AstraZeneca

DRUG PRODUCT	Symbicort Turbuhaler M3	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/Formoterol	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-039-CR-0618		
VERSION NO.	01		
STUDY CODE	SD-039-0618		
DATE	18 October, 2000		

FINAL

Efficacy of Symbicort Turbuhaler® compared with fluticasone Diskus™ in asthmatic patients

STUDY CENTRES

Thirtyseven (37) centres in six countries participated, distributed as follows: Germany 9 centres; Greece 3 centres; Israel 6 centres; the Netherlands 6 centres; Portugal 7 centres and South Africa 6 centres.

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	991101	IIIB
- DATE OF LAST PATIENT COMPLETED	000608	

PUBLICATION (REFERENCE)

Not applicable

OBJECTIVES

The primary objective of the study was to compare the clinical efficacy of Symbicort Turbuhaler, 160/4.5 μg b.i.d., with fluticasone Diskus, 250 μg b.i.d. with respect to the change in morning Peak Expiratory Flow (mPEF) from baseline to a 12 week treatment period.

A secondary objective of the study was to evaluate the cost-effectiveness of the two treatments expressed as cost per episode free day recorded in diary cards and CRF from baseline to a 12 week treatment period. Another secondary objective was to study the safety of Symbicort Turbuhaler assessed as adverse events.

STUDY DESIGN

Multicentre study of a parallel group, double-blind, double-dummy design with patients who despite regular use of inhaled glucocorticosteroids (GCS) was not well controlled.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria

Out-patients (men or women), age 18 years or older with perennial asthma diagnosed at least 6 months before Visit 1. Baseline FEV_1 60-90% of predicted normal. Reversibility in $FEV_1 \geq 12\%$ of baseline. Daily usage of 200-1000 μg inhaled GCSs (dose fixed for 30 days prior to inclusion). Written informed consent.

Exclusion criteria

Significant disease or disorder. Use of oral steroids or significant respiratory infection within 30 days of visit 1. Women who were pregnant, breast-feeding or planning a pregnancy or not using acceptable contraceptives. Tobacco smokers or previous smokers (>10 pack years). Participation in a clinical study within 30 days of visit 1.

Randomisation criteria: Ability to use PEF meter correctly. Baseline diary data (morning PEF data) recorded on at least 7 (any 7) of the last 10 days prior to visit 2.

Criteria for discontinuation: Incorrect inclusion, non-compliance, pregnancy, and patients who needed treatment with β-blockers, oral, inhaled (other than study medication), parenteral, or rectal GCS.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Symbicort (budesonide/formoterol) Turbuhaler® 160/4.5 μg b.i.d. by inhalation. Batch No: AF19 and ZM16.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Fluticasone Diskus™ 250 μg b.i.d. by inhalation. Batch No: WP306T and WP31KR.

DURATION OF TREATMENT

During the two-week run-in period patients received Pulmicort Turbuhaler 200 μg b.i.d. and placebo Diskus b.i.d.

During the twelve-week treatment period patients received either Symbicort Turbuhaler 160/ 4.5 μg b.i.d. or fluticasone Diskus 250 μg b.i.d.

MAIN VARIABLES:

- **EFFICACY**

The primary efficacy variable was morning PEF.

Secondary variables were:

Costs and effectiveness (assessed by use of resources including physician visits, hospitalisation, medication, absence from work, episode free days), evening PEF, asthma symptoms, use of short-acting β_2-agonist day and night, and awakenings as recorded in diary cards, and lung function measurements (FEV_1 and FVC) assessed at the clinics.

- **SAFETY**

Safety was assessed as adverse events.

STATISTICAL METHODS

Diary card data was reduced to one baseline value and one value on treatment by taking period means over the last 10 days during run-in and the whole treatment period. For clinic visit data the last available measurement was used in each period. The basic analysis was an analysis of variance of the value on treatment, using the baseline value as covariate and treatment and country and their interaction as factors. Treatment contrasts was weighted over countries according to precision. Time to first exacerbation was compared between the two groups using a logrank test.

For the cost-effectiveness study, all resource use variables was combined with official prices, to generate the average cost of treatment per patient. Full details on the Health Economics analysis is presented in the Health Economics report.

PATIENTS

	Symbicort	**Fluticasone**	**Total**
No. planned	155	155	310
No. randomized and treated	168	176	344
Males/Females	70/98	78/98	148/196
Mean age (range)	42.6 (18-75)	41.8 (17-74)	42.2 (17-75)
Baseline values			
Mean inhaled GCS dose (μg)	591	597	594
Mean morning PEF	354 (128-647)	363 (121-673)	359 (121-673)
Mean FEV_1 (%predicted)	77.2 (46-124)	79.2 (45-124)	78.2 (45-124)
Mean reversibility (%)	20.5 (12-54)	20.9 (5-60)	20.7 (5-60)
No. analysed for efficacy	168	176	344
No. analysed for safety	168	176	344
No. completed	153	156	309

SUMMARY

- EFFICACY RESULTS

Variable	Treatment	Mean	Difference	95% CL	p-value
Change in morning PEF (L/min)	Symbicort	27.43	19.74	13.61-25.87	<0.001
	fluticasone	7.69			
Change in evening PEF (L/min)	Symbicort	23.98	17.15	11.16 - 23.15	<0.001
	fluticasone	6.83			
Asthma symptoms sum score (0-6)	Symbicort	0.76	-0.09	-0.22 - 0.04	n.s.
	fluticasone	0.85			
Change in β_2-agonist inhalations	Symbicort	-0.31	-0.18	-0.35 - -0.01	0.042
	fluticasone	-0.13			
Nighttime awakening due to asthma (%)	Symbicort	7.95	-1.69	-4.55 - 1.16	n.s.
	fluticasone	9.64			
Symptom free days (%)	Symbicort	60.41	4.89	-1.13 - 10.91	n.s.
	fluticasone	55.52			
Rescue use free days (%)	Symbicort	75.46	9.09	3.85 - 14.32	<0.001
	fluticasone	66.37			
Asthma control days (%)	Symbicort	57.77	5.38	-1.05 - 11.81	n.s.
	fluticasone	52.39			

There was a shorter time to the first mild exacerbation in the fluticasone treated patients compared to Symbicort.

For the effectiveness variable (episode free days) there was no difference between the two treatment groups. Overall the Symbicort treatment group had lower healthcare use and fewer days absent from work than fluticasone. The results of this in terms of cost-effectiveness is presented in a separate health economics report.

- SAFETY RESULTS

The AEs had a similar distribution between the treatment groups.