with this study.

10.0 STUDY SPONSORSHIP

10.1 STUDY TERMINATION

Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** reserves the right to terminate the study in its entirety or at a specific site at any time.

10.2 REPORTING AND PUBLICATION

All data generated in this study will be the property of Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.*** An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be dependent on mutual agreement between the Investigator and Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.***

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must provide the following to Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to Forest Research Institute, Inc***., an affiliate of Actavis, Inc.,*** for submission to the FDA
- A fully executed contract
- A signed, dated (within 1 year) curricula vitae for the Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/EC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/EC, as stated in Section 5.1
- A copy of the IRB/EC-approved ICF
- A copy of the HIPAA authorization form, or other applicable local privacy forms
- A list of the IRB/EC members or the Department of Health and Human Services general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the Investigator
- Financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. The Investigator and all Sub-Investigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study

11.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 STEERING AND MACE ADJUDICATION COMMITTEES

Steering Committee: Scientific advice on the study design, procedures, and assessments were obtained from a steering committee composed of scientific experts.

MACE Adjudication Committee: This committee is an independent expert advisory group responsible for reviewing data to confirm diagnoses of potential cardiovascular events.

11.4 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-Investigators listed on Form FDA 1572. The investigational product must be stored in a safe and secure place. At study initiation, a representative of Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** will inventory the investigational product at the study center. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** will supply forms on which to record the date the investigational product was received and a dispensing record in which to record each patient's use. All unused investigational product must be returned to Forest Laboratories, ***LLC, an affiliate of Actavis, Inc.*** It is the Investigator's responsibility to ensure that patients return their investigational product.

11.5 CASE REPORT FORMS

All data relating to the study will be recorded on eCRFs to be provided by Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** through the EDC system and other sources (cardiac safety, IVRS, and central laboratory databases). The eCRFs should be completed at the time of the patient's visit, except for results of tests performed outside the Investigator's office. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate. The Investigator must sign the completed eCRF before its submission to Forest ***Research, Inc., an affiliate of Actavis, Inc.***

11.6 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, regulatory documents, clinical laboratory results or reports (including, but not limited to, all local and central laboratory results and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator of the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

For Canadian study sites only: All records and documents pertaining to the conduct of the study must be retained for a 25-year period in accordance with the Canadian Food and Drugs Act and Regulations.

11.7 PATIENT CONFIDENTIALITY

All patient records will be identified only by initials and PID number. Patients' names are not to be transmitted to Forest Research Institute, Inc.***, an affiliate of Actavis, Inc.*** The Investigator will keep a master patient list on which the PID number and the full name, address, and telephone number of each patient are listed.

12.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this Amended Protocol#***5*** ROF-MD-07, dated [redacted], and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____
Investigator's Signature Date

_____
Investigator's Name

13.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's legally authorized representative. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research, a description of the procedures to be followed and the identification of any procedures that are experimental, and the expected duration of the patient's participation

- A description of any reasonably foreseeable risks or discomforts to the patient

- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, Forest Research Institute, Inc., ***an affiliate of Actavis, Inc.,*** the IRB, or an authorized contract research organization may inspect the records

- A statement notifying the patient that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained

- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient.
  (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation

- A statement that significant new findings may develop during the course of the research that may affect to the patient's willingness to continue participation will be provided to the patient

- The approximate number of patients involved in the study

- A statement of consent (eg, "I agree to participate ...")

- A place for the patient's signature and date of signing

A copy of the signed consent form should be given to the patient.

APPENDIX II. CONCOMITANT MEDICATIONS

Drug Class	***Frequency of Use***		***Restrictions***
	Episodic (PRN)	***Chronic***	
Long-acting muscarinic antagonists (LAMA) (eg, tiotropium) and oral, intranasal or parenteral anticholinergics	N	Y	Patients must be on stable dose ≥ 3 months prior to Screening (Visit 1). Patients should withhold LAMA treatment 22 hours prior to every clinic visit. (Limited to 60% of total patient population)
Short-acting muscarinic antagonists (SAMA) (eg, ipratropium, oxitropium)	Y	Y	Patients should withhold SAMA treatment 6 hours prior to every clinic visit. (Prohibited in patients in the LAMA stratum)
Short-acting β_2-adrenergic agonists (eg, salbutamol, albuterol) ***NOTE: ONLY AS PROVIDED BY SPONSOR***	Y	Y	Patients should withhold SABA treatment 4 hours prior to every clinic visit
Long-acting β_2-adrenergic agonists (eg, salmeterol, formoterol, indacaterol)	N	N	All patients will be on background LABA/ICS therapy; LABA monotherapy is not allowed. Patients should withhold FDC LABA/ICS treatment 10 hours prior to every clinic visit
Combivent Aerosol (combination of ipratropium bromide and albuterol)	N	N	12-hour washout prior to Screening (Visit 1) is required
Oral or parenteral corticosteroids	Y	N	Oral or parenteral corticosteroids are allowed in the event of a moderate or severe COPD exacerbation.(see Section 9.5.1.1.3) 2 week washout prior to Screening (Visit 1) is required
Inhaled Corticosteroid	N	N	All patients will be on background LABA/ICS therapy; LABA monotherapy is not allowed. Patients should withhold FDC LABA/ICS treatment 10 hours prior to every clinic visit
Antibiotics	Y	N	2 week washout prior to Screening (Visit 1) is required for chronic antibiotic treatment only
Intranasal corticosteroids (eg, fluticasone)	Y	Y	
Oral β_2- agonists	N	N	3 day washout prior to Screening (Visit 1) is required

Drug Class	***Frequency of Use***		***Restrictions***
	Episodic (PRN)	***Chronic***	
Theophylline and/or derivatives (aminophylline, diprophylline) or combinations thereof or any other theophylline containing products	N	N	2-week washout prior to Screening (Visit 1) is required
Phosphodiesterase 4 (PDE4) inhibitors (with exception of the IP provided by the sponsor)	N	N	Commercially approved roflumilast treatment (Daliresp or Daxas) will need to be withdrawn at Screening (Visit 1). There is no wash out period required before Visit 1.
Cyclosporins, Methotrexate, Azathioprine	N	N	1-month washout prior to Screening (Visit 1) is required
Anti-TNF (Tumor Necrosis Factor) agents (eg infliximab, adalimumab)	N	N	2-month washout prior to Screening (Visit 1) is required
Omalizumab	N	N	6-month washout prior to Screening (Visit 1) is required
H1-antihistamines (loratadine, etc)	Y	N	7 day washout prior to Screening (Visit 1) is required
Leukotriene and 5LO modifiers (eg, montelukast, zafirlukast, zileuton)	N	N	48-hour washout prior to Screening (Visit 1) is required

COPD = chronic obstructive pulmonary disease; FDC = fixed-dose combination; ICS = inhaled corticosteroid; IP = investigational product; LABA = long-acting β2 agonist; long-acting muscarinic antagonist; N = no, not allowed; PRN = as needed; SAMA = short-acting muscarinic antagonist; Y = yes, allowed

APPENDIX III. PULMONARY FUNCTION TESTS

A centralized spirometry company (ERT) will provide the spirometers or pneumotach and all necessary equipment (computer, calibration syringe, printer, paper, ink, etc.), a detailed study manual, and training (for qualification of technicians in charge of conducting spirometries) to all sites involved in this clinical trial. These spirometers are only to be used for this specific clinical trial. Spirometers will measure FVC (maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration) and FEV1 (volume of air expressed in liters exhaled during the first second of performance of the FVC) and will meet American Thoracic Society and European Respiratory Society recommendations for accuracy and precision (Miller et al, 2005).

Instrument recommendations should be followed to provide accurate and comparable spirometric data, and calibration should be performed every day the system is used or after disassembling, cleaning, and/or sensor replacement.

Spirometries must be performed at temperatures between 17°C and 40°C. Efforts should be made to perform all maneuvers at approximately the same temperature. A notebook must be maintained to document daily (at least for those days spirometric procedures have to be done) ambient temperature and pressure. In case of changes in temperature and/or barometric pressure within the same day, calibration must be repeated before any other spirometry is done.

Before the first spirometry, the trained operator should demonstrate the procedure using a detached mouthpiece and then allow 3 practice attempts. (Note: Training is not required if, for example. the patient is familiar with spirometry testing from prior experience). A copy of the spirogram tracings (including calibration) should be printed and kept in the patient's medical records as source documentation.

The technician performing the test must properly wash his/her hands or use gloves to avoid any possible contamination. Reusable mouthpieces, breathing tubes, valves, and manifolds should be properly disinfected or sterilized regularly.

Spirometry Maneuvers

Pulmonary function tests will be performed by highly experienced personnel. At each time point, 3 technically adequate measurements should be performed according to the acceptability and repeatability criteria of the ATS/ERS (Miller et al, 2005).They will be automatically evaluated by the computerized spirometer via preprogrammed checks. This information will be displayed in the form of messages to the technicians at the site so that they may continue performing the necessary attempts.

Patients should be able to produce repeatable pulmonary function testing (ie, the three best acceptable spirograms must have FEV_1 and FVC values that do not vary by more than more than 150 mL). If both the acceptability and repeatability criteria are met, the test session may be concluded. If one or both of these criteria are not met, additional maneuvers will be requested by the equipment until both criteria are met OR a total of 8 tests have been performed, unless the patient cannot continue.

These data will be electronically transmitted by the investigator to the central Data Management Center of the centralized spirometry company, eRT. The contact address of this company is as follows:

[redacted]

Throughout the study, a centralized reading of spirometric values is performed by an independent, blinded, spirometric expert at the centralized spirometry company and values that meet the American Thoracic Society and European Respiratory Society criteria for acceptability, as judged and approved by the Investigator, are considered acceptable. At each time point, only the greatest acceptable FEV_1 value and other corresponding spirometric measures (FVC, FEV_1/FVC) will be used for all analyses. The data will be periodically transmitted to the Data Management Group in charge of the full study data.

The circumstances of the test should be similar on all occasions with respect to time of the day, temperature and pressure as well as the technician. Smoking should be avoided for at least 1 hour before each visit, and exposure to cold air, dust, and polluted air should be limited to the extent possible for at least 8 hours before each visit; both should be avoided until the completion of all study procedures. For patients having difficulty not smoking, nicotine gums or patches may be used.

Patients should be at rest for 15 minutes before the test and comfortable; tight clothing should be loosened to allow the thorax to move freely. Measurements are to be made with the patient seated in an upright posture and wearing a nose clip.

The procedure should be carefully described to the patient, with an emphasis on the need to avoid leaks around the mouthpiece. The following order of the spirometric maneuvers must be followed for forced maneuvers for measuring FEV_1 and FVC:

- Place the mouthpiece in the mouth and close the lips around the mouthpiece
- Breathe normally about 3 times
- Inhale completely and rapidly with a pause of < 1 second at total lung capacity

- Exhale maximally during at least 6 seconds, maintaining an upright posture and taking care that the lips are sealed around the mouthpiece

- Breathe in again and relax

At the time of forced maneuver, the technician performing the measurement should prompt the patient to blast, not just blow, the air from the lungs; continue to encourage him/her to fully exhale. Throughout all complete maneuvers, the technician should enthusiastically coach the patient by word and body language.

Any bronchoconstriction that appears after consecutive measurements should be noted on the eCRF.

APPENDIX IV. PK BLOOD SAMPLING AND SHIPPING INSTRUCTIONS

BLOOD SAMPLING GUIDE

Blood Collection Procedure

- Adhere the provided label to the Vacutainer tube
- Prechill (eg, in a water/ice bath) a 6-mL Vacutainer tube (with lithium heparin as the anticoagulant)
- After blood is drawn, place the tube upright in an ice bath until centrifugation
- Within 20 to 30 minutes from the time blood is drawn, centrifuge the tube at no less than 1600*g* for 15 minutes in a refrigerated centrifuge at 4°C

Plasma Collection Procedure

- Transfer harvested plasma immediately into prechilled, labeled cryotubes (provided by the central laboratory)
- Immediately flash-freeze plasma samples in a dry ice and isopropyl alcohol bath or in a deep freezer
- Place the frozen tubes in a freezer set at –30°C or colder. (If the samples are stored at –20°C they must be shipped within 1 week of the blood draw)

Sample Shipping Guide From the Study Center to the Central Laboratory

Primary sample will be shipped from the study center to the central laboratory on the first available appropriate date after sample collection. The central laboratory will provide packaging, labeling, and shipping instructions to the Investigator. Plasma samples will be shipped on sufficient dry ice to keep them frozen for at least 96 hours.

Once [redacted] confirms the first frozen PK sample is received and valid, the site will ship the 2nd and 3rd backup samples within a month if stored at –30°C or colder , colder, or within a week if stored at –20°C to ICON in separate shipments to minimize loss of samples due to courier issues.

The PK samples will be analyzed by [redacted]. ***A***ny remaining samples/aliquots will be kept in a -70 freezer until the study data is finalized**.** Six months after completion of the Clinical Study Report, the samples will be destroyed.

Sample Packing Guide From the Study Center to the Central Laboratory

- Affix a coded label, provided by the central laboratory ([redacted]), to each sample
- Wrap the samples in bundles by PID number and place the samples into freezer bags
- Put bagged samples into a thick foam shipping box (eg, 19" × 19" × 12") that has a slab of dry ice on the bottom and on 2 of the 4 sides. Pack remaining spaces with dry ice
- Make a note in source documents of the estimated weight of dry ice used per box
- Put on the lid and seal with tape
- Attach a Sample Transfer Record and a Requisition Form (both provided by [redacted]) containing an inventory of the samples included in the shipment (eg, ROF-MD-07, plasma samples, PID number, sample time point) to the lid of the shipping box. Please make a clear note of any scheduled samples (indicate sample time points) that may have been missed or not included in the shipment.
- Put box into a cardboard shipping carton, if available, and seal
- Samples are to be shipped to:

[redacted]

Notification Guide From the Study Center to [redacted].

- Notify [redacted] by telephone, fax, or email immediately after the samples have left your premises. The notification will include:
    - Name of courier or transport company
    - Time and date the shipment left your premises
    - Airway bill number
    - Forest's study number and visit number
    - Name, telephone number, and fax number of the appropriate contact person at your study center

The key contact name at the CRO is [redacted].

The PK samples can be shipped to [redacted], to the attention of:

[redacted]

APPENDIX V. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

(Administer "Baseline" version of C-SSRS at Visit 1)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline
Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____

Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (***Self-Injurious Behavior without suicidal intent If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

(Administer "Since Last Visit" version of C-SSRS at Visits 2 through 8)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

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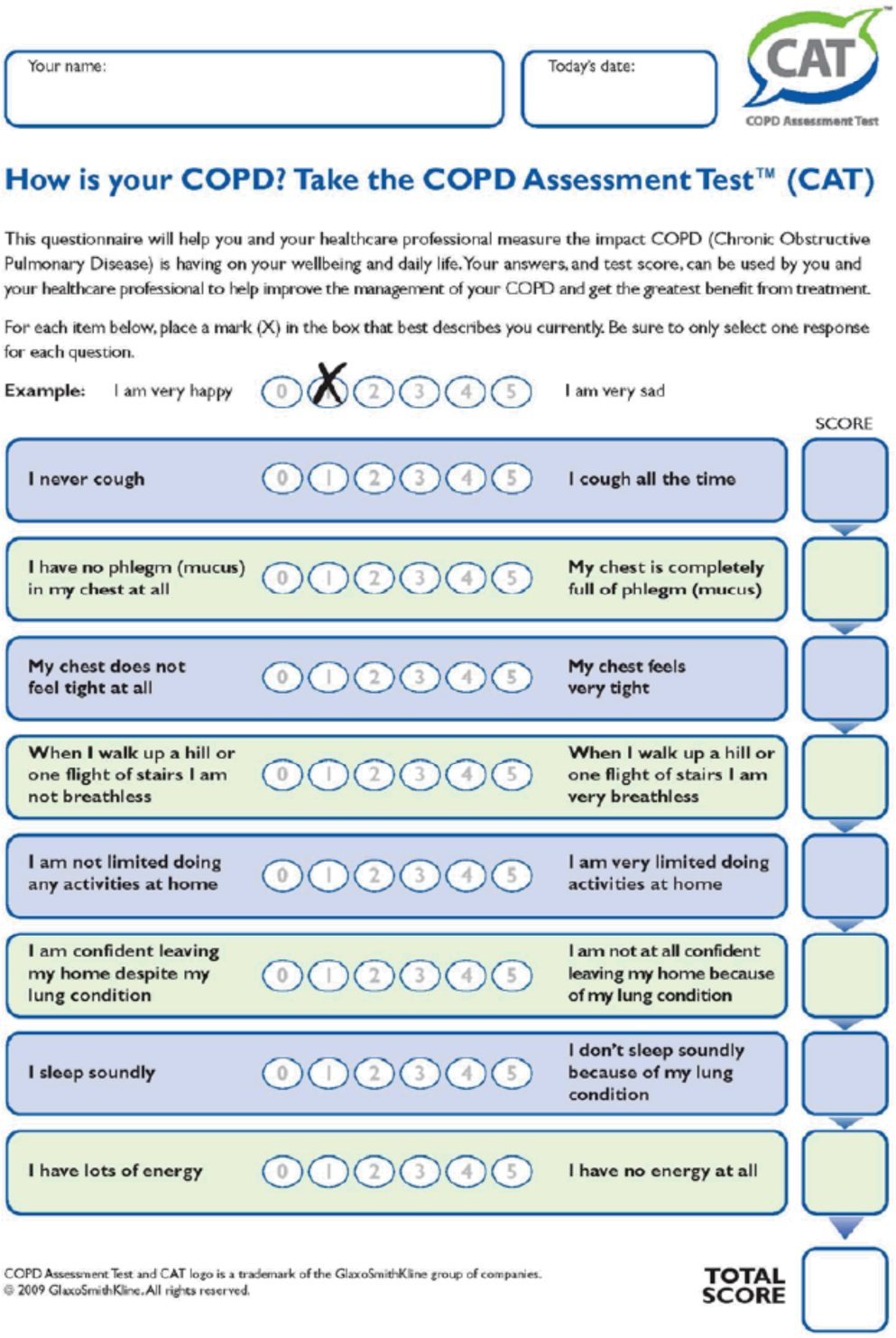
SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____

Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐

Completed Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX VI. COPD ASSESSMENT TEST- CAT



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

APPENDIX VII. DALIRESP PACKAGE INSERT

DALIRESP- roflumilast tablet
AstraZeneca Pharmaceuticals LP

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DALIRESP safely and effectively. See full prescribing information for DALIRESP.

DALIRESP® (roflumilast) tablets
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

DALIRESP is a selective phosphodiesterase 4 inhibitor indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. (1, 14)
Limitations of Use*:* DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm. (1, 14)

DOSAGE AND ADMINISTRATION

The recommended dosage for patients with COPD is one 500 mcg tablet per day, with or without food. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 500 mcg (3)

CONTRAINDICATIONS

- Moderate to severe liver impairment (Child-Pugh B or C) (4)

WARNINGS AND PRECAUTIONS

- Acute bronchospasm: Do not use for the relief of acute bronchospasm. (5.1)
- Psychiatric Events including Suicidality: Advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Carefully weigh the risks and benefits of treatment with DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior. (5.2)
- Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of DALIRESP. (5.3)
- Drug Interactions: Use with strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥ 2%) are diarrhea, weight decrease, nausea, headache, back pain, influenza, insomnia, dizziness and decreased appetite. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Use with inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (e.g, erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) will increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. (7.2)

USE IN SPECIFIC POPULATIONS

Nursing Mothers: DALIRESP should not be used by women who are nursing as excretion of roflumilast and/or its metabolites into human milk is probable and there are no human studies that have investigated effects of DALIRESP on breast-fed infants. (8.3)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

3 DOSAGE FORMS AND STRENGTHS

DALIRESP is supplied as white to off-white, round tablets, embossed with “D” on one side and “500” on the other side. Each tablet contains 500 mcg of roflumilast.

4 CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following condition:

Moderate to severe liver impairment (Child-Pugh B or C) [*see Clinical Pharmacology (12.3) and Use in Special Populations (8.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

5.2 Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) *[see Adverse Reactions (6.1)]*. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo. Cases of suicidal ideation and behavior, including completed suicide, have been observed in the post-marketing setting in patients with or without a history of depression.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

5.3 Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1)*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant

weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

5.4 Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2)]*
- Weight Decrease *[see Warnings and Precautions (5.3)]*

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP** (**N**=4438) n (%)	**Placebo** (**N**=4192) n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)

Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting

Infections and infestations - rhinitis, sinusitis, urinary tract infection,

Musculoskeletal and connective tissue disorders - muscle spasms

Nervous system disorders - tremor

Psychiatric disorders - anxiety, depression

6.2 Postmarketing Experience

The following adverse reactions have been identified from spontaneous reports of DALIRESP received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to DALIRESP. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to DALIRESP exposure: hypersensitivity reactions including angioedema, urticaria, and rash.

7 DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [*see Clinical Pharmacology (12.3)*].

7.1 Drugs That Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)]*.

7.3 Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses > 2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

8.2 Labor and Delivery

DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of > 2 mg/kg/day).

8.3 Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

8.4 Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

8.5 Geriatric Use

Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh [redacted]ts, as

compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Human Experience

No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

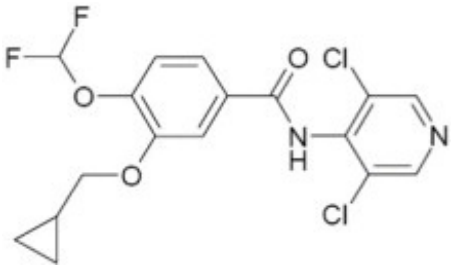
10.2 Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

11 DESCRIPTION

The active ingredient in DALIRESP tablets is roflumilast. Roflumilast and its active metabolite (roflumilast N-oxide) are selective phosphodiesterase 4 (PDE4) inhibitors. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22.

The chemical structure is:



The drug substance is a white to off-white non-hygroscopic powder with a melting point of 160°C. It is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone.

DALIRESP is supplied as white to off-white, round tablets, embossed with “D” on one side and “500” on the other side. Each tablet contains 500 mcg of roflumilast.

Each tablet of DALIRESP for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, povidone and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3′,5′-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue) activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism(s) by which DALIRESP exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells.

12.2 Pharmacodynamics

In COPD patients, 4 week treatment with DALIRESP 500 mcg oral once daily reduced sputum neutrophils and eosinophils by 31%, and 42%, respectively. In a pharmacodynamic study in healthy volunteers, DALIRESP 500 mcg once daily reduced the number of total cells, neutrophils and eosinophils found in bronchoalveolar lavage fluid following segmental pulmonary lipopolysaccharide (LPS) challenge by 35%, 38% and 73%, respectively. The clinical significance of these findings is unknown.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentrations (C_{max}) of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state while plateau-like maximum concentrations of the N-oxide metabolite are reached in approximately eight hours (ranging from 4 to 13 hours). Food has no effect on total drug absorption, but delays time to maximum concentration (T_{max}) of roflumilast by one hour and reduces C_{max} by approximately 40%, however, C_{max} and T_{max} of roflumilast N-oxide are unaffected. An *in vitro* study showed that roflumilast and roflumilast N-oxide did not inhibit P-gp transporter.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier.

Metabolism

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide were detected in urine.

While roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE4 enzyme *in vitro*, the plasma AUC of roflumilast N-oxide on average is about 10-fold greater than the plasma AUC of roflumilast.

In vitro studies and clinical drug-drug interaction studies suggest that the biotransformation of roflumilast to its N-oxide metabolite is mediated by CYP 1A2 and 3A4. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP 2B6 by roflumilast.

Elimination

The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing. Following intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Special Populations

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUC of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Use in Specific Populations (8.6)]*.

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, roflumilast and roflumilast N-oxide AUCs were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Use in Specific Populations (8.7)]*.

Age

Roflumilast 500 mcg once daily for 15 days was studied in young, middle aged, and elderly healthy subjects. The exposure in elderly (> 65 years of age) were 27% higher in AUC and 16% higher in C_{max} for roflumilast and 19% higher in AUC and 13% higher in C_{max} for roflumilast-N-oxide than that in young volunteers (18-45 years old). No dosage adjustment is necessary for elderly patients *[see Use in Specific Populations (8.5)]*.

Gender

In a Phase I study evaluating the effect of age and gender on the pharmacokinetics of roflumilast and roflumilast N-oxide, a 39% and 33% increase in roflumilast and roflumilast N-oxide AUC were noted in healthy female subjects as compared to healthy male subjects. No dosage adjustment is necessary based on gender.

Smoking

The pharmacokinetics of roflumilast and roflumilast N-oxide were comparable in smokers as compared to non-smokers. There was no difference in C_{max} between smokers and non-smokers when roflumilast 500 mcg was administered as a single dose to 12 smokers and 12 non-smokers. The AUC of roflumilast in smokers was 13% less than that in non-smokers while the AUC of roflumilast N-oxide in smokers was 17% more than that in non-smokers.

Race

As compared to Caucasians, African Americans, Hispanics, and Japanese showed 16%, 41%, and 15% higher AUC, respectively, for roflumilast and 43%, 27%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, African Americans, Hispanics, and Japanese showed 8%, 21%, and 5% higher C_{max}, respectively, for roflumilast and 43%, 27%, and 17% higher C_{max},

respectively, for roflumilast N-oxide. No dosage adjustment is necessary for race.

Drug Interactions

Drug interaction studies were performed with roflumilast and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction [*see Drug Interactions (7)]*. No significant drug interactions were observed when 500 mcg oral roflumilast was administered with inhaled salbutamol, formoterol, budesonide and oral montelukast, digoxin, theophylline, warfarin, sildenafil, midazolam, or antacids.

The effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide is shown in the Figure 1 below.

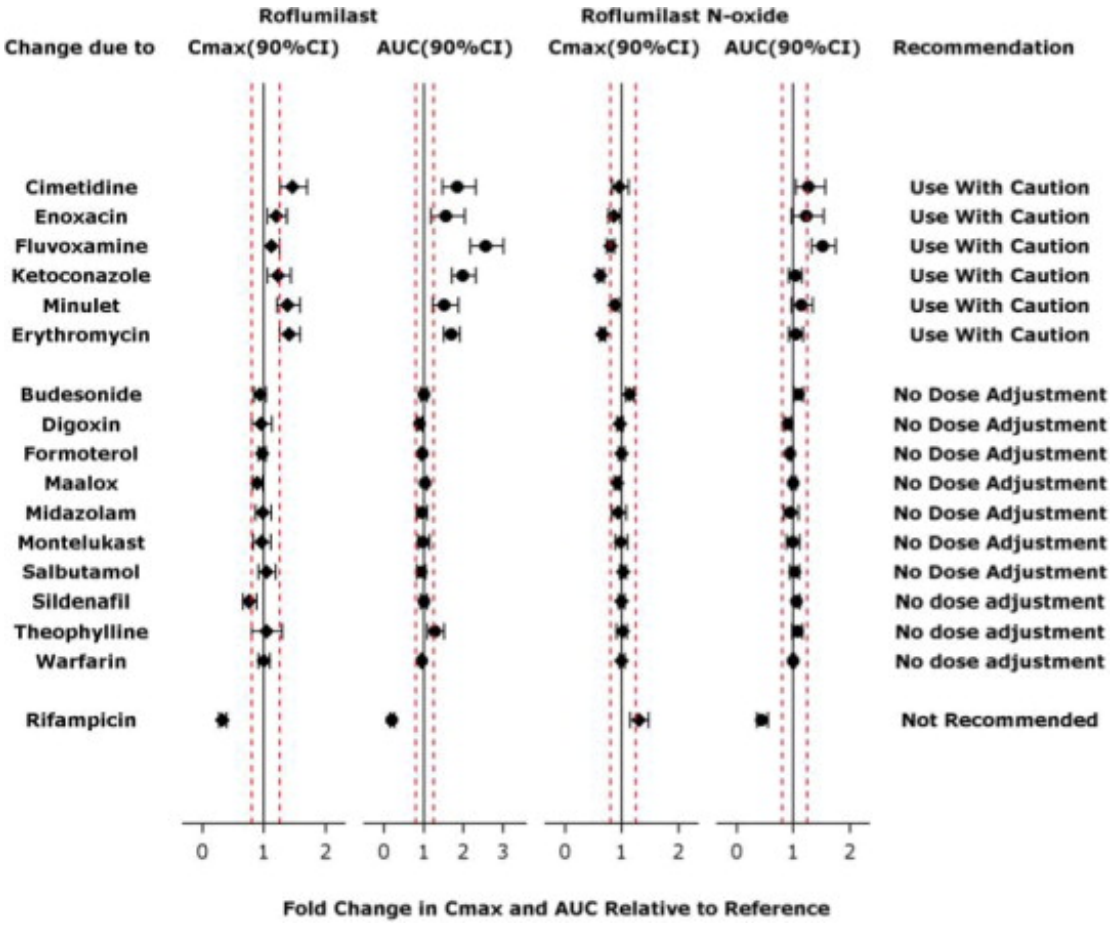


Figure 1. Effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide. Note that the dashed lines indicate the lower and higher bounds (0.8-1.25) of the 90% confidence interval of the geometric mean ratio of C_{max} or AUC for roflumilast or roflumilast N-oxide for Treatment (DALIRESP+Coadministered Drug) vs. Reference (DALIRESP). The dosing regimens of coadministered drugs was: Midazolam:2mg po SD; Erythromycin:500mg po TID; Ketoconazole:200mg po BID; Rifampicin:600mg po QD; Fluvoxamine:50mg po QD; Digoxin:250ug po SD; Maalox:30mL po SD; Salbutamol:0.2mg pi TID; Cimetidine:400mg po BID; Formoterol:40ug po BID; Budesonide:400ug po BID; Theophylline:375mg po BID; Warfarin:250mg po SD; Enoxacin:400mg po BID; Sildenafil:100mg SD; Minulet (combination oral contraceptive):0.075mg gestodene/0.03mg ethinylestradiol po QD; Montelukast:10mg po QD

Drug interactions considered to be significant are described in more detail below *[also see Drug Interactions (5.4) and Drug Interactions (7)]*.

Inhibitors of CYP3A4 and CYP1A2:

Erythromycin: In an open-label crossover study in 16 healthy volunteers, the coadministration of CYP 3A4 inhibitor erythromycin (500 mg three times daily for 13 days) with a single oral dose of 500 mcg DALIRESP resulted in 40% and 70% increase in C_{max} and AUC for roflumilast, respectively, and a 34% decrease and a 4% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

Ketoconazole: In an open-label crossover study in 16 healthy volunteers, the coadministration of a strong CYP 3A4 inhibitor ketoconazole (200 mg twice daily for 13 days) with a single oral dose of 500 mcg DALIRESP resulted in 23% and 99% increase in C_{max} and AUC for roflumilast, respectively, and a 38% reduction and 3% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

Fluvoxamine: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor fluvoxamine (50 mg daily for 14 days) with a single oral dose of 500 mcg DALIRESP showed a 12% and 156% increase in roflumilast C_{max} and AUC along with a 210% decrease and 52% increase in roflumilast N-oxide C_{max} and AUC, respectively.

Enoxacin: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor enoxacin (400 mg twice daily for 12 days) with a single oral dose of 500 mcg DALIRESP resulted in an increased C_{max} and AUC of roflumilast by 20% and 56%, respectively. Roflumilast N-oxide C_{max} was decreased by 14% while roflumilast N-oxide AUC was increased by 23%.

Cimetidine: In an open-label crossover study in 16 healthy volunteers, the coadministration of a dual CYP 3A4/1A2 inhibitor cimetidine (400 mg twice daily for 7 days) with a single dose of 500 mcg oral DALIRESP resulted in a 46% and 85% increase in roflumilast C_{max} and AUC; and a 4% decrease in C_{max} and 27% increase in AUC for roflumilast N-oxide, respectively.

Oral Contraceptives containing Gestodene and Ethinyl Estradiol:

In an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of 500 mcg DALIRESP with repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state caused a 38% increase and 12% decrease in C_{max} of roflumilast and roflumilast N-oxide, respectively. Roflumilast and roflumilast N-oxide AUCs were increased by 51% and 14%, respectively.

Inducers of CYP enzymes:

Rifampicin: In an open-label, three-period, fixed-sequence study in 15 healthy volunteers, coadministration of the strong CYP3A4 inducer rifampicin (600 mg once daily for 11 days) with a single oral dose of 500 mcg DALIRESP resulted in reduction of roflumilast C_{max} and AUC by 68% and 79%, respectively; and an increase of roflumilast N-oxide C_{max} by 30% and reduced roflumilast N-oxide AUC by 56%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in hamsters and mice with roflumilast to evaluate its carcinogenic potential. In 2-year oral gavage carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated carcinomas of nasal epithelium in hamsters at ≥ 8 mg/kg/day (approximately 11 times the MRHD based on summed AUCs of roflumilast and its metabolites). The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of 4-amino-3,5-dichloro-pyridine N-oxide (ADCP N-oxide). No evidence of tumorigenicity was observed in mice at roflumilast oral doses up to 12 and 18 mg/kg/day in females and males, respectively (approximately 10 and 15 times the MRHD, respectively, based on summed AUCs of roflumilast and its metabolites).

Roflumilast tested positive in an *in vivo* mouse micronucleus test, but negative in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosome aberration assay in human lymphocytes, *in*

vitro HPRT test with V79 cells, an *in vitro* micronucleus test with V79 cells, DNA adduct formation assay in rat nasal mucosa, liver and testes, and *in vivo* mouse bone marrow chromosome aberration assay. Roflumilast N-oxide was negative in the Ames test and in vitro micronucleus test with V79 cells.

In a human spermatogenesis study, roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period. In a fertility study, roflumilast decreased fertility rates in male rats at 1.8-mg/kg/day (approximately 29 times the MRHD on a mg/m^2 basis). These rats also showed increases in the incidence of tubular atrophy, degeneration in the testis and spermiogenic granuloma in the epididymides. No effect on male rat fertility rate or reproductive organ morphology was observed at 0.8 mg/kg/day (approximately 13 times the MRHD on a mg/m^2 basis). No effect on female fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats (approximately 24 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Chronic Obstructive Pulmonary Disease (COPD)

The efficacy and safety of DALIRESP (roflumilast) in COPD was evaluated in 8 randomized double-blind, controlled, parallel group clinical trials in 9394 adult patients (4425 receiving DALIRESP 500 mcg) 40 years of age and older with COPD. Of the 8 trials, two were placebo-controlled dose selection trials (Trials 1 and 2) of 6 months duration that evaluated the efficacy of DALIRESP 250 mcg and 500 mcg once daily, four were placebo-controlled 1-year trials (Trials 3, 4, 5, and 6) primarily designed to evaluate the efficacy of DALIRESP on COPD exacerbations, and two were 6-month efficacy trials (Trials 7 and 8) which assessed the effect of DALIRESP as add-on therapy to a long-acting beta agonist or long-acting anti-muscarinic. The 8 trials enrolled patients with nonreversible obstructive lung disease (FEV_1/FVC ≤ 70% and ≤ 12% or 200 mL improvement in FEV_1 in response to 4 puffs of albuterol/salbutamol) but the severity of airflow obstruction at baseline was different among the trials. Patients enrolled in the dose selection trials had the full range of COPD severity (FEV1 30-80% predicted); median age of 63 years, 73% male, and 99% Caucasian. Patients enrolled in the four exacerbation trials had severe COPD (FEV_1 ≤ 50% predicted); median age of 64 years, 74% male, and 90% Caucasian. Patients enrolled in the two 6-month efficacy trials had moderate to severe COPD (FEV_1 40-70% predicted); median age of 65 years, 68% male, and 97% Caucasian. COPD exacerbations and lung function (FEV_1) were co-primary efficacy outcome measures in the four 1-year trials. In the two 6-month supportive efficacy trials, lung function (FEV_1) alone was the primary efficacy outcome measure.

The two 6-month dose-selection efficacy trials (Trials 1 and 2) explored doses of 250 mcg and 500 mcg once daily in a total of 1929 patients (751 and 724 on DALIRESP 250 and 500 mcg, respectively). The selection of the 500 mcg dose was primarily based on nominal improvements in lung function (FEV_1) over the 250 mcg dose. The once daily dosing regimen was primarily based on the determination of a plasma half-life of 17 hours for roflumilast and 30 hours for its active metabolite roflumilast N-oxide [*see Clinical Pharmacology (12.3)*].

Effect on Exacerbations

The effect of DALIRESP 500 mcg once daily on COPD exacerbations was evaluated in four 1-year trials (Trials 3, 4, 5, and 6).

Two of the trials (Trials 3 and 4) conducted initially enrolled a population of patients with severe COPD (FEV_1 ≤ 50% of predicted) inclusive of those with chronic bronchitis and/or emphysema who had a history of smoking of at least 10 pack years. Inhaled corticosteroids were allowed as concomitant medications and used in 61% of both DALIRESP and placebo-treated patients and short-acting beta agonists were allowed as rescue therapy. The use of long-acting beta agonists, long-acting anti-muscarinics, and theophylline were prohibited. The rate of moderate or severe COPD exacerbations was a co-primary endpoint in both trials. There was not a symptomatic definition of exac[redacted]n

these 2 trials. Exacerbations were defined in terms of severity requiring treatment with a moderate exacerbation defined as treatment with systemic glucocorticosteroids in Trial 3 or systemic glucocorticosteroids and/or antibiotics in Trial 4 and a severe exacerbation defined as requiring hospitalizations and/or leading to death in Trial 3 or requiring hospitalization in Trial 4. The trials randomized 1176 patients (567 on DALIRESP) in Trial 3 and 1514 patients (760 on DALIRESP) in Trial 4. Both trials failed to demonstrate a significant reduction in the rate of COPD exacerbations.

Exploratory analyses of the results of Trials 3 and 4 identified a subpopulation of patients with severe COPD associated with chronic bronchitis and COPD exacerbations within the previous year that appeared to demonstrate a better response in the reduction of the rate of COPD exacerbations compared to the overall population. As a result, two subsequent trials (Trial 5 and Trial 6) were conducted that enrolled patients with severe COPD but associated with chronic bronchitis, at least one COPD exacerbation in the previous year, and at least a 20 pack-year smoking history. In these trials, long-acting beta agonists and short-acting anti-muscarinics were allowed and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively. The use of inhaled corticosteroids was prohibited. As in trials 3 and 4, the rate of moderate exacerbations (defined as requiring intervention with systemic glucocorticosteroids) or severe exacerbations (defined as leading to hospitalization and/or to death) was a co-primary endpoint.

Trial 5 randomized a total of 1525 patients (765 on DALIRESP) and Trial 6 randomized a total of 1571 patients (772 on DALIRESP). In both trials, DALIRESP 500 mcg once daily demonstrated a significant reduction in the rate of moderate or severe exacerbations compared to placebo (Table 2). These two trials provide the evidence to support the use of DALIRESP for the reduction of COPD exacerbations.

Table 2. Effect of DALIRESP on Rate of Moderate or Severe Exacerbations

Study	Exacerbations Per Patient-Year					
	DALIRESP	Placebo	Absolute Reduction[1]	RR[2]	95% CI	Percent Reduction[3]
Trial 5	1.1	1.3	0.2	0.85	0.74, 0.98	15
Trial 6	1.2	1.5	0.3	0.82	0.71, 0.94	18

1. Absolute reduction measured as difference between placebo and roflumilast treated patients.
2. RR is Rate Ratio.
3. Percent reduction is defined as 100 (1-RR).

For patients in Trials 5 and 6 who received concomitant long-acting beta agonists or short-acting anti-muscarinics, reduction of moderate or severe exacerbations with DALIRESP was similar to that observed for the overall populations of the two trials.

Effect on Lung Function

While DALIRESP is not a bronchodilator, all 1-year trials (Trials 3, 4, 5, and 6) evaluated the effect of DALIRESP on lung function as determined by the difference in FEV_1 between DALIRESP and placebo-treated patients (pre-bronchodilator FEV_1 measured prior to study drug administration in three of the trials and post-bronchodilator FEV_1 measured 30 minutes after administration of 4 puffs of albuterol/salbutamol in one trial) as a co-primary endpoint. In each of these trials DALIRESP 500 mcg once daily demonstrated a statistically significant improvement in FEV_1 which averaged approximately 50 mL across the four trials. Table 3 shows FEV_1 results from Trials 5 and 6 which had demonstrated a significant reduction in COPD exacerbations.

Table 3. Effect of DALIRESP on FEV_1

Study	Change in FEV_1 from Baseline, mL			
	DALIRESP	Placebo	Effect[1]	95% CI
Trial 5	46	8	39	18, 60

Trial 6	33	-25	58	41, 75

[1] Effect measured as difference between DALIRESP and placebo treated patients.

Lung function was also evaluated in two 6-month trials (Trials 7 and 8) to assess the effect of DALIRESP when administered as add-on therapy to treatment with a long-acting beta agonist or a long-acting anti-muscarinic. These trials were conducted in a different population of COPD patients [moderate to severe COPD (FEV_1 40 to 70% of predicted) without a requirement for chronic bronchitis or frequent history of exacerbations] from that for which efficacy in reduction of exacerbations has been demonstrated and provide safety support to the DALIRESP COPD program.

No trials have been conducted to assess the effects of DALIRESP on COPD exacerbations when added to a fixed-dose combination product containing a long-acting beta agonist and inhaled corticosteroid.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DALIRESP is supplied as white to off-white, round tablets, embossed with “D” on one side and “500” on the other side. Each tablet contains 500 mcg of roflumilast.

DALIRESP tablets are available:

Bottles of 30:	NDC 0310-0095-30
Bottles of 90:	NDC 0310-0095-90
2X10 Unit Dose:	NDC 0310-0095-39

16.2 Storage and Handling

Store DALIRESP 500 mcg tablets at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

- **Bronchospasm**

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm. *[see Warnings and Precautions (5.1)].*

- **Psychiatric Events including Suicidality**

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In clinical trials, 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse events were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively). Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo. Cases of suicidal ideation and behavior, including completed suicide, have been observed in the post-marketing setting in patients with or without a history of depression.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior,

prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur *[see Warnings and Precautions (5.2)]*.

- **Weight Decrease**

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo. In two placebo-controlled clinical trials of one year duration in which weight was prospectively assessed, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo and 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered *[see Warnings and Precautions (5.3)]*.

- **Drug Interactions**

The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

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MEDICATION GUIDE

DALIRESP® (da'-li-resp)

(roflumilast)

Tablets

Read this Medication Guide before you start taking DALIRESP® and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about DALIRESP?

DALIRESP can cause serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while taking DALIRESP.

1. **DALIRESP may cause mental health problems including suicidal thoughts and behavior.** Some people taking DALIRESP may develop mood or behavior problems including:

   - thoughts of suicide or dying

- attempt to commit suicide
- trouble sleeping (insomnia)
- new or worse anxiety
- new or worse depression
- acting on dangerous impulses
- other unusual changes in your behavior or mood

2. **Weight loss.** DALIRESP can cause weight loss. You should check your weight on a regular basis. You will also need to see your healthcare provider regularly to have your weight checked. If you notice that you are losing weight, call your healthcare provider. Your healthcare provider may ask you to stop taking DALIRESP if you lose too much weight.

DALIRESP may affect the way other medicines work, and other medicines may affect how DALIRESP works. Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

What is DALIRESP?

DALIRESP is a prescription medicine used in adults with severe Chronic Obstructive Pulmonary Disease (COPD) to decrease the number of flare-ups or the worsening of COPD symptoms (exacerbations).

DALIRESP is not a bronchodilator and should not be used for treating sudden breathing problems. Your healthcare provider may give you other medicine to use for sudden breathing problems.

It is not known if DALIRESP is safe and effective in children.

Who should not take DALIRESP?

Do not take DALIRESP if you:

- have certain liver problems. Talk with your healthcare provider before you take DALIRESP if you have liver problems.

What should I tell my healthcare provider before taking DALIRESP?

Before you take DALIRESP, tell your healthcare provider if you:

- have or have had a history of mental health problems including depression and suicidal behavior.
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if DALIRESP will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if DALIRESP passes into your breast milk. You and your healthcare provider should decide if you will take DALIRESP or breastfeed. You should not do both.

How should I take DALIRESP?

- Take DALIRESP exactly as your healthcare provider tells you to take it.
- DALIRESP can be taken with or without food.
- If you take more than your prescribed dose of DALIRESP, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of DALIRESP?

DALIRESP can cause serious side effects, including:

See "**What is the most important information I should know about DALIRESP?**"

The most common side effects of DALIRESP include:

- diarrhea
- weight loss
- nausea
- headache
- back pain
- flu like symptoms
- problems sleeping (insomnia)
- dizziness
- decreased appetite

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of DALIRESP.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store DALIRESP Tablets?

- **Store DALIRESP at 68°F to 77°F (20°C to 25°C); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature].**

Keep DALIRESP Tablets and all medicines out of the reach of children.

General information about DALIRESP

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DALIRESP for a condition for which it was not prescribed. Do not give DALIRESP to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about DALIRESP. For more information about DALIRESP, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about DALIRESP that is written for health professionals.

For more information about DALIRESP call 1-800-236-9933.

What are the ingredients in DALIRESP?

Active ingredient: roflumilast
Inactive ingredients: lactose monohydrate, corn starch, povidone and magnesium stearate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Principal Display Panel – 30 Tablets Bottle Label

Rx Only NDC 0310-0095-30

Daliresp®

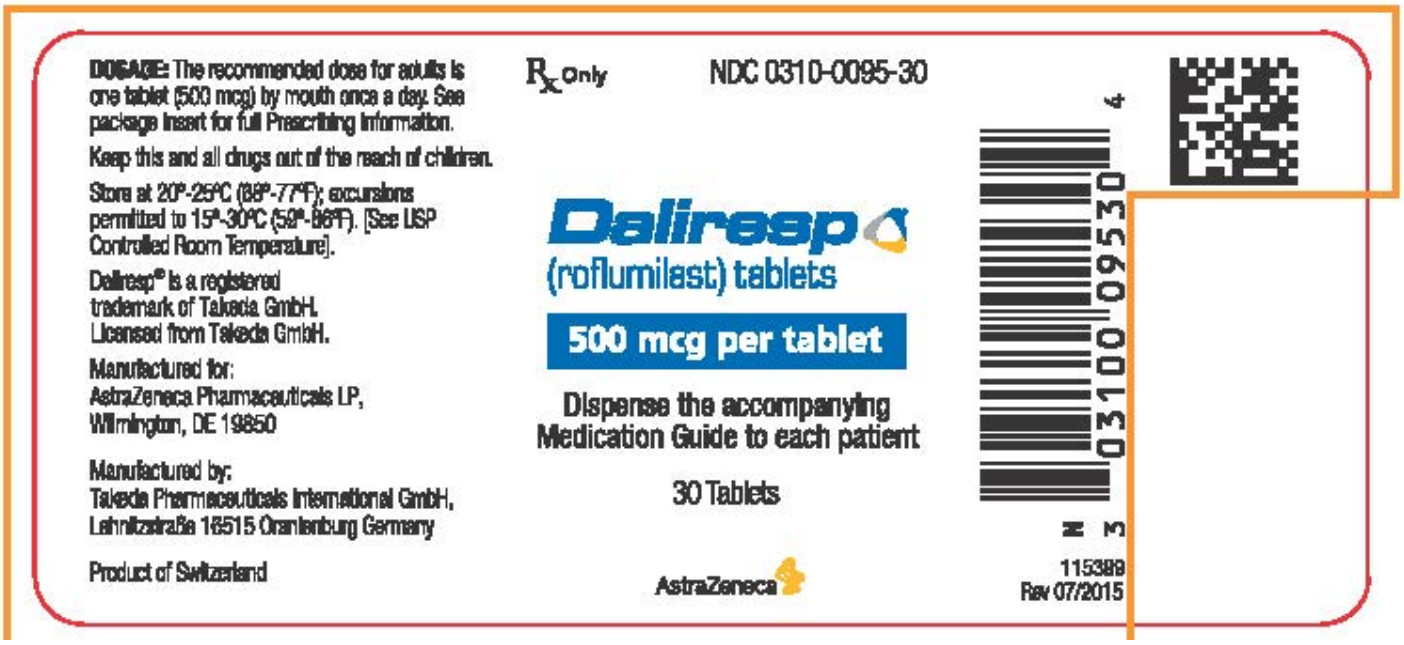
(roflumilast) tablets

500 mcg per tablet

Dispense the accompanying Medication Guide to each patient

30 Tablets

AstraZeneca



Principal Display Panel – Carton Label

Rx Only NDC 0310-0095-39

Daliresp®

(roflumilast) tablets

500 mcg

Each tablet contains 500 mcg of roflumilast.

Dispense the accompanying Medication Guide to each patient.

20 Tablets (2 x 10 blister cards).

APPENDIX VIII. ADVAIR PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADVAIR DISKUS safely and effectively. See full prescribing information for ADVAIR DISKUS.

ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)
ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)
ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)
FOR ORAL INHALATION USE
Initial U.S. Approval: 2000

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. A US trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)**
- **When treating patients with asthma, only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1.1, 5.1)**

----------INDICATIONS AND USAGE----------
ADVAIR DISKUS is a combination product containing a corticosteroid and a LABA indicated for:
- Treatment of asthma in patients aged 4 years and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitation:
- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

---------- DOSAGE AND ADMINISTRATION ----------
For oral inhalation only.
- Treatment of asthma in patients aged 12 years and older: 1 inhalation of ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Inhalation Powder. Inhaler containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

----------CONTRAINDICATIONS----------
- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS----------
- LABA increase the risk of asthma-related death and asthma-related hospitalizations. Prescribe only for recommended patient populations. (5.1)
- Do not initiate in acutely deteriorating asthma or COPD. Do not use to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3)
- *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- If paradoxical bronchospasm occurs, discontinue ADVAIR DISKUS and institute alternative therapy. (5.10)
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta-adrenergic stimulation. (5.12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Monitor growth of pediatric patients. (5.14)
- Close monitoring for glaucoma and cataracts is warranted. (5.15)
- Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥3%) include:
- Asthma: Upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: Pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------
Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2014

[redacted]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

ADVAIR DISKUS is indicated for the treatment of asthma in patients aged 4 years and older.

LABA, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1)]*. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Important Limitation of Use: ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. ADVAIR DISKUS 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength ADVAIR DISKUS 500/50 over ADVAIR DISKUS 250/50 has not been demonstrated.

Important Limitation of Use: ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered as 1 inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

More frequent administration or a greater number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using ADVAIR DISKUS should not use additional LABA for any reason. *[See Warnings and Precautions (5.3, 5.12).]*

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

Adult and Adolescent Patients Aged 12 Years and Older: For patients aged 12 years and older, the dosage is 1 inhalation twice daily, approximately 12 hours apart.

The recommended starting dosages for ADVAIR DISKUS for patients aged 12 years and older are based upon patients' asthma severity.

The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

Improvement in asthma control following inhaled administration of ADVAIR DISKUS can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR DISKUS with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, initiating oral corticosteroids) should be considered.

Pediatric Patients Aged 4 to 11 Years: For patients with asthma aged 4 to 11 years who are not controlled on an inhaled corticosteroid, the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily, approximately 12 hours apart.

2.2 Chronic Obstructive Pulmonary Disease

The recommended dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS 250/50 twice daily, approximately 12 hours apart.

If shortness of breath occurs in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Inhaler containing a foil blister strip of powder formulation for oral inhalation. The strip contains a combination of fluticasone propionate 100, 250, or 500 mcg and salmeterol 50 mcg per blister.

4 CONTRAINDICATIONS

The use of ADVAIR DISKUS is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required *[see Warnings and Precautions (5.2)]*
- Severe hypersensitivity to milk proteins *[see Warnings and Precautions (5.11), Adverse Reactions (6.3), Description (11)]*

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

LABA, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

A large placebo-controlled US trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized double-blind trial that enrolled LABA-naive subjects with asthma to assess the safety of salmeterol 42 mcg twice daily over 28 weeks compared with placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of subjects had been enrolled (N = 26,355), which led to premature termination of the trial. The results of the interim analysis showed that subjects receiving salmeterol were at increased risk for fatal asthma events (see Table 1 and Figure 1). In the total population, a higher rate of asthma-related death occurred in subjects treated with salmeterol than those treated with placebo (0.10% versus 0.02%; relative risk: 4.37 [95% CI: 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in subjects treated with salmeterol than in subjects treated with placebo (0.07% versus 0.01%; relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in subjects treated with salmeterol than those treated with placebo (0.31% versus 0.04%; relative risk: 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in subjects treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American subjects (see Table 1). Given the similar basic mechanisms of action of $beta_2$-agonists, the findings seen in the SMART trial are considered a class effect.

Post-hoc analyses in pediatric subjects aged 12 to 18 years were also performed. Pediatric subjects accounted for approximately 12% of subjects in each treatment arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12% [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

The data from the SMART trial are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR DISKUS, or other long-term asthma control therapy mitigates the risk of asthma-related death.

Table 1. Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (%[a])	**Placebo n (%[a])**	**Relative Risk[b] (95% Confidence Interval)**	**Excess Deaths Expressed per 10,000 Subjects[c] (95% Confidence Interval)**
Total Population[d] Salmeterol: n = 13,176 Placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: n = 9,281 Placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: n = 2,366 Placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

[a] Life-table 28-week estimate, adjusted according to the subjects' actual lengths of exposure to trial treatment to account for early withdrawal of subjects from the trial.

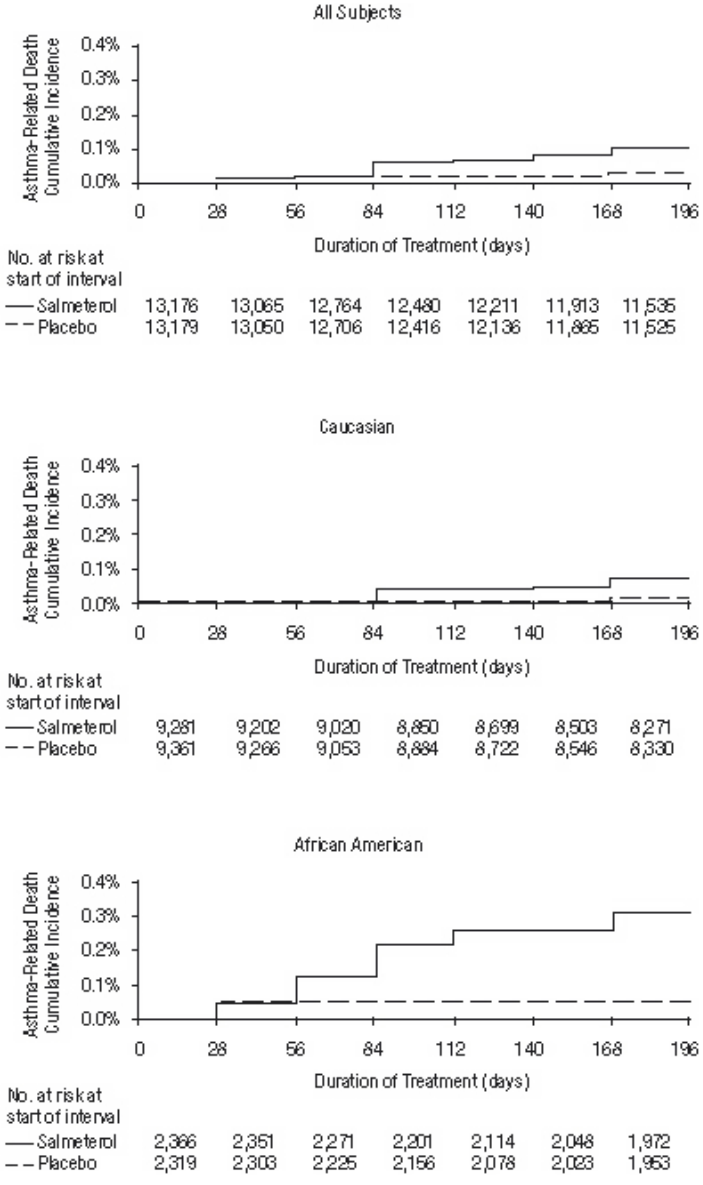
[b] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-

related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[c] Estimate of the number of additional asthma-related deaths in subjects treated with salmeterol in SMART, assuming 10,000 subjects received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[d] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those subjects whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Figure 1. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



A 16-week clinical trial performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) trial, showed results similar to the SMART trial. In the SNS trial, the rate of asthma-related death was numerically, though not statistically significantly, greater in subjects with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol

(180 mcg 4 times daily) added to usual asthma therapy.

The SNS and SMART trials enrolled subjects with asthma. No trials have been conducted that were primarily designed to determine whether the rate of death in patients with COPD is increased by LABA.

5.2 Deterioration of Disease and Acute Episodes

ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. ADVAIR DISKUS has not been studied in subjects with acutely deteriorating asthma or COPD. The initiation of ADVAIR DISKUS in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting $beta_2$-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting $beta_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily of ADVAIR DISKUS.

ADVAIR DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting $beta_2$-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms such as shortness of breath. When prescribing ADVAIR DISKUS, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily use of ADVAIR DISKUS.

When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of ADVAIR DISKUS and Use With Other Long-Acting $Beta_2$-Agonists

ADVAIR DISKUS should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in

association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR DISKUS should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with ADVAIR DISKUS. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with ADVAIR DISKUS continues, but at times therapy with ADVAIR DISKUS may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. In 2 replicate 1-year trials in 1,579 subjects with COPD, there was a higher incidence of pneumonia reported in subjects receiving ADVAIR DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the subjects treated with ADVAIR DISKUS was higher in subjects older than 65 years (9%) compared with the incidence in subjects younger than 65 years (4%). *[See Adverse Reactions (6.2), Use in Specific Populations (8.5).]*

In a 3-year trial in 6,184 subjects with COPD, there was a higher incidence of pneumonia reported in subjects receiving ADVAIR DISKUS 500/50 compared with placebo (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year trials with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in subjects older than 65 years (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with subjects younger than 65 years (14% with ADVAIR DISKUS 500/50 versus 8% with placebo). *[See Adverse Reactions (6.2), Use in Specific Populations (8.5).]*

5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for

complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ADVAIR DISKUS may control asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ADVAIR DISKUS. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ADVAIR DISKUS. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to ADVAIR DISKUS may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ADVAIR DISKUS.

Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with ADVAIR DISKUS should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, ADVAIR DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of asthma symptoms should be considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medicines, ADVAIR DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator; ADVAIR DISKUS should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving ADVAIR DISKUS.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of ADVAIR DISKUS. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not use ADVAIR DISKUS *[see Contraindications (4)]*.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10)]*. Therefore, ADVAIR DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating ADVAIR DISKUS and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

2-Year Fluticasone Propionate Trial: A 2-year trial in 160 subjects (females aged 18 to 40 years, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

3-Year Bone Mineral Density Trial: Effects of treatment with ADVAIR DISKUS 250/50 or salmeterol 50 mcg on BMD at the L_1-L_4 lumbar spine and total hip were evaluated in 186 subjects with COPD (aged 43 to 87 years) in a 3-year double-blind trial. Of those enrolled, 108 subjects (72 males and 36 females) were followed for the entire 3 years. BMD evaluations were conducted at baseline and at 6-month intervals. Conclusions cannot be drawn from this trial regarding BMD decline in subjects treated with ADVAIR DISKUS versus salmeterol due to the inconsistency of treatment differences across gender and between lumbar spine and total hip.

In this trial there were 7 non-traumatic fractures reported in 5 subjects treated with ADVAIR DISKUS and 1 non-traumatic fracture in 1 subject treated with salmeterol. None of the non-traumatic fractures occurred in the vertebrae, hip, or long bones.

3-Year Survival Trial: Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 subjects (females and males aged 40 to 80 years) with COPD in the 3-year survival trial. BMD evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be drawn from this trial because of the large number of dropouts (>50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.

Fracture risk was estimated for the entire population of subjects with COPD in the survival trial (N = 6,184). The probability of a fracture over 3 years was 6.3% for ADVAIR DISKUS, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ADVAIR DISKUS routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, titrate each patient's dosage to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.1), Use in Specific Populations (8.4)]*.

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 subjects with COPD in the 3-year survival trial. Ophthalmic examinations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be drawn from this trial because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of subjects treated with ADVAIR DISKUS 500/50 who were eligible and available for evaluation of cataracts at the end of the trial (n = 53). The incidence of newly diagnosed glaucoma was 2% with ADVAIR DISKUS 500/50, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR DISKUS, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the

introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

ADVAIR DISKUS, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with ADVAIR DISKUS at recommended doses.

6 ADVERSE REACTIONS

LABA, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol *[see Warnings and Precautions (5.1)]*. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1)]*.

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Pneumonia in patients with COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Growth effects *[see Warnings and Precautions (5.14)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Subjects Aged 12 Years and Older: The incidence of adverse reactions associated with ADVAIR DISKUS in Table 2 is based upon two 12-week, placebo-controlled, US clinical trials (Trials 1 and 2). A total of 705 adult and adolescent subjects (349 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo. The average duration of exposure was 60 to 79 days in the active treatment groups compared with 42 days in the placebo group.

Table 2. Adverse Reactions With ADVAIR DISKUS With ≥3% Incidence and More Common Than Placebo in Adult and Adolescent Subjects With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (n = 92) %	ADVAIR DISKUS 250/50 (n = 84) %	Fluticasone Propionate 100 mcg (n = 90) %	Fluticasone Propionate 250 mcg (n = 84) %	Salmeterol 50 mcg (n = 180) %	Placebo (n = 175) %
Ear, nose, and throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea and vomiting	4	6	3	4	1	1
Gastrointestinal discomfort and pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2

Non-site specific Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal Musculoskeletal pain	4	2	1	5	3	3

The types of adverse reactions and events reported in Trial 3, a 28-week non-US clinical trial in 503 subjects previously treated with inhaled corticosteroids who were treated twice daily with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg, were similar to those reported in Table 2.

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by subjects with asthma treated with ADVAIR DISKUS compared with subjects treated with placebo include the following: lymphatic signs and symptoms; muscle injuries; fractures; wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; keratitis and conjunctivitis; dental discomfort and pain; gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory signs and symptoms; pneumonia; muscle stiffness, tightness, and rigidity; bone and cartilage disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms; fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and acquired ichthyosis; disorders of sweat and sebum.

Pediatric Subjects Aged 4 to 11 Years: The safety data for pediatric subjects aged 4 to 11 years is based upon 1 US trial of 12 weeks' treatment duration. A total of 203 subjects (74 females and 129 males) who were receiving inhaled corticosteroids at trial entry were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily. Common adverse reactions (≥3% and greater than placebo) seen in the pediatric subjects but not reported in the adult and adolescent clinical trials include: throat irritation and ear, nose, and throat infections.

Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in ≥1% of subjects in clinical trials. The elevations were transient and did not lead to discontinuation from the trials. In addition, there were no clinically relevant changes noted in glucose or potassium.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Short-Term (6 Months to 1 Year) Trials: The short-term safety data are based on exposure to ADVAIR DISKUS 250/50 twice daily in one 6-month and two 1-year clinical trials. In the 6-month trial, a total of 723 adult subjects (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder, or placebo. The mean age of the subjects was 64, and the majority (93%) was Caucasian. In this trial, 70% of the subjects treated with ADVAIR DISKUS reported an adverse reaction compared with 64% on placebo. The average duration of exposure to

ADVAIR DISKUS 250/50 was 141.3 days compared with 131.6 days for placebo. The incidence of adverse reactions in the 6-month trial is shown in Table 3.

Table 3. Overall Adverse Reactions With ADVAIR DISKUS 250/50 With ≥3% Incidence in Subjects With Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis

Adverse Event	ADVAIR DISKUS 250/50 (n = 178) %	Fluticasone Propionate 250 mcg (n = 183) %	Salmeterol 50 mcg (n = 177) %	Placebo (n = 185) %
Ear, nose, and throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise and fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps and spasms	3	3	1	1

In the two 1-year trials, ADVAIR DISKUS 250/50 was compared with salmeterol in 1,579 subjects (863 males and 716 females). The mean age of the subjects was 65 years, and the majority (94%) was Caucasian. To be enrolled, all of the subjects had to have had a COPD exacerbation in the previous 12 months. In this trial, 88% of the subjects treated with ADVAIR DISKUS and 86% of the subjects treated with salmeterol reported an adverse event. The most common events that occurred with a frequency of >5% and more frequently in the subjects treated with ADVAIR DISKUS were nasopharyngitis, upper respiratory tract infection, nasal congestion, back pain, sinusitis, dizziness, nausea, pneumonia, candidiasis, and dysphonia. Overall, 55 (7%) of the subjects treated with ADVAIR DISKUS and 25 (3%) of the subjects treated with salmeterol developed pneumonia.

The incidence of pneumonia was higher in subjects older than 65 years, 9% in the subjects treated with ADVAIR DISKUS compared with 4% in the subjects treated with ADVAIR DISKUS younger than 65 years. In the subjects treated with salmeterol, the incidence

of pneumonia was the same (3%) in both age-groups. *[See Warnings and Precautions (5.5), Use in Specific Populations (8.5).]*

Long-Term (3 Years) Trial: The safety of ADVAIR DISKUS 500/50 was evaluated in a randomized, double-blind, placebo-controlled, multicenter, international, 3-year trial in 6,184 adult subjects with COPD (4,684 males and 1,500 females). The mean age of the subjects was 65 years, and the majority (82%) was Caucasian. The distribution of adverse events was similar to that seen in the 1-year trials with ADVAIR DISKUS 250/50. In addition, pneumonia was reported in a significantly increased number of subjects treated with ADVAIR DISKUS 500/50 and fluticasone propionate 500 mcg (16% and 14%, respectively) compared with subjects treated with salmeterol 50 mcg or placebo (11% and 9%, respectively). When adjusted for time on treatment, the rates of pneumonia were 84 and 88 events per 1,000 treatment-years in the groups treated with fluticasone propionate 500 mcg and with ADVAIR DISKUS 500/50, respectively, compared with 52 events per 1,000 treatment-years in the salmeterol and placebo groups. Similar to what was seen in the 1-year trials with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in subjects older than 65 years (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with subjects younger than 65 years (14% with ADVAIR DISKUS 500/50 versus 8% with placebo). *[See Warnings and Precautions (5.5), Use in Specific Populations (8.5).]*

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by subjects with COPD treated with ADVAIR DISKUS compared with subjects treated with placebo include the following: syncope; ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection; hypothyroidism; dry eyes; eye infections; gastrointestinal signs and symptoms; oral lesions; abnormal liver function tests; bacterial infections; edema and swelling; viral infections.

Laboratory Abnormalities: There were no clinically relevant changes in these trials. Specifically, no increased reporting of neutrophilia or changes in glucose or potassium was noted.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Endocrine Disorders: Cushing's syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

Eye Disorders: Glaucoma.

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

Infections and Infestations: Esophageal candidiasis.

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

Nervous System Disorders: Paresthesia, restlessness.

Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders: Dysmenorrhea.

Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Vascular Disorders: Pallor.

7 DRUG INTERACTIONS

ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting $beta_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD without adverse drug reactions *[see Clinical Pharmacology (12.2)]*. No formal drug interaction trials have been performed with ADVAIR DISKUS.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of ADVAIR DISKUS, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: *Fluticasone Propionate:* A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations *[see Clinical Pharmacology (12.3)]*. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole: *Fluticasone Propionate:* Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction trial in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta$_2$-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

ADVAIR DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ADVAIR DISKUS with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with ADVAIR DISKUS in pregnant women. Corticosteroids and beta$_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ADVAIR DISKUS.

Fluticasone Propionate and Salmeterol: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum recommended human daily inhalation dose (MRHDID) (on a mg/m^2 basis at a maternal subcutaneous dose of 150 mcg/kg/day) combined with oral salmeterol at a dose approximately 410 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 10 mg/kg/day) produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 40 mcg/kg/day) and doses of salmeterol up to approximately 55 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 1.4 mg/kg/day). In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 100 mcg/kg/day) and a dose of salmeterol at approximately 810 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 10 mg/kg/day) produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining fluticasone propionate subcutaneously at a dose less than the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 30 mcg/kg/day) and an oral dose of salmeterol at approximately 80 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 1 mg/kg/day).

Fluticasone Propionate: Mice and rats at fluticasone propionate doses less than or equivalent to the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 45 and 100 mcg/kg/day, respectively) showed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in rats at doses approximately equivalent to the MRHDID (on a mg/m^2 basis at maternal inhaled doses up to 68.7 mg/kg/day).

In rabbits, fetal weight reduction and cleft palate were observed at a fluticasone propionate dose less than the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 4 mcg/kg/day). However, no teratogenic effects were reported at fluticasone propionate doses up to approximately 5 times the MRHDID (on a mg/m^2 basis at a maternal oral dose up to 300 mcg/kg/day). No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration *[see Clinical Pharmacology (12.3)]*.

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: No teratogenic effects occurred in rats at salmeterol doses approximately 160 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 2 mg/kg/day). In

pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1 mg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 20 times the MRHDID (on an AUC basis at a maternal oral dose of 0.6 mg/kg/day).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 1,600 times the MRHDID on a mg/m^2 basis at a maternal oral dose of 10 mg/kg/day. Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery

There are no well-controlled human trials that have investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of tritiated fluticasone propionate resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing mothers, caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

8.4 Pediatric Use

Use of ADVAIR DISKUS 100/50 in patients aged 4 to 11 years is supported by extrapolation of efficacy data from older subjects and by safety and efficacy data from a trial of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)]*. The safety and effectiveness of ADVAIR DISKUS in children with asthma younger than 4 years have not been established.

Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents *[see Warnings and Precautions (5.14)]*. The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, should be monitored.

A 52-week placebo-controlled trial to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT® ROTADISK®) at 50 and 100 mcg twice daily was

conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the trial revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children in this trial, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The clinical relevance of these growth data is not certain.

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma *[see Dosage and Administration (2.1)]*.

8.5 Geriatric Use

Clinical trials of ADVAIR DISKUS for asthma did not include sufficient numbers of subjects aged 65 years and older to determine whether older subjects with asthma respond differently than younger subjects.

Of the total number of subjects in clinical trials receiving ADVAIR DISKUS for COPD, 1,621 were aged 65 years and older and 379 were aged 75 years and older. Subjects with COPD aged 65 years and older had a higher incidence of serious adverse events compared with subjects younger than 65 years. Although the distribution of adverse events was similar in the 2 age-groups, subjects older than 65 years experienced more severe events. In two 1-year trials, the excess risk of pneumonia that was seen in subjects treated with ADVAIR DISKUS compared with those treated with salmeterol was greater in subjects older than 65 years than in subjects younger than 65 years *[see Adverse Reactions (6.2)]*. As with other products containing beta$_2$-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.

No relationship between fluticasone propionate systemic exposure and age was observed in 57 subjects with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are

predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with renal impairment.

10 OVERDOSAGE

No human overdosage data has been reported for ADVAIR DISKUS.

ADVAIR DISKUS contains both fluticasone propionate and salmeterol; therefore, the risks associated with overdosage for the individual components described below apply to ADVAIR DISKUS. Treatment of overdosage consists of discontinuation of ADVAIR DISKUS together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Propionate

Chronic overdosage of fluticasone propionate may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in subjects were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

10.2 Salmeterol

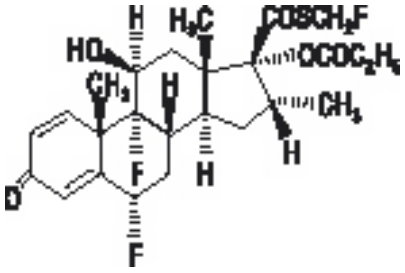
The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias.

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of salmeterol.

11 DESCRIPTION

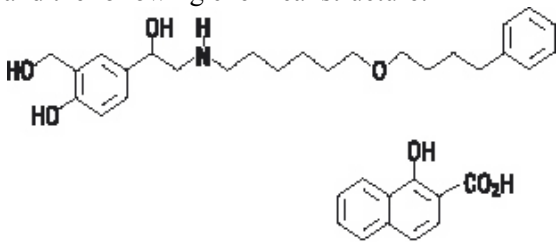
ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate and the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS is a purple plastic inhaler containing a foil blister strip. Each blister on the strip contains a white powder mix of micronized fluticasone propionate (100, 250, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (mean FEV_1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through the DISKUS® inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) subjects with asthma inhaling maximally through the DISKUS inhaler show mean PIF of 122.2 L/min (range: 81.6 to 152.1 L/min). Inhalation profiles for pediatric subjects with asthma inhaling maximally through the DISKUS inhaler show a mean PIF of 75.5 L/min (range: 49.0 to 104.8 L/min) for the 4-year-old subject set (N = 20) and 107.3 L/min (range: 82.8 to 125.6 L/min) for the 8-year-old subject set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADVAIR DISKUS: ADVAIR DISKUS contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors

in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor–induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

12.2 Pharmacodynamics

ADVAIR DISKUS: *Healthy Subjects: Cardiovascular Effects:* Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) trials were conducted with healthy adult subjects: (1) a single-dose crossover trial using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose trial using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose trial for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose trial using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or placebo. In these trials no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in these trials.

Hypothalamic-Pituitary-Adrenal Axis Effects: No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

Subjects With Asthma: Adult and Adolescent Subjects: Cardiovascular Effects: In clinical trials with ADVAIR DISKUS in adult and adolescent subjects aged 12 years and older with asthma, no significant differences were observed in the systemic

pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adult and adolescent subjects with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

Hypothalamic-Pituitary-Adrenal Axis Effects: In a 28-week trial in adult and adolescent subjects with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week trial in adult and adolescent subjects with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo. For most subjects, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One subject (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 subjects (6%) who received placebo, 2 subjects (6%) who received fluticasone propionate 250 mcg, and no subjects who received salmeterol.

In a repeat-dose, 3-way crossover trial, 1 inhalation twice daily of ADVAIR DISKUS 100/50, FLOVENT® DISKUS® 100 mcg (fluticasone propionate inhalation powder, 100 mcg), or placebo was administered to 20 adult and adolescent subjects with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and placebo.

Pediatric Subjects: Hypothalamic-Pituitary-Adrenal Axis Effects: In a 12-week trial in subjects with asthma aged 4 to 11 years who were receiving inhaled corticosteroids at trial entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at trial entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Subjects With Chronic Obstructive Pulmonary Disease: Cardiovascular Effects: In clinical trials with ADVAIR DISKUS in subjects with COPD, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a trial of ADVAIR DISKUS 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250-mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 subjects had a prolonged QTc interval at baseline.

In a 24-week trial, 130 subjects with COPD received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500-mcg treatment groups).

In 24-week clinical trials in subjects with COPD, the incidence of clinically significant ECG abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for subjects who received salmeterol (1%, 9 of 688 subjects who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 were observed on pulse rate and systolic and diastolic blood pressure in a subset of subjects with COPD who underwent 12-hour serial vital sign measurements after the first dose (n = 183) and after 12 weeks of therapy (n = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo.

Hypothalamic-Pituitary-Adrenal Axis Effects: Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 subjects with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most subjects, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) subject (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 subjects (9%) who received fluticasone propionate 250 mcg, 2 subjects (7%) who received salmeterol 50 mcg, and 1 subject (4%) who received placebo following 24 weeks of treatment or early discontinuation from trial.

After 36 weeks of dosing, serum cortisol concentrations in a subset of subjects with COPD (n = 83) were 22% lower in subjects receiving ADVAIR DISKUS 500/50 and 21% lower in subjects receiving fluticasone propionate 500 mcg than in subjects receiving placebo.

Other Fluticasone Propionate Products: *Subjects With Asthma: Hypothalamic-Pituitary-Adrenal Axis Effects:* In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in subjects receiving fluticasone propionate and in subjects receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year trial carried out with

the DISKHALER® inhalation device in 64 subjects with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no subject receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 subject receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another subject receiving fluticasone propionate (5%) had an abnormal response at 2 years. No subject on placebo had an abnormal response at 1 or 2 years.

Subjects With Chronic Obstructive Pulmonary Disease: Hypothalamic-Pituitary-Adrenal Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of subjects with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250- and 500-mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Other Salmeterol Xinafoate Products: *Subjects With Asthma: Cardiovascular Effects:* Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium *[see Warnings and Precautions (5.12, 5.18)]*. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in subjects with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adult and adolescent subjects receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Concomitant Use of ADVAIR DISKUS With Other Respiratory Medications: *Short-Acting $Beta_2$-Agonists:* In clinical trials in subjects with asthma, the mean daily need for albuterol by 166 adult and adolescent subjects aged 12 years and older using ADVAIR DISKUS was approximately 1.3 inhalations/day and ranged from 0 to 9 inhalations/day. Five percent (5%) of subjects using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse events was observed among subjects who averaged 6 or more inhalations per day.

In a clinical trial in subjects with COPD, the mean daily need for albuterol for subjects using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of subjects using ADVAIR DISKUS 250/50 averaged 6 or more inhalations of albuterol per day over the

course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among subjects who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent subjects aged 12 years and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials in subjects with asthma, 39 subjects receiving ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 subjects receiving ADVAIR DISKUS without theophylline. Similar results were observed in subjects receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

In a clinical trial in subjects with COPD, 17 subjects receiving ADVAIR DISKUS 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 subjects receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent subjects aged 12 years and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between subjects who were taking FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

12.3 Pharmacokinetics

Absorption: *Fluticasone Propionate: Healthy Subjects:* Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose crossover trial, a higher-than-recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR® HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 versus 832 pg•h/mL, respectively), but approximately

half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

Subjects With Asthma and COPD: Peak steady-state fluticasone propionate plasma concentrations in adult subjects with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS inhaler. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male subjects with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS inhaler and from 14 female and 43 male subjects with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range: 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (n = 30) and 84 pg/mL (range: 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (n = 27) via the fluticasone propionate DISKUS inhaler. In another trial in subjects with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range: 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via the fluticasone propionate DISKUS inhaler (n = 15) and 105 pg/mL (range: 22.5 to 299.0 pg/mL) via ADVAIR DISKUS (n = 24).

Salmeterol Xinafoate: Healthy Subjects: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.

In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg) and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 versus 169 pg•h/mL) and peak salmeterol concentrations were lower (196 versus 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Subjects With Asthma: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 subjects with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: *Fluticasone Propionate:* Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Salmeterol: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: *Fluticasone Propionate:* The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

Elimination: *Fluticasone Propionate:* Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (greater than 99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR DISKUS.

Special Populations: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 subjects with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the

combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT® HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution.

Age: When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]). However, in clinical trials of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 subjects aged 4 to 57 years. The geometric mean AUC was 325 pg•h/mL (90% CI: 309, 341) in adolescents and adults.

The population pharmacokinetic analysis included 160 subjects with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in clinical trials of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared with adolescents and adults who received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical trials of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and in children, no differences in systemic effects of $beta_2$-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Gender: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In the repeat- and single-dose trials, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given alone or in combination via the DISKUS. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 subjects with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with $beta_2$-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Fluticasone Propionate: In a placebo-controlled crossover trial in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction trial in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects (2

with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: Fluticasone Propionate: In a multiple-dose drug interaction trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose trial in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], $P = 0.12$), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], $P<0.04$), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], $P = 0.34$), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times the MRHDID for adults and children, respectively, on a mg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

No evidence of impairment of fertility was observed in rats at subcutaneous doses up to 50 mcg/kg (less than the MRHDID on a mg/m^2 basis). Prostate weight was significantly reduced.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHDID for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the MRHDID for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Subjects Aged 12 Years and Older: In clinical trials comparing ADVAIR DISKUS with its individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Trials Comparing ADVAIR DISKUS With Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adult and adolescent subjects (aged 12 years and older, baseline FEV_1 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as 1 inhalation from the DISKUS inhaler twice daily, and other maintenance therapies were discontinued.

Trial 1: Clinical Trial With ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, US trial compared ADVAIR DISKUS 100/50 with its individual components, fluticasone propionate 100 mcg and salmeterol 50 mcg. The trial was stratified according to baseline asthma maintenance therapy; subjects were using either inhaled corticosteroids (n = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (n = 106). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled trial. Worsening asthma was defined as a clinically important decrease in FEV_1 or PEF, increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer subjects receiving ADVAIR DISKUS 100/50 were

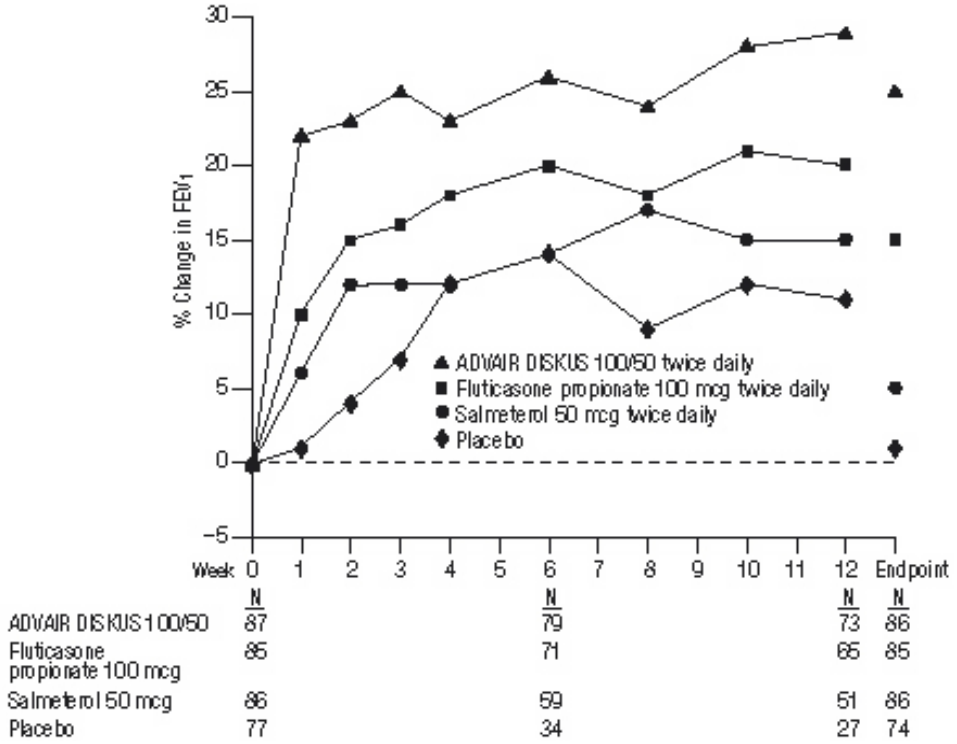
withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 4. Percent of Subjects Withdrawn Due to Worsening Asthma in Subjects Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Trial 1)

ADVAIR DISKUS 100/50 (n = 87)	Fluticasone Propionate 100 mcg (n = 85)	Salmeterol 50 mcg (n = 86)	Placebo (n = 77)
3%	11%	35%	49%

The FEV_1 results are displayed in Figure 2. Because this trial used predetermined criteria for worsening asthma, which caused more subjects in the placebo group to be withdrawn, FEV_1 results at Endpoint (last available FEV_1 result) are also provided. Subjects receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV_1 (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV_1 with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (inhaled corticosteroids or salmeterol).

Figure 2. Mean Percent Change From Baseline in FEV_1 in Subjects With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Trial 1)



The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 5.

Table 5. Peak Expiratory Flow Results for Subjects With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Trial 1)

Efficacy Variable[a]	ADVAIR DISKUS 100/50 (n = 87)	Fluticasone Propionate 100 mcg (n = 85)	Salmeterol 50 mcg (n = 86)	Placebo (n = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

[a] Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on subjects' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Subjects receiving ADVAIR DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared with placebo).

Trial 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US trial compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 subjects with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this trial were similar to those observed in Trial 1. Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV_1 (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer subjects receiving ADVAIR DISKUS 250/50 were withdrawn from this trial for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Subjects receiving ADVAIR DISKUS 250/50 also had clinically meaningful improvements in overall asthma-specific quality of life as described in Trial 1 (difference in AQLQ score of 1.29 compared with placebo).

Trial 3: Clinical Trial With ADVAIR DISKUS 500/50: This 28-week, non-US trial compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 subjects with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the trial. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. Morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled US trials. Following the first dose, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) in most subjects was seen within 30 to 60 minutes. Maximum improvement in FEV_1 generally occurred within 3 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3). Following the initial dose, predose FEV_1 relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in both trials. No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV_1 following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-hour FEV_1 in Subjects With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)

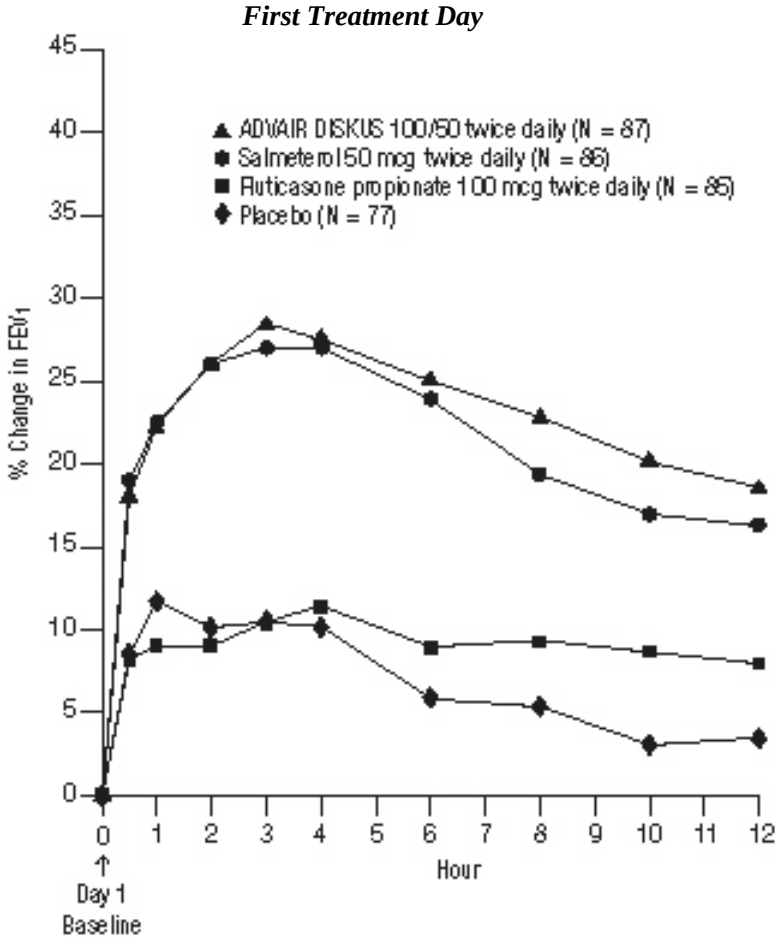
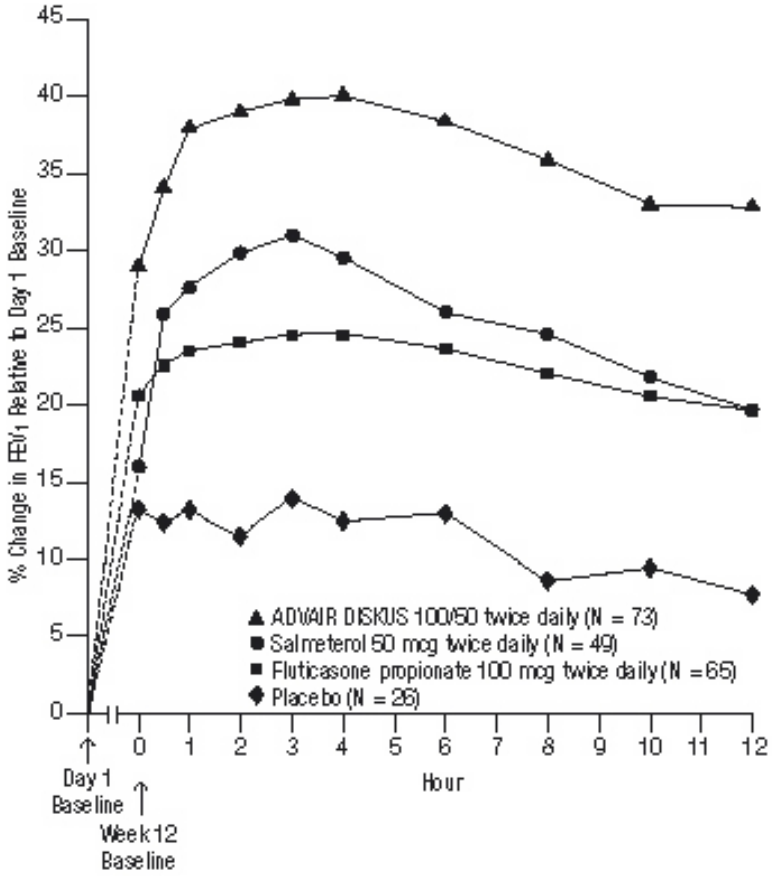


Figure 4. Percent Change in Serial 12-hour FEV_1 in Subjects With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)

Last Treatment Day (Week 12)



Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both trials.

Pediatric Subjects: In a 12-week US trial, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At trial entry, the children were symptomatic on low doses of inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this trial was to determine

the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder 100 mcg in this age-group; however, the trial also included secondary efficacy measures of pulmonary function. Morning predose FEV_1 was obtained at baseline and Endpoint (last available FEV_1 result) in children aged 6 to 11 years. In subjects receiving ADVAIR DISKUS 100/50, FEV_1 increased from 1.70 L at baseline (n = 79) to 1.88 L at Endpoint (n = 69) compared with an increase from 1.65 L at baseline (n = 83) to 1.77 L at Endpoint (n = 75) in subjects receiving fluticasone propionate 100 mcg.

The findings of this trial, along with extrapolation of efficacy data from subjects aged 12 years and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the treatment of asthma in subjects aged 4 to 11 years.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 in the treatment of subjects with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult subjects aged 40 years and older. These trials were primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

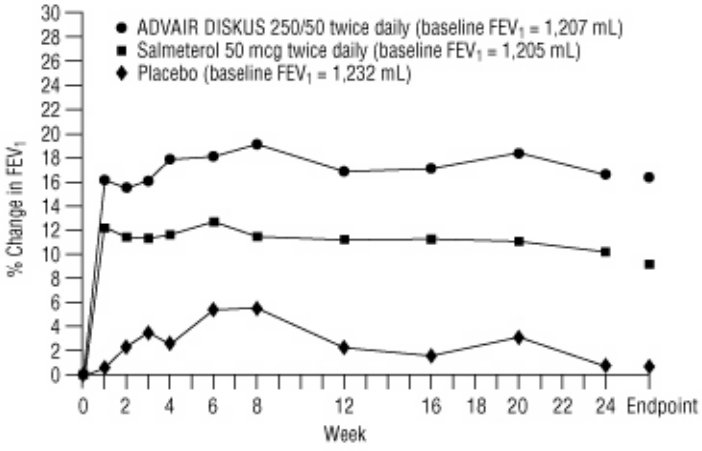
Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function were conducted in 1,414 subjects with COPD associated with chronic bronchitis. In these 2 trials, all the subjects had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One trial evaluated the efficacy of ADVAIR DISKUS 250/50 compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the other trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with its components fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Trial treatments were inhalation powders given as 1 inhalation from the DISKUS inhaler twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The subjects had a mean pre-bronchodilator FEV_1 of 41% and 20% reversibility at trial entry. Percent reversibility was calculated as 100 times (FEV_1 post-albuterol minus FEV_1 pre-albuterol)/FEV_1 pre-albuterol.

Improvements in lung function (as defined by predose and postdose FEV_1) were significantly greater with ADVAIR DISKUS than with fluticasone propionate, salmeterol, or placebo. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50.

Figures 5 and 6 display predose and 2-hour postdose, respectively, FEV_1 results for the trial with ADVAIR DISKUS 250/50. To account for subject withdrawals during the trial, FEV_1 at Endpoint (last evaluable FEV_1) was evaluated. Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV_1 at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5). Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in

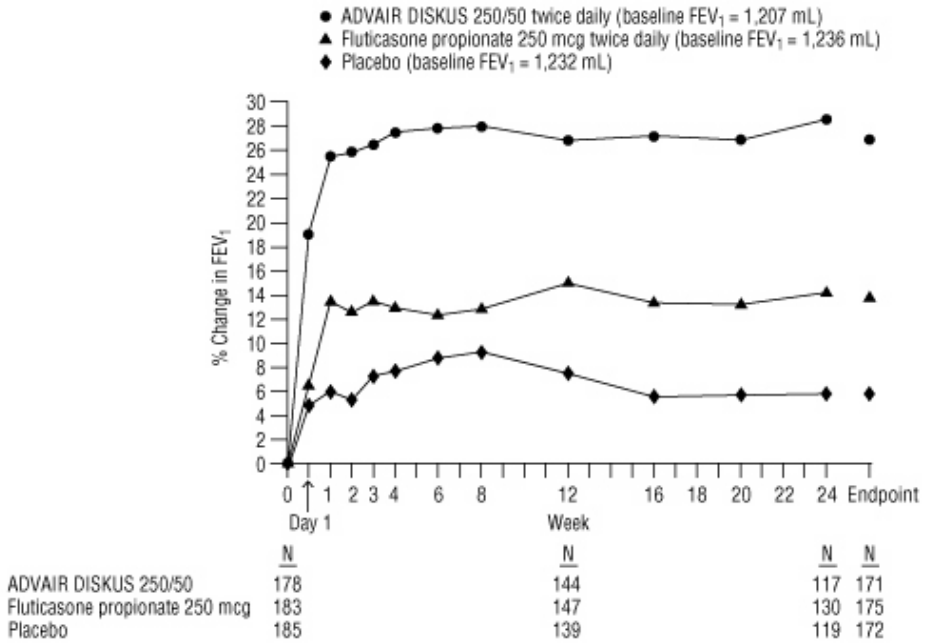
postdose FEV_1 at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 6).

Figure 5. Predose FEV_1: Mean Percent Change From Baseline in Subjects With Chronic Obstructive Pulmonary Disease



	N	N	N	N
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

Figure 6. Two-Hour Postdose FEV_1: Mean Percent Changes From Baseline Over Time in Subjects With Chronic Obstructive Pulmonary Disease



The third trial was a 1-year trial that evaluated ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 subjects. The subjects had an established history of COPD and exacerbations, a pre-bronchodilator FEV_1 <70% of predicted at trial entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-bronchodilator FEV_1 in the groups receiving ADVAIR DISKUS 500/50 or placebo. Subjects treated with ADVAIR DISKUS 500/50 had greater improvements in FEV_1 (113 mL, 10%) compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

Exacerbations: Two trials were primarily designed to evaluate the effect of ADVAIR DISKUS 250/50 on exacerbations. In these 2 trials, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and were considered severe if hospitalization was required.

Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with ADVAIR DISKUS 500/50. There was not a symptomatic definition of exacerbation in these 2

trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

The 2 exacerbation trials with ADVAIR DISKUS 250/50 were identical trials designed to evaluate the effect of ADVAIR DISKUS 250/50 and salmeterol 50 mcg, each given twice daily, on exacerbations of COPD over a 12-month period. A total of 1,579 subjects had an established history of COPD (but no other significant respiratory disorders). Subjects had a pre-bronchodilator FEV_1 of 33% of predicted, a mean reversibility of 23% at baseline, and a history of ≥1 COPD exacerbation in the previous year that was moderate or severe. All subjects were treated with ADVAIR DISKUS 250/50 twice daily during a 4-week run-in period prior to being assigned trial treatment with twice-daily ADVAIR DISKUS 250/50 or salmeterol 50 mcg. In both trials, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], $P<0.001$) in the first trial and (30.4% reduction [95% CI: 16.9, 41.7], $P<0.001$) in the second trial. Subjects treated with ADVAIR DISKUS 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with subjects treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], $P<0.001$) in the first trial and (34.3% reduction [95% CI: 18.6, 47.0], $P<0.001$) in the second trial. Secondary endpoints including pulmonary function and symptom scores improved more in subjects treated with ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both trials.

Exacerbations were evaluated in the 1- and the 3-year trials with ADVAIR DISKUS 500/50 as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when compared with its components (7.5% reduction compared with fluticasone propionate [95% CI: -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with each of the other treatment groups (25.1% reduction compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6, 19.2]).

There were no trials conducted to directly compare the efficacy of ADVAIR DISKUS 250/50 with ADVAIR DISKUS 500/50 on exacerbations. Across trials, the reduction in exacerbations seen with ADVAIR DISKUS 500/50 was not greater than the reduction in exacerbations seen with ADVAIR DISKUS 250/50.

Survival: A 3-year multicenter, international trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo on survival in 6,112 subjects with COPD. During the trial subjects were permitted usual COPD therapy with the exception of other inhaled corticosteroids and long-acting bronchodilators. The subjects were aged 40 to 80 years with an established history of COPD, a pre-bronchodilator FEV_1 <60% of predicted at trial entry, and <10% of predicted reversibility. Each subject who

withdrew from double-blind treatment for any reason was followed for the full 3-year trial period to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival with ADVAIR DISKUS 500/50 was not significantly improved compared with placebo or the individual components (all-cause mortality rate 12.6% ADVAIR DISKUS versus 15.2% placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes, including pulmonary function (post-bronchodilator FEV_1), improved with ADVAIR DISKUS 500/50, salmeterol 50 mcg, and fluticasone propionate 500 mcg compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADVAIR DISKUS 100/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0695-04).

ADVAIR DISKUS 250/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0696-04).

ADVAIR DISKUS 500/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0697-04).

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

ADVAIR DISKUS should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death: **Inform patients with asthma that salmeterol, one of the active ingredients in ADVAIR DISKUS, increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**

Not for Acute Symptoms: Inform patients that ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting $Beta_2$-Agonists: Instruct patients not to use other LABA for asthma and COPD.

Local Effects: Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth with water without swallowing after inhalation is advised to help reduce the risk of thrush.

Pneumonia: Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Advise patients that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS.

Immediate Hypersensitivity Reactions: Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of ADVAIR DISKUS. Patients should discontinue ADVAIR DISKUS if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not take ADVAIR DISKUS.

Reduction in Bone Mineral Density: Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Inform patients that orally inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

GlaxoSmithKline
Research Triangle Park, NC 27709

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MEDICATION GUIDE

ADVAIR DISKUS® [*ad′vair disk′us*] 100/50
(fluticasone propionate 100 mcg and
salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50
(fluticasone propionate 250 mcg and
salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50
(fluticasone propionate 500 mcg and
salmeterol 50 mcg inhalation powder)

Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information. This Medication

Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ADVAIR DISKUS?

ADVAIR DISKUS can cause serious side effects, including:

- **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), have an increased risk of death from asthma problems.** It is not known whether fluticasone propionate, the other medicine in ADVAIR DISKUS, reduces the risk of death from asthma problems seen with LABA medicines.
- **It is not known if LABA medicines such as salmeterol increase the risk of death in people with COPD.**
- **Call your healthcare provider if breathing problems worsen over time while using ADVAIR DISKUS.** You may need different treatment.
- **Get emergency medical care if:**
  - your breathing problems worsen quickly.
  - you use your rescue inhaler, but it does not relieve your breathing problems.
- ADVAIR DISKUS should be used only if your healthcare provider decides that your asthma is not well controlled with a long-term asthma control medicine, such as an inhaled corticosteroid. When your asthma is well controlled, your healthcare provider may tell you to stop taking ADVAIR DISKUS. Your healthcare provider will decide if you can stop ADVAIR DISKUS without loss of asthma control. Your healthcare provider may prescribe a different asthma control medicine for you, such as an inhaled corticosteroid.
- Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is ADVAIR DISKUS?

- ADVAIR DISKUS combines the inhaled corticosteroid (ICS) medicine fluticasone propionate and the LABA medicine salmeterol.
- ICS medicines such as fluticasone propionate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
- LABA medicines such as salmeterol help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest

tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.

- ADVAIR DISKUS is not used to relieve sudden breathing problems.
- It is not known if ADVAIR DISKUS is safe and effective in children younger than 4 years.
- ADVAIR DISKUS is used for asthma and COPD as follows:

  Asthma:

  ADVAIR DISKUS is a prescription medicine used to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children aged 4 years and older.

  ADVAIR DISKUS contains salmeterol [the same medicine found in SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder)]. LABA medicines such as salmeterol increase the risk of death from asthma problems.

  ADVAIR DISKUS is not for adults and children with asthma who are well controlled with an asthma control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.

  COPD:

  ADVAIR DISKUS 250/50 is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ADVAIR DISKUS 250/50 is used long term as 1 inhalation 2 times each day to improve symptoms of COPD for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).

Who should not use ADVAIR DISKUS?

Do not use ADVAIR DISKUS if you:

- have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- are allergic to fluticasone propionate, salmeterol, or any of the ingredients in ADVAIR DISKUS. See “What are the ingredients in ADVAIR DISKUS?” below for a complete list of ingredients.

What should I tell my healthcare provider before using ADVAIR DISKUS?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems.

- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems such as glaucoma or cataracts.
- are allergic to any of the ingredients in ADVAIR DISKUS, any other medicines, or food products. See “What are the ingredients in ADVAIR DISKUS?” below for a complete list of ingredients.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if ADVAIR DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in ADVAIR DISKUS pass into your milk and if they can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take antifungal or anti-HIV medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use ADVAIR DISKUS?

Read the step-by-step instructions for using ADVAIR DISKUS at the end of this Medication Guide.

- **Do not** use ADVAIR DISKUS unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Children should use ADVAIR DISKUS with an adult’s help, as instructed by the child’s healthcare provider.

- ADVAIR DISKUS comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use ADVAIR DISKUS exactly as your healthcare provider tells you to use it. **Do not** use ADVAIR DISKUS more often than prescribed.
- Use 1 inhalation of ADVAIR DISKUS 2 times each day. Use ADVAIR DISKUS at the same time each day, about 12 hours apart.
- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at 1 time.
- If you take too much ADVAIR DISKUS, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **ADVAIR DISKUS does not relieve sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.
  - you need to use 4 or more inhalations of your rescue inhaler in 24 hours for 2 or more days in a row.
  - you use 1 whole canister of your rescue inhaler in 8 weeks.
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using ADVAIR DISKUS regularly for 1 week.

What are the possible side effects with ADVAIR DISKUS?

ADVAIR DISKUS can cause serious side effects, including:

- **See "What is the most important information I should know about ADVAIR DISKUS?"**
- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water without swallowing after using ADVAIR DISKUS to help reduce your chance of getting thrush.
- **pneumonia.** People with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of getting pneumonia. Call your healthcare provider if you notice any of the following symptoms:
  - increase in mucus (sputum) production
  - change in mucus color
  - fever
  - chills
  - increased cough
  - increased breathing problems
- **weakened immune system and increased chance of getting infections (immunosuppression)**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled steroid (such as ADVAIR DISKUS). When your body is under stress such as from fever, trauma (such as a car accident), infection, surgery, or worse COPD symptoms, adrenal insufficiency can get worse and may cause death.

  Symptoms of adrenal insufficiency include:
  - feeling tired
  - lack of energy
  - weakness
  - nausea and vomiting
  - low blood pressure
- **sudden breathing problems immediately after inhaling your medicine**
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems

- **effects on heart**
  - increased blood pressure
  - a fast or irregular heartbeat
  - chest pain
- **effects on nervous system**
  - tremor
  - nervousness
- **bone thinning or weakness (osteoporosis)**
- **slowed growth in children.** A child's growth should be checked often.
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR DISKUS.
- **changes in laboratory blood values (sugar, potassium, certain types of white blood cells)**

Common side effects of ADVAIR DISKUS include:

Asthma:
- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
- bronchitis
- cough
- headache
- nausea and vomiting

In children with asthma, infections in the ear, nose, and throat are common.

COPD:
- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
- throat irritation
- hoarseness and voice changes
- viral respiratory infections
- headache
- muscle and bone pain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with ADVAIR DISKUS. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ADVAIR DISKUS?

- Store ADVAIR DISKUS at room temperature between 68°F and 77°F (20°C and 25°C). Keep in a dry place away from heat and sunlight.
- Store ADVAIR DISKUS in the unopened foil pouch and only open when ready for use.
- Safely throw away ADVAIR DISKUS in the trash 1 month after you open the foil pouch or when the counter reads **0**, whichever comes first.
- **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

General information about ADVAIR DISKUS

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give your ADVAIR DISKUS to other people, even if they have the same condition that you have. It may harm them.

This Medication Guide summarizes the most important information about ADVAIR DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR DISKUS that was written for healthcare professionals.

For more information about ADVAIR DISKUS, call 1-888-825-5249 or visit our website at www.advair.com.

What are the ingredients in ADVAIR DISKUS?

Active ingredients: fluticasone propionate, salmeterol xinafoate
Inactive ingredient: lactose monohydrate (contains milk proteins)

Instructions for Use

For Oral Inhalation Only

Your ADVAIR DISKUS inhaler

Figure A

Read this information before you start using your ADVAIR DISKUS inhaler:

- Take ADVAIR DISKUS out of the foil pouch just before you use it for the first time. Safely throw away the pouch. The DISKUS will be in the closed position.
- Write the date you opened the foil pouch in the first blank line on the label. **See Figure A.**
- Write the "use by" date in the second blank line on the label. **See Figure A.** That date is 1 month after the date you wrote in the first line.
- The counter should read **60**. If you have a sample (with "Sample" on the back label) or institutional (with "INSTITUTIONAL PACK" on the foil pouch) pack, the counter should read **14**.

How to use your ADVAIR DISKUS inhaler

Follow these steps every time you use ADVAIR DISKUS.

Step 1. Open your ADVAIR DISKUS.

- Hold the DISKUS in your left hand and place the thumb of your right hand in the thumb grip. Push the thumb grip away from you as far as it will go until the mouthpiece shows and snaps into place. **See Figure B.**

Step 2. Slide the lever until you hear it click.

- **Hold the DISKUS in a level, flat position** with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it **clicks**. **See Figure C.**

Figure B

Figure C

- The number on the counter will count down by 1. The DISKUS is now ready to use.

Follow the instructions below so you will not accidentally waste a dose:

- **Do not** close the DISKUS.
- **Do not** tilt the DISKUS.
- **Do not** move the lever on the DISKUS.

Step 3. Inhale your medicine.

- Before you breathe in your dose from the DISKUS, breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. **See Figure D.** Do not breathe into the mouthpiece.
- Put the mouthpiece to your lips. **See Figure E.** Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Figure D

Figure E

- Remove the DISKUS from your mouth **and hold your breath for about 10 seconds,** or for as long as is comfortable for you.
- **Breathe out slowly as long as you can. See Figure D.**

- The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. **Do not** take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS.

- Place your thumb in the thumb grip and slide it back towards you as far as it will go. **See Figure F.** Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Figure F

- The DISKUS is now ready for you to take your next scheduled dose in about 12 hours. **When you are ready to take your next dose, repeat Steps 1 through 4.**

Step 5. Rinse your mouth.

- **Rinse your mouth with water after breathing in the medicine.** Spit out the water. Do not swallow it. **See Figure G.**

Figure G

When should you get a refill?

The counter on top of the DISKUS shows you how many doses are left. After you have taken **55** doses (**9** doses from the sample or institutional pack), the numbers **5** to **0** will show in red. **See Figure H.** These numbers warn you there are only a few doses left and are a reminder to get a refill.

Figure H

For correct use of the DISKUS, remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device.

If you have questions about ADVAIR DISKUS or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.advair.com.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

ADVAIR DISKUS, DISKUS, and SEREVENT are registered trademarks of the GSK group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

April 2014
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APPENDIX IX. SYMBICORT PACKAGE INSERT

2791103

SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg)
Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg)
Inhalation Aerosol

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMBICORT safely and effectively. See full prescribing information for SYMBICORT.

SYMBICORT® 80/4.5 *(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol*
SYMBICORT® 160/4.5 *(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol*

FOR ORAL INHALATION
Initial US Approval: 2006

WARNING: ASTHMA-RELATED DEATH *(See full prescribing information for complete boxed warning.)*

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)**
- **When treating patients with asthma, prescribe SYMBICORT only for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (1.1, 5.1)**

RECENT MAJOR CHANGES

Boxed Warning	May 2010
Indications and Usage, Treatment of Asthma (1.1)	May 2010
Dosage and Administration, Asthma (2.1)	May 2010
Warnings and Precautions, Asthma-Related Death (5.1)	May 2010

INDICATIONS AND USAGE

SYMBICORT is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist indicated for:

- Treatment of asthma in patients 12 years of age and older. (1.1)
- Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. (1.2)

Important limitations:

- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- Treatment of asthma in patients ≥12 years: 2 inhalations twice daily of SYMBICORT 80/4.5 or 160/4.5. Starting dosage is based on asthma severity. (2.1)
- Maintenance treatment of airflow obstruction in COPD: 2 inhalations of SYMBICORT 160/4.5 twice daily (2.2)

DOSAGE FORMS AND STRENGTHS

Metered-dose inhaler containing a combination of budesonide (80 or 160 mcg) and formoterol (4.5 mcg) as an inhalation aerosol (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Hypersensitivity to any of the ingredients in SYMBICORT (4)

WARNINGS AND PRECAUTIONS

- Asthma-related death: Long-acting beta$_2$-adrenergic agonists increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia and other potential lung infections. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to SYMBICORT. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue SYMBICORT slowly. (5.8)
- Strong cytochrome P450 3A4 Inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with SYMBICORT. (5.9)
- Paradoxical bronchospasm: Discontinue SYMBICORT and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3%) are:

- Asthma: nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis. (6.1)
- COPD: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, upper respiratory tract infections. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects.
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of formoterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

USE IN SPECIFIC POPULATIONS

Hepatic Impairment: Monitor patients for signs of increased drug exposure. (8)

SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised 05/2012

FULL PRESCRIBING INFORMATION: CONTENTS†

† Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids [see *Warnings and Precautions* (5.1)].

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 12 years of age and older.

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients [see **Warnings and Precautions** (5.1)]. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only approved dosage for the treatment of airflow obstruction in COPD.

Important Limitations of Use: SYMBICORT is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

SYMBICORT should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing [see **Patient Counseling Information** (17.4)].

Prime SYMBICORT before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing two test sprays into the air away from the face.

More frequent administration or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT is not recommended as some patients are more likely to experience adverse effects with higher doses of formoterol. Patients using SYMBICORT should not use additional long-acting beta$_2$-agonists for any reason [see **Warnings and Precautions** (5.3, 5.12)].

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for SYMBICORT for patients 12 years of age and older are based upon patients' asthma severity.

The maximum recommended dosage is SYMBICORT 160/4.5 mcg twice daily.

Improvement in asthma control following inhaled administration of SYMBICORT can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacement with SYMBICORT 160/4.5 may provide additional asthma control.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, (e.g., replacing the lower strength of SYMBICORT with the higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids) should be considered.

2.2 Chronic Obstructive Pulmonary Disease (COPD)

For patients with COPD the recommended dose is SYMBICORT 160/4.5, two inhalations twice daily.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

SYMBICORT is available as a metered-dose inhaler containing a combination of budesonide (80 or 160 mcg) and formoterol (4.5 mcg) as an inhalation aerosol in the following two strengths: 80/4.5 and 160/4.5. Each dosage strength contains 60 or 120 actuations per canister. Each strength of SYMBICORT is supplied with a red plastic actuator with a gray dust cap.

4 CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). This finding with salmeterol is considered a class effect of the LABA, including formoterol, one of the active ingredients in SYMBICORT. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

5.2 Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath. When prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of SYMBICORT.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of SYMBICORT and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional long-acting beta$_2$-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

5.4 Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Patients should rinse the mouth after inhalation of SYMBICORT.

5.5 Pneumonia and Other Lower Respiratory Tract Infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6 month study of 1,704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month study of 1,964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6 month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

5.6 Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta2-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see **Drug Interactions** (7.1), **Clinical Pharmacology** (12.3)].

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see **Overdosage** (10)]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **Dosage and Administration** (2.1), **Use in Specific Populations** (8.4)].

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss

syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

5.17 Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see **Clinical Pharmacology** (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

6 ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **Warnings and Precautions** (5.1)].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **Warnings and Precautions** (5.4)]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **Warnings and Precautions** (5.5)]
- Immunosuppression [see **Warnings and Precautions** (5.6)]
- Hypercorticism and adrenal suppression [see **Warnings and Precautions** (5.8)]
- Growth effects in pediatric patients [see **Warnings and Precautions** (5.14)]
- Glaucoma and cataracts [see **Warnings and Precautions** (5.15)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 mcg N = 277 %**	**160/4.5 mcg N = 124 %**	**80 mcg N = 121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 mcg N = 771 %**	**160 mcg N = 275 %**	**4.5 mcg N = 779 %**	**N = 781 %**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

7 DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

7.1 Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) [see **Warnings and Precautions** (5.9)].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

SYMBICORT

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis.

Budesonide

Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis and in rats at doses approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Umbilical hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Brachygnathia was observed in rat fetuses at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Pregnancy was prolonged at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. No teratogenic effects were observed at oral doses up to 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

8.2 Labor and Delivery

There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [see **Clinical Pharmacology, Pharmacokinetics** (12.3)]. For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness of SYMBICORT in asthma patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily [see **Clinical Studies** (14.1)]. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Overall 1447 asthma patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see **Dosage and Administration** (2)].

8.5 Geriatric Use

Of the total number of patients in asthma clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old and above and of those, 73 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

As with other products containing beta$_2$-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists.

Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment. However, since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

10 OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m^2 basis).

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur [see **Warnings and Precautions** (5)]. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m^2 basis).

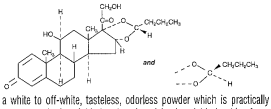
11 DESCRIPTION

SYMBICORT 80/4.5 and SYMBICORT 160/4.5 each contain micronized budesonide and micronized formoterol fumarate dihydrate for oral inhalation only.

Each SYMBICORT 80/4.5 and SYMBICORT 160/4.5 canister is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing either 60 or 120 actuations [see **Dosage Forms and Strengths** (3) and **How Supplied/Storage and Handling** (16)]. After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg, or 160/4.5 mcg (budesonide micronized/formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. SYMBICORT also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

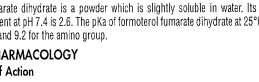
SYMBICORT should be primed before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds before each spray and releasing two test sprays into the air away from the face.

One active component of SYMBICORT is budesonide, a corticosteroid designated chemically as (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder which is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6 x 10^3.

The other active component of SYMBICORT is formoterol fumarate dihydrate, a selective beta$_2$-agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino-ethyl]phenyl]formamide, (E)-2-butenedioate(2:1), dihydrate. The empirical formula of formoterol is $C_{42}H_{56}N_4O_{14}$ and its molecular weight is 840.9. Its structural formula is:



Formoterol fumarate dihydrate is a powder which is slightly soluble in water. Its octanol-water partition coefficient at pH 7.4 is 2.6. The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to SYMBICORT. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Budesonide

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of COPD and asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in COPD and asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85%-95%), and the low potency of formed metabolites.

Formoterol

Formoterol fumarate is a long-acting selective beta$_2$-adrenergic agonist (beta$_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at beta$_2$-receptors than at beta1-receptors. The *in vitro* binding selectivity to beta$_2$- over beta$_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta$_2$-selectivity ratio than formoterol.

Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

12.2 Pharmacodynamics

Asthma

Cardiovascular effects: In a single-dose cross-over study involving 201 patients with persistent asthma, single-dose treatments of 4.5, 9, and 18 mcg of formoterol in combination with 320 mcg of budesonide delivered via SYMBICORT were compared to budesonide 320 mcg alone. Dose-

ordered improvements in FEV_1 were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained postdose. For SYMBICORT, small mean increases in serum glucose and decreases in serum potassium (+0.44 mmol/L and -0.18 mmol/L at the highest dose, respectively) were observed with increasing doses of formoterol, compared to budesonide. In ECGs, SYMBICORT produced small dose-related mean increases in heart rate (approximately 3 bpm at the highest dose), and QTc intervals (3-6 msec) compared to budesonide alone. No subject had a QT or QTc value ≥500 msec.

In the United States, five 12-week, active- and placebo-controlled studies evaluated 2152 patients aged 12 years and older with asthma. Systemic pharmacodynamic effects of formoterol (heart/pulse rate, blood pressure, QTc interval, potassium, and glucose) were similar in patients treated with SYMBICORT, compared with patients treated with formoterol dry inhalation powder 4.5 mcg, two inhalations twice daily. No patient had a QT or QTc value ≥500 msec during treatment.

In three placebo-controlled studies in adolescents and adults with asthma, aged 12 years and older, a total of 1232 patients (553 patients in the SYMBICORT group) had evaluable continuous 24-hour electrocardiographic monitoring. Overall, there were no important differences in the occurrence of ventricular or supraventricular ectopy and no evidence of increased risk for clinically significant dysrhythmia in the SYMBICORT group compared to placebo.

HPA axis effects: Overall, no clinically important effects on HPA axis, as measured by 24-hour urinary cortisol, were observed for SYMBICORT treated adult or adolescent patients at doses up to 640/18 mcg/day compared to budesonide.

Chronic Obstructive Pulmonary Disease:

Cardiovascular effects: In 2 clinical studies, 6 months and 12 months in duration including 3668 COPD patients, no clinically important differences were seen in pulse rate, blood pressure, potassium, and glucose between SYMBICORT, the individual components of SYMBICORT, and placebo. [see **Clinical Studies** (14.2)].

ECGs recorded at multiple clinic visits on treatment in both studies showed no clinically important differences for heart rate, PR interval, QRS duration, heart rate, signs of cardiac ischemia or arrhythmias between SYMBICORT 160/4.5 the monoproducts and placebo, all administered as two inhalations twice daily. Based on ECGs, 6 patients treated with SYMBICORT 160/4.5, 6 patients treated with formoterol 4.5, and 6 patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline. There were no cases of nonsustained ventricular tachycardia in the SYMBICORT 160/4.5, formoterol 4.5, or placebo groups.

In the 12-month study, 520 patients had evaluable continuous 24-hour ECG (Holter) monitoring prior to the first dose and after approximately 1 and 4 months on treatment. No clinically important differences in ventricular or supraventricular arrhythmias, ventricular or supraventricular ectopic beats, or heart rate were observed among the groups treated with SYMBICORT 160/4.5, formoterol or placebo taken as two inhalations twice daily. Based on ECG (Holter) monitoring, one patient on SYMBICORT 160/4.5, no patients on formoterol 4.5, and three patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline.

HPA axis effects: Twenty-four hour urinary cortisol measurements were collected in a pooled subset (n=616) of patients from two COPD studies. The data indicated approximately 30% lower mean 24-hour urinary free cortisol values following chronic administration (>6 months) of SYMBICORT relative to placebo. SYMBICORT appeared to exhibit comparable cortisol suppression to budesonide 160 mcg alone or coadministration of budesonide 160 mcg and formoterol 4.5 mcg. For patients treated with SYMBICORT or placebo for up to 12 months, the percentage of patients who shifted from normal to low for this measure were generally comparable.

Other Budesonide Products

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide, despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Inhaled budesonide has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pretreatment with inhaled budesonide, 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that in both adults and children with asthma the systemic exposure to budesonide is lower with SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler [see **Clinical Pharmacology, Pharmacokinetics, SYMBICORT** (12.3)]. Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler [see **Use in Specific Populations, Pediatric Use** (8.4)].

HPA Axis Effects: The effects of inhaled budesonide administered via a dry powder inhaler on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with budesonide treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13%, respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800, and 1600 mcg of inhaled budesonide twice daily for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10-mg prednisone resulted in a 35% reduction. In this study, no patient on budesonide at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated-cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal- and stimulated-plasma cortisol) of budesonide when administered at recommended doses. In patients who had previously been oral-steroid-dependent, use of budesonide in recommended doses was associated with higher stimulated-cortisol response compared to baseline following 1 year of therapy.

Other Formoterol Products

While the pharmacodynamic effect is via stimulation of beta-adrenergic receptors, excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose. Inhaled formoterol, like other $beta_2$-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [see **Warnings and Precautions** (5)]. For SYMBICORT, these effects are detailed in the **Clinical Pharmacology, Pharmacodynamics, SYMBICORT** (12.2) section.

Use of long-acting $beta_2$-adrenergic agonist drugs can result in tolerance to bronchoprotective and bronchodilatory effects.

Rebound bronchial hyperresponsiveness after cessation of chronic long-acting beta-agonist therapy has not been observed.

12.3 Pharmacokinetics

SYMBICORT

Absorption: *Budesonide: Healthy Subjects:* Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6%-13% due to extensive first pass metabolism. In contrast, most of the budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lung (as assessed by plasma concentration method and using a budesonide-containing dry powder inhaler) with an absolute systemic availability of 39% of the metered dose.

Following administration of SYMBICORT 160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of budesonide generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.32 for budesonide.

Asthma Patients: In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak budesonide plasma concentration of 4.5 nmol/L occurred at 20 minutes following dosing. This study demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of SYMBICORT, the half-life of the budesonide component was 4.7 hours.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak budesonide plasma concentration of 1.2 nmol/L occurred at 21 minutes in asthma patients. Peak budesonide plasma concentration was 27% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of budesonide was comparable to that in asthma patients.

Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both single and repeated dosing of inhaled budesonide.

COPD Patients: In a single-dose study, 12 inhalations of SYMBICORT 80/4.5 mcg (total dose 960/54 mcg) were administered to patients with COPD. Mean budesonide peak plasma concentration of 3.3 nmol/L occurred at 30 minutes following dosing. Budesonide systemic exposure was comparable between SYMBICORT pMDI and coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same higher dose of SYMBICORT. For budesonide, COPD patients exhibited 12% greater AUC and 10% lower C_{max} compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of budesonide was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. Budesonide systemic exposure (AUC and C_{max}) increased proportionally with doses from 80 mcg to 160 mcg and was generally similar between the 3 treatment groups receiving the same dose of budesonide (SYMBICORT pMDI 160/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together).

Formoterol:

Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Healthy Subjects: Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of formoterol generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.77 for formoterol.

Asthma patients: In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentration for formoterol of 136 pmol occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak formoterol plasma concentration of 28 pmol/L occurred at 10 minutes in asthma patients. Peak formoterol plasma concentration was about 42% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of formoterol was comparable to that in asthma patients.

COPD patients: Following single-dose administration of 12 inhalations of SYMBICORT 80/4.5, mean peak formoterol plasma concentration of 167 pmol/L was rapidly achieved at 15 minutes after dosing. Formoterol exposure was slightly greater (~16-18%) from SYMBICORT pMDI compared to coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (total dose of budesonide 960 mcg and formoterol 54 mcg). In the same study, an open label group of moderate asthma patients received the same dose of SYMBICORT. COPD patients exhibited 12-15% greater AUC and Cmax for formoterol compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of formoterol was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5. mcg, formoterol 4.5 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. The systemic exposure of formoterol as evidenced by AUC, was about 30% and 16% higher from SYMBICORT pMDI compared to formoterol alone treatment arm and coadministration of individual components of budesonide and formoterol treatment arm, respectively.

Distribution: *Budesonide:* The volume of distribution of budesonide was approximately 3 L/kg. It was 85%-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood plasma ratio of about 0.8.

Formoterol: Over the concentration range of 10-500 nmol/L, plasma protein binding for the RR and SS enantiomers of formoterol was 46% and 58%, respectively. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

Metabolism: *Budesonide: In vitro* studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Formoterol: The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Elimination: *Budesonide:* Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine.

No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose.

Formoterol: The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces.

Special Populations

Geriatric

The pharmacokinetics of SYMBICORT in geriatric patients have not been specifically studied.

Pediatric

Plasma concentrations of budesonide were measured following administration of four inhalations of SYMBICORT 160/4.5 mcg in a single-dose study in pediatric patients with asthma, 6-11 years of age. Urine was collected for determination of formoterol excretion. Peak budesonide concentrations of 1.4 nmol/L occurred at 20 minutes post-dose. Approximately 3.5% of the delivered formoterol dose was recovered in the urine as unchanged formoterol. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler that was also evaluated at the same delivered dose.

Gender/Race

Specific studies to examine the effects of gender and race on the pharmacokinetics of SYMBICORT have not been conducted. Population PK analysis of the SYMBICORT data indicates that gender does not affect the pharmacokinetics of budesonide and formoterol. No conclusions can be drawn on the effect of race due to the low number of non-Caucasians evaluated for PK.

Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breastfeeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) [see **Use in Specific Populations, Nursing Mothers** (8.3)].

Renal or Hepatic Insufficiency

There are no data regarding the specific use of SYMBICORT in patients with hepatic or renal impairment. Reduced liver function may affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous budesonide pharmacokinetics was, however, similar in cirrhotic patients and in healthy subjects. Specific data with formoterol is not available, but because formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment.

Drug-Drug Interactions

A single-dose crossover study was conducted to compare the pharmacokinetics of eight inhalations of the following: budesonide, formoterol, and budesonide plus formoterol administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of SYMBICORT.

Inhibitors of cytochrome P450 enzymes

Ketoconazole: Ketoconazole, a strong inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide.

Cimetidine: At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Specific drug-drug interaction studies with formoterol have not been performed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Budesonide

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol at oral doses of 0.1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 60 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Other beta-agonist drugs have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2

basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Reproductive Toxicology Studies:

SYMBICORT

SYMBICORT has been shown to be teratogenic and embryocidal in rats when given at inhalation doses of 12/0.66 mcg/kg (budesonide/formoterol) and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed for fetuses at doses of 12/0.66 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No teratogenic or embryocidal effects were detected at 2.5/0.14 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Budesonide

As with other corticosteroids, budesonide has been shown to be teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg/day (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed in rat fetuses at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Pregnancy was prolonged at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol fumarate has been shown to be teratogenic in rabbits when given at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

14 CLINICAL STUDIES

14.1 Asthma

SYMBICORT has been studied in patients with asthma 12 years of age and older. In two clinical studies comparing SYMBICORT with the individual components, improvements in most efficacy end points were greater with SYMBICORT than with the use of either budesonide or formoterol alone. In addition, one clinical study showed similar results between SYMBICORT and the concurrent use of budesonide and formoterol at corresponding doses from separate inhalers.

The safety and efficacy of SYMBICORT were demonstrated in two randomized, double-blind, placebo-controlled US clinical studies involving 1076 patients 12 years of age and older. Fixed SYMBICORT dosages of 160/9 mcg, and 320/9 mcg twice daily (each dose administered as two inhalations of the 80/4.5 and 160/4.5 mcg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information about appropriate dosing to cover a range of asthma severity.

Study 1: Clinical Study with SYMBICORT 160/4.5

This 12-week study evaluated 596 patients 12 years of age and older by comparing SYMBICORT 160/4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, budesonide 160 mcg, formoterol 4.5 mcg, and placebo; each administered as two inhalations twice daily. The study included a 2-week run-in period with budesonide 80 mcg, two inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of inhaled corticosteroids prior to study entry. Randomization was stratified by previous inhaled corticosteroid treatment (71.6% on moderate- and 28.4% on high-dose inhaled corticosteroid). Mean percent predicted FEV_1 at baseline was 68.1% and was similar across treatment groups. The coprimary efficacy end points were 12-hour-average postdose FEV_1 at week 2, and predose FEV_1 averaged over the course of the study. The study also required that patients who satisfied a predefined asthma-worsening criterion be withdrawn. The predefined asthma-worsening criteria were a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in rescue albuterol use, nighttime awakening due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other asthma-worsening criteria were met. The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 3.

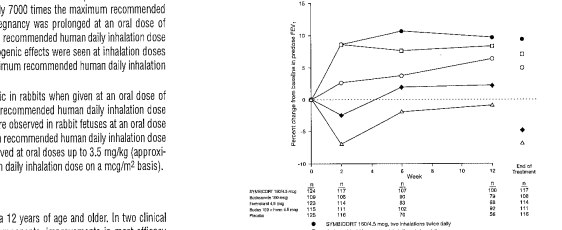
Table 3 The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 1)

	SYMBICORT 160/4.5 mcg n=124	Budesonide 160 mcg plus Formoterol 4.5 mcg n=115	Budesonide 160 mcg n=109	Formoterol 4.5 mcg n=123	Placebo n=125
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event*†	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV_1	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakenings‡	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (13.8)	16 (12.8)

* These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1, which was assessed at each clinic visit.
† Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.
‡ For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in FEV_1 measured immediately prior to dosing (predose) over 12 weeks is displayed in Figure 1. Because this study used predefined withdrawal criteria for worsening asthma, which caused a differential withdrawal rate in the treatment groups, predose FEV_1 results at the last available study visit (end of treatment, EOT) are also provided. Patients receiving SYMBICORT 160/4.5 mcg had significantly greater mean improvements from baseline in predose FEV_1 at the end of treatment (0.19 L, 9.4%), compared with budesonide 160 mcg (0.10 L, 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%), and placebo (-0.17 L, -6.9%).

Figure 1 - Mean Percent Change From Baseline in Pre-dose FEV_1 Over 12 Weeks (Study 1)



The effect of SYMBICORT 160/4.5 mcg two inhalations twice daily on selected secondary efficacy variables, including morning and evening PEF, albuterol rescue use, and asthma symptoms over 24 hours on a 0-3 scale is shown in Table 4.

Table 4 Mean values for selected secondary efficacy variables (Study 1)

Efficacy Variable	SYMBICORT 160/4.5 (n*=124)	Budesonide 160 mcg plus Formoterol 4.5 mcg (n*=115)	Budesonide 160 mcg (n*=109)	Formoterol 4.5 mcg (n*=123)	Placebo (n*=125)
AM PEF (L/min)					
Baseline	341	338	342	339	355
Change from Baseline	35	28	9	-9	-18
PM PEF (L/min)					
Baseline	351	348	357	354	369
Change from Baseline	34	26	7	-7	-18
Albuterol rescue use					
Baseline	2.1	2.3	2.7	2.5	2.4
Change from Baseline	-1.0	-1.5	-0.8	-0.3	0.8
Average symptom score/day (0-3 scale)					
Baseline	0.99	1.03	1.04	1.04	1.08
Change from Baseline	-0.28	-0.32	-0.14	-0.05	0.10

* Number of patients (n) varies slightly due to the number of patients for whom data were available for each variable. Results shown are based on last available data for each variable.

The subjective impact of asthma on patients' health-related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). Patients receiving SYMBICORT 160/4.5 had clinically meaningful improvement in overall asthma-specific quality of life, as defined by a mean difference between treatment groups of >0.5 points in change from baseline in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93], compared to placebo).

Study 2: Clinical Study with SYMBICORT 80/4.5

This 12-week study was similar in design to Study 1, and included 480 patients 12 years of age and older. This study compared SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as two inhalations twice daily. The study included a 2-week placebo run-in period. Most patients had mild to moderate asthma and were using low to moderate doses of inhaled corticosteroids prior to study entry. Mean percent predicted FEV_1 at baseline was 71.3% and was similar across treatment groups. Efficacy variables and end points were identical to those in Study 1.

The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 5. The method of assessment and criteria used were identical to that in Study 1.

Table 5 The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)

	SYMBICORT 80/4.5 (n=123)	Budesonide 80 mcg (n=121)	Formoterol 4.5 mcg (n=114)	Placebo (n=122)
Patients withdrawn due to predefined asthma event*	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)
Patients with a predefined asthma event*†	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)
Decrease in FEV_1	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)
Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)
Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)
Nighttime awakening‡	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

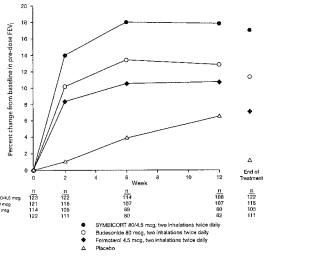
* These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1, which was assessed at each clinic visit.

† Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.

‡ For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in predose FEV_1 over 12 weeks is displayed in Figure 2.

Figure 2 - Mean Percent Change From Baseline in Pre-dose FEV_1 Over 12 Weeks (Study 2)



Efficacy results for other secondary end points, including quality of life, were similar to those observed in Study 1.

Onset and Duration of Action and Progression of Improvement in Asthma Control

The onset of action and progression of improvement in asthma control were evaluated in the two pivotal clinical studies. The median time to onset of clinically significant bronchodilation (>15% improvement in FEV_1) was seen within 15 minutes. Maximum improvement in FEV_1 occurred within 3 hours, and clinically significant improvement was maintained over 12 hours. Figures 3 and 4 show the percent change from baseline in post-dose FEV_1 over 12 hours on the day of randomization and on the last day of treatment for Study 1.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables was maintained over the 12 weeks of therapy.

Following the initial dose of SYMBICORT, FEV1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12 for both studies.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg, as assessed by FEV_1, following 12 weeks of therapy or at the last available visit.

FEV_1 data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in Figures 3 and 4.

Figure 3 - Mean Percent Change From Baseline in FEV_1 on Day of Randomization (Study 1)

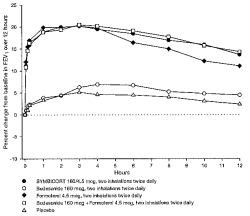
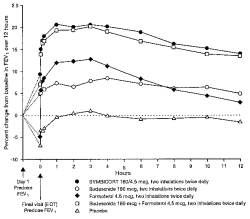


Figure 4 - Mean Percent Change From Baseline in FEV_1 At End of Treatment (Study 1)



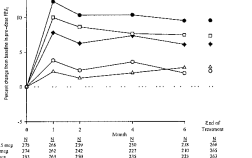
14.2 Chronic Obstructive Pulmonary Disease (COPD)

The efficacy of SYMBICORT 80/4.5 and SYMBICORT 160/4.5 in the maintenance treatment of airflow obstruction in COPD patients was evaluated in two randomized, double-blind, placebo-controlled multinational studies, conducted over 6 months (Study 1) and 12 months (Study 2), in a total of 3668 patients (2416 males and 1252 females). The majority of patients (93%) were Caucasian. All patients were required to be at least 40 years of age, with a FEV_1 of less than or equal to 50% predicted, a clinical diagnosis of COPD with symptoms for at least 2 years, and a smoking history of at least 10 pack years, prior to entering the trial. The mean prebronchodilator FEV_1 at baseline of the patients enrolled in the study was 34% predicted. Forty-eight percent of the patients enrolled were on inhaled corticosteroids and 52.7% of patients were on short-acting anticholinergic bronchodilators during run-in. On randomization, inhaled corticosteroids were discontinued, and ipratropium bromide was allowed at a stable dose for those patients previously treated with short-acting anticholinergic bronchodilators. The co-primary efficacy variables in both studies were the change from baseline in average pre-dose and 1-hour post-dose FEV_1 over the treatment period. The results of both studies 1 and 2 are described below.

Study 1

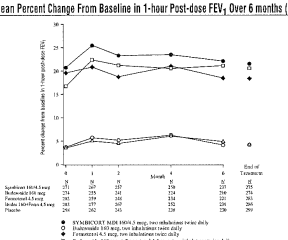
This was a 6-month, placebo-controlled study of 1704 COPD patients (mean % predicted FEV_1 at baseline ranging from 33.5% -34.7%) conducted to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. The patients were randomized to one of the following treatment groups: SYMBICORT 160/4.5 (n=277), SYMBICORT 80/4.5 (n=281), budesonide 160 mcg + formoterol 4.5 mcg (n=287), budesonide 160 mcg (n=275), formoterol 4.5 mcg (n=284), or placebo (n=300). Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater mean improvements from baseline in pre-dose FEV_1 averaged over the treatment period [0.08 L, 10.7%] compared with formoterol 4.5 mcg [0.04 L, 6.9%] and placebo [0.01 L, 2.2%] (See Figure 5). Patients receiving SYMBICORT 80/4.5 mcg, two inhalations twice daily, did not have significantly greater improvement from baseline in the pre-dose FEV_1 averaged over the treatment period compared with formoterol 4.5 mcg.

Figure 5 - Mean Percent Change From Baseline in Pre-dose FEV_1 Over 6 months (Study 1)



Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater mean improvements from baseline in 1-hour post-dose FEV_1 averaged over the treatment period [0.20 L, 22.6%], compared with budesonide 160 mcg [0.03 L, 4.9%] and placebo [0.03 L, 4.1%] (See Figure 6)

Figure 6 Mean Percent Change From Baseline in 1-hour Post-dose FEV_1 Over 6 months (Study 1)



Study 2

This was a 12-month, placebo-controlled study of 1964 COPD patients (mean % predicted FEV_1 at baseline ranging from 33.7% -35.5%) conducted to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. The patients were randomized to one of the following treatment groups: SYMBICORT 160/4.5 (n=494), SYMBICORT 80/4.5 (n=494), formoterol 4.5 mcg (n=495), or placebo (n=481). Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater improvements from baseline in mean pre-dose FEV_1 averaged over the treatment period [0.10 L, 10.8%] compared with formoterol 4.5 mcg [0.06 L, 7.2%] and placebo [0.01 L, 2.8%]. Patients receiving SYMBICORT 80/4.5 mcg, two inhalations twice daily, did not have significantly greater improvements from baseline in the mean pre-dose FEV_1 averaged over the treatment period compared to formoterol. Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, also had significantly greater mean improvements from baseline in 1-hour post-dose FEV_1 averaged over the treatment period [0.21 L, 24.0%] compared with placebo [0.02 L, 5.2%].

Serial FEV_1 measures over 12 hours were obtained in a subset of patients in Study 1 (n=99) and Study 2 (n=121). The median time to onset of bronchodilation, defined as an FEV_1 increase of 15% or greater from baseline, occurred at 5 minutes post-dose. Maximum improvement (calculated as the average change from baseline at each timepoint) in FEV_1 occurred at approximately 2 hours post-dose.

In both Studies 1 and 2, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of SYMBICORT 160/4.5.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBICORT is available in two strengths and is supplied in the following package sizes:

Dosage Forms and Strengths

Package Size			NDC
SYMBICORT	80/4.5,	120 inhalations	0186-0372-20
SYMBICORT	80/4.5,	60 inhalations (institutional pack)	0186-0372-28
SYMBICORT	160/4.5,	120 inhalations	0186-0370-20
SYMBICORT	160/4.5,	60 inhalations (institutional pack)	0186-0370-28

Each strength is supplied as a pressurized aluminium canister with an attached counting device, a red plastic actuator body with a white mouthpiece, and attached gray dust cap. Each 120 inhalation canister has a net fill weight of 10.2 grams and each 60 inhalation canister has a net fill weight of 6.9 grams (SYMBICORT 80/4.5) or 6 grams (SYMBICORT 160/4.5). Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed into a carton. Each carton contains one canister and a Medication Guide.

The SYMBICORT canister should only be used with the SYMBICORT actuator, and the SYMBICORT actuator should not be used with any other inhalation drug product.

The correct amount of medication in each inhalation cannot be ensured after the labeled number of inhalations from the canister have been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of inhalations have been used or within 3 months after removal from the foil pouch. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP]. Store the inhaler with the mouthpiece down.

For best results, the canister should be at room temperature before use. Shake well for 5 seconds before using.

Keep out of the reach of children.

CONTENTS UNDER PRESSURE.

Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures over 120°F may cause bursting. Never throw container into fire or incinerator.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6)

17.1 Asthma-Related Death

Patients with asthma should be informed that formoterol fumarate dihydrate, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. They should also be informed that currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

17.2 Not for Acute Symptoms

SYMBICORT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting $Beta_2$-Agonists

When patients are prescribed SYMBICORT, other long-acting $beta_2$-agonists for asthma and COPD should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with SYMBICORT, but at times therapy with SYMBICORT may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Patients should be advised that SYMBICORT may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to SYMBICORT.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Medication Guide

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France
Product of France
Rev. 5/12 2791103 8/13

AstraZeneca

SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg)
Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg)
Inhalation Aerosol

Read the Medication Guide that comes with SYMBICORT before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMBICORT?

SYMBICORT can cause serious side effects, including:

1. **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines such as formoterol (one of the medicines in SYMBICORT) have an increased risk of death from asthma problems. It is not known whether budesonide, the other medicine in SYMBICORT, reduces the risk of death from asthma problems seen with formoterol.**
   - **Call your healthcare provider if breathing problems worsen over time while using SYMBICORT. You may need different treatment.**
   - **Get emergency medical care if:**
     - breathing problems worsen quickly, and
     - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
2. **SYMBICORT should be used only if your healthcare provider decides that your asthma is not well controlled with a long-term asthma-control medicine, such as an inhaled corticosteroid.**
3. When your asthma is well controlled, your healthcare provider may tell you to stop taking SYMBICORT. Your healthcare provider will decide if you can stop SYMBICORT without loss of asthma control. Your healthcare provider may prescribe a different long-term asthma-control medicine for you, such as an inhaled corticosteroid.
4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is SYMBICORT?

SYMBICORT combines an inhaled corticosteroid medicine, budesonide (the same medicine found in PULMICORT FLEXHALER), and a long-acting beta$_2$-agonist medicine (LABA), formoterol (the same medicine found in FORADIL AEROLIZER).

- Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
- LABA medicines are used in patients with chronic obstructive pulmonary disease (COPD) and asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.

SYMBICORT is used for asthma and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

SYMBICORT is used to control symptoms of asthma, and prevent symptoms such as wheezing in adults and children ages 12 and older.

SYMBICORT contains formoterol (the same medicine found in FORADIL AEROLIZER). LABA medicines such as formoterol increase the risk of death from asthma problems. SYMBICORT is not for adults and children with asthma who:

- are well controlled with an asthma-control medicine such as a low to medium dose of an inhaled corticosteroid medicine
- have sudden asthma symptoms

It is not known if SYMBICORT is safe and effective in children ages 6 to less than 12 years of age with asthma.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. SYMBICORT 160/4.5 mcg is used long term, 2 times each day to help improve lung function for better breathing in adults with COPD.

Who should not use SYMBICORT?

Do not use SYMBICORT:

- to treat sudden severe symptoms of asthma or COPD.
- if you are allergic to any of the ingredients in SYMBICORT. See the end of the Medication Guide for a list of ingredients in SYMBICORT.

What should I tell my healthcare provider before using SYMBICORT?

Tell your healthcare provider about all of your health conditions, including if you:

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**
- **have osteoporosis**
- **have an immune system problem**
- **have eye problems such as increased pressure in the eye, glaucoma, or cataracts**
- **are allergic to any medicines**
- **are exposed to chicken pox or measles**
- **are pregnant or planning to become pregnant.** It is not known if SYMBICORT may harm your unborn baby.
- **are breastfeeding.** Budesonide, one of the active ingredients in SYMBICORT, passes into breast milk. You and your healthcare provider should decide if you will take SYMBICORT while breast-feeding.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMBICORT and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take antifungal and anti-HIV medicines.

Know all the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How do I use SYMBICORT?

See the step-by-step instructions for using SYMBICORT at the end of this Medication Guide. Do not use SYMBICORT unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Use SYMBICORT exactly as prescribed. **Do not use SYMBICORT more often than prescribed.** SYMBICORT comes in 2 strengths. Your healthcare provider has prescribed the strength that is best for you. Note the differences between SYMBICORT and your other inhaled medications, including the differences in prescribed use and physical appearance.
- SYMBICORT should be taken every day as 2 puffs in the morning and 2 puffs in the evening.
- If you miss a dose of SYMBICORT, you should take your next dose at the same time you normally do. Do not take SYMBICORT more often or use more puffs than you have been prescribed.
- Rinse your mouth with water and spit the water out after each dose (2 puffs) of SYMBICORT. Do not swallow the water. This will help to lessen the chance of getting a fungus infection (thrush) in the mouth and throat.
- Do not spray SYMBICORT in your eyes. If you accidentally get SYMBICORT in your eyes, rinse your eyes with water, and if redness or irritation persists, consult your healthcare provider.
- Do not change or stop any medicines used to control or treat your breathing problems. Your healthcare provider will change your medicines as needed.

- **While you are using SYMBICORT 2 times each day, do not use other medicines that contain a long-acting beta$_2$-agonist (LABA) for any reason.**
- Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- SYMBICORT does not relieve sudden symptoms. Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with SYMBICORT
  - you need to use your rescue inhaler medicine more often than usual
  - your rescue inhaler medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of rescue inhaler medicine for 2 or more days in a row
  - you use one whole canister of your rescue inhaler medicine in 8 weeks' time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - your symptoms do not improve after using SYMBICORT regularly for 1 week.

What are the possible side effects with SYMBICORT?

SYMBICORT can cause serious side effects

- See "What is the most important information I should know about SYMBICORT?"
- **Pneumonia and other lower respiratory tract infections.** People with COPD have a higher chance of getting pneumonia and other lung infections. Inhaled corticosteroids may increase the chance of getting pneumonia. Call your healthcare provider if you notice any of these symptoms:
  - increase in mucus (sputum) production
  - change in mucus color
  - fever
  - chills
  - increased cough
  - increased breathing problems
- **Serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- **Immune system effects and a higher chance for infections.**
  Tell your healthcare provider about any signs of infection such as:
  - fever
  - pain
  - body aches
  - chills
  - feeling tired
  - nausea
  - vomiting
- **Adrenal insufficiency.** Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines and start inhaled corticosteroid medicine.
- **Using too much of a LABA medicine may cause:**
  - chest pain
  - increased blood pressure
  - a fast and irregular heartbeat
  - headache
  - tremor
  - nervousness
- **Increased wheezing right after taking SYMBICORT.** Always have a rescue inhaler with you to treat sudden wheezing.
- **Eye problems including glaucoma and cataracts.** You should have regular eye exams while using SYMBICORT.
- **Lower bone mineral density.** This can happen in people who have a high chance for low bone mineral density (osteoporosis). Your healthcare provider should check you for this during treatment with SYMBICORT.
- **Slowed growth in children.** A child's growth should be checked regularly while using SYMBICORT.
- **Swelling of your blood vessels.** This can happen in people with asthma. Tell your healthcare provider right away if you have:
  - a feeling of pins and needles or numbness of your arms or legs
  - flu like symptoms
  - rash
  - pain and swelling of the sinuses
- Decreases in blood potassium levels (hypokalemia)
- Increases in blood sugar levels (hyperglycemia)

Common side effects of SYMBICORT include:

Patients with asthma:

- throat irritation
- upper respiratory tract infection
- inflammation of mucous membranes of the sinuses (sinusitis)
- flu
- nasal congestion
- vomiting
- headache
- throat pain
- back pain
- stomach discomfort
- thrush in the mouth and throat

Patients with COPD:

- throat irritation
- thrush in the mouth and throat
- lower respiratory tract infections, mostly infections and/or inflammation of the mucous membranes of the bronchial tubes (bronchitis)
- inflammation of mucous membranes in the sinuses (sinusitis)
- upper respiratory tract infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects of SYMBICORT. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

You may also report side effects to ASTRAZENECA at 1-800-236-9933.

How do I store SYMBICORT?

- Store SYMBICORT at room temperature between 68°F to 77°F (20°C to 25°C).
- Store with the mouthpiece down.
- The contents of your SYMBICORT canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120°F may cause the canister to burst.
- Throw away SYMBICORT when the counter reaches zero ("0") or 3 months after you take SYMBICORT out of its foil pouch, whichever comes first.
- **Keep SYMBICORT and all medicines out of the reach of children.**

General Information about SYMBICORT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYMBICORT for a condition for which it was not prescribed. Do not give your SYMBICORT to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about SYMBICORT. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SYMBICORT that was written for healthcare professionals. For more information, call 1-800-236-9933 or go to www.MySymbicort.com.

What are the ingredients in SYMBICORT?

Active ingredient: micronized budesonide and micronized formoterol fumarate dihydrate

Inactive ingredients: hydrofluroalkane (HFA 227), povidone K25 USP, and polyethylene glycol 1000 NF

How to Use SYMBICORT

Follow the instructions below for using SYMBICORT. You will breathe-in (inhale) the medicine. If you have any questions, ask your doctor or pharmacist.

SYMBICORT® (budesonide/formoterol) Inhalation Aerosol Medication Guide 14

Preparing your inhaler for use

1. Take your SYMBICORT out of the moisture-protective foil pouch before you use it for the first time and throw the foil away. Write the date that you open the foil pouch on the box.
2. A counter is attached to the top of the metal canister. The counter will count down each time you release a puff of SYMBICORT. The arrow points to the number of inhalations (puffs) left in the canister. The counter will stop counting at zero ("0").

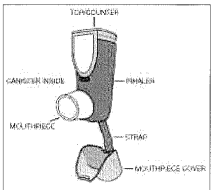


Figure 1
Upright Position

3. Use the SYMBICORT canister only with the red SYMBICORT inhaler supplied with the product. Parts of the SYMBICORT inhaler should not be used with parts from any other inhalation product.
4. Shake your SYMBICORT inhaler well for 5 seconds right before each use. Remove the mouthpiece cover by squeezing gently at both sides, then pulling out (see Figure 2). Check the mouthpiece for foreign objects before use.

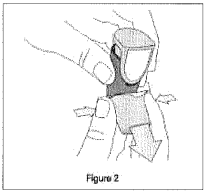


Figure 2

5. **Priming** Before you use SYMBICORT for the first time, you will need to prime it. To prime SYMBICORT, hold it in the upright position. See figure 1 above. Shake the SYMBICORT inhaler well for 5 seconds. Hold your SYMBICORT inhaler facing away from you and then release a test spray. Then shake it again for 5 seconds and release a second test spray. Your SYMBICORT inhaler is now primed and ready for use. After you have primed the SYMBICORT inhaler for the first time, the counter will read either 120 or 60, depending on which size was provided to you.

If you do not use your SYMBICORT inhaler for more than 7 days or if you drop it, you will need to prime again.

Ways to hold the SYMBICORT inhaler for use

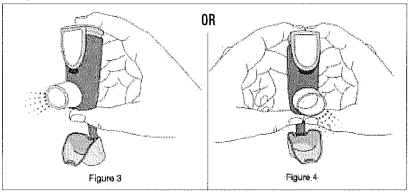


Figure 3 Figure 4

Using your SYMBICORT inhaler

6. Shake your SYMBICORT inhaler well for 5 seconds. Remove the mouthpiece cover. Check the mouthpiece for foreign objects.
7. Breathe out fully (exhale). Hold the SYMBICORT inhaler up to your mouth. Place the white mouthpiece fully into your mouth and close your lips around it. Make sure that the SYMBICORT inhaler is upright and that the opening of the mouthpiece is pointing towards the back of your throat (see Figure 5).

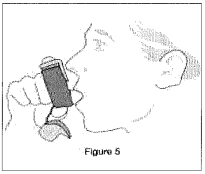


Figure 5

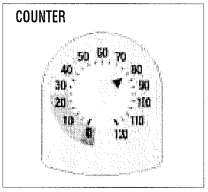
8. Breathe in (inhale) deeply and slowly through your mouth. Press down firmly and fully on the top of the counter on the SYMBICORT inhaler to release the medicine (see Figures 3 and 4).
9. Continue to breathe in (inhale) and hold your breath for about 10 seconds, or for as long as is comfortable. Before you breathe out (exhale), release your finger from the top of the counter. Keep the SYMBICORT inhaler upright and remove from your mouth.
10. Shake the SYMBICORT inhaler again for 5 seconds and repeat steps 7 to 9.

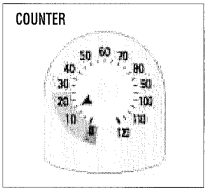
After using your SYMBICORT inhaler

11. After use, close the mouthpiece cover by pushing until it clicks in place.
12. After you finish taking SYMBICORT (two puffs), rinse your mouth with water. Spit out the water. Do not swallow it.

Reading the counter

- The arrow on the counter on the top of the SYMBICORT inhaler points to the number of inhalations (puffs) left in your inhaler.
- The counter will count down each time you release a puff of medicine (either when preparing your SYMBICORT inhaler for use or when taking the medicine).
- When the arrow on the counter approaches 20, you will notice the beginning of a yellow area letting you know that it is time to call your healthcare provider for a refill.
- It is important that you pay attention to the number of inhalations (puffs) left in your SYMBICORT inhaler by reading the counter. Throw away SYMBICORT when the counter shows zero ("0"). Your SYMBICORT inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it. Use a new SYMBICORT inhaler and follow the instructions for priming (instruction 5 above).





How to clean your SYMBICORT inhaler

Clean the white mouthpiece of your SYMBICORT inhaler every 7 days. To clean the mouthpiece:

- Remove the grey mouthpiece cover
- Wipe the inside and outside of the white mouthpiece opening with a clean, dry cloth
- Replace the mouthpiece cover
- **Do not put the SYMBICORT inhaler into water**
- Do not try to take apart your **SYMBICORT** inhaler

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By: AstraZeneca Dunkerque Production, Dunkerque, France
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14.0 REFERENCES

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