AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort Turbuhaler
ACTIVE INGREDIENT: **B**udesonide/Formoterol

Study No: NCT01232335

Developmental Phase: post-marketing
Study Completion Date: June 2013
Date of Report: December 2013

OBJECTIVES:

The purpose to confirm ADR development condition by long-term use (observation period: 1 year), safety at the maximum dose (8 DF/day), and asthma control level by long-term use under actual use of Symbicort.

METHODS: Observational Study

RESULTS:

1. Safety

1) Adverse drug reactions (ADRs) were confirmed in 144 of 1382 safety evaluable patients (10.4%). ADRs reported for more than 5 patients were Palpitations (28 patients, 2.0%), Dysphonia (25 patients, 1.8%), Tremor (13 patients, 0.9%), Muscle spasms (8 patients, 0.6%), Asthma (7 patients, 0.5%), Oral candidasis (6 patients, 0.4%), and Stomatitis (5 patients, 0.4%). Serious ADRs were reported in 10 patients (0.7%): Pneumonia (3 patients), Asthma (3 patients), Asthma bronchial (2 patients), Bronchitis (1 patient), Syncope (1 patient), Hypertension (1 patient), Chronic obstructive pulmonary disease (1 patient), Respiratory failure (1 patient), and Muscle spasms (1 patient). As the causality with the underlying disease (bronchial asthma) or the concomitant disease(s) such as chronic obstructive pulmonary disease was suspected, no new measures should be taken. Regarding ADR development by onset period, no increase of ADR incidence was recognized with long-term administration.

Unexpected ADRs reported for more than 3 patients were Asthma (7 patients, 0.5%) and Stomatits (5 patients, 0.4%). As the causality was suspected for the underlying disease or other factors in all cases, and as the numbers of reported events were small, no new measures should be taken.

2) Serious AEs were confirmed in 50 of 1382 patients (3.6%). The main AEs were Asthma in 14 patients (1.0%) and Pneumonia in 10 patients (0.7%). Regarding serious asthma-related AEs (Asthma, Cough, and Dyspnoea), 20 events were reported in 16 patients (1.2%) without fatal case. Regarding serious lung infection-related AEs (Pneumonia, Bronchopneumonia, and Bronchopulmonary aspergillosis), 15 events were reported in 11 patients (0.8%) including predominantly patients with COPD and elderly patients.

3) In the ADR development by patient background factor and by treatment factor, significant difference in the ADR incidence ($p<0.05$) was recognized for sex ($p=0.0184$), severity prior to this drug (Fisher's exact probability test: $p=0.1107$, Cochran-Armitage test: $p=0.0248$), with/without atopic predisposition ($p=0.0069$), dosage of combination of ICS/LABA as previous therapeutic drug for asthma (Fisher's exact probability test: $p=0.0409$, Cochran-Armitage test: $p=0.7766$), with/without concomitant disease ($p=0.0009$), maximum daily dose (Fisher's exact probability test: $p=0.0001$, Cochran-Armitage test: $p<0.0001$), average daily dose (Fisher's exact probability test: $p=0.1658$, Cochran-Armitage test: $p=0.0301$), and with/without concomitant drug ($p=0.0209$). As the result of reviewing these factors, no new issue requiring any new measures was found.

4) The key investigation items were examined: i) safety at the maximum dose (8 DF/day), ii) ADRs possibly related to the pharmacological action of beta 2 stimulant, iii) systemic ADRs possibly related to steroid.

i) The number of patients who took the maximum daily dose (8 DF/day) was 727 (52.6%), and the ADR incidence was 13.6% (99/727 patients). A significant increasing tendency of ADR incidence was recognized as the daily dose increased. The same result was shown in the CEI of Symbicort.

ii) Sixty events of ADRs possibly related to the pharmacological action of beta 2 stimulant were reported in 51 patients (3.7%). The ADRs were Palpitations (28 patients, 2.0%), Tremor (13 patients, 0.9%), Muscle spasms (8 patients, 0.6%), Headache (2 patients, 0.1%), Hypertension (2 patients, 0.1%), Blood pressure increased (2 patients, 0.1%), Essential tremor (1 patient, 0.1%), Atrial fibrillation (1 patient, 0.1%), Muscle twitching (1 patient, 0.1%), and Blood potassium decreased (1 patient, 0.1%). All of these ADR events except Hypertension (1 patient) and Muscle spasms (1 patient) were non-serious, and the outcomes were recovery for 43 events, improvement for 10 events, and not-recovered for 7 events. The ADRs occurred more frequently in the female patients compared to the male patients, and the incidence increased as the number of doses increased.

However, as the package insert has already included 'Palpitations, Tremor, Muscle spasm, Headache, Atrial fibrillation, Blood pressure increased and serious Hypokalaemia for attention attracting in the section of 4. Adverse Drug Reactions of Precautions for Use, and as most of the reported events were non-serious, no new measures should be taken.

iii) Fifty-two events of ADRs possibly related to steroid were reported in 45 patients (3.3%). The ADRs were Dysphonia (25 patients, 1.8%), Oral candidasis (6 patients,

0.4%), Bronchitis (3 patients, 0.2%), Pharyngitis (3 patients, 0.2%), Pneumonia (3 patients, 0.2%), Bronchopneumonia (2 patients, 0.1%), Blood cortisol decreased (2 patients, 0.1%), Laryngitis (1 patient, 0.1%), Nasopharyngitis (1 patient, 0.1%), Oropharyngeal candidiasis (1 patient, 0.1%), Cushingoid (1 patient, 0.1%), and Upper respiratory tract inflammation (1 patient, 0.1%). The ADR events other than Pneumonia (3 events), Bronchopneumonia (2 events), and Bronchitis (1 event) were non-serious, and the outcomes were recovery for 31 events, improvement for 9 events, not-recovered for 4 events, and unknown for 8 events. As for systemic ADRs possibly related to steroid, there was no issue requiring any new measures.

3. Efficacy

In this investigation, to grasp the asthma-control level under actual long-term use of Symbicort, ACQ scores, SABA use and its frequency, and peak flow rate were checked before and after Symbicort treatment.

1) Regarding 579 patients whose ACQ scores at the start of Symbicort and Year 1 are available, the mean variation of ACQ score from the start to Year 1 was -1.70 +- 1.52, indicating significant decrease of ACQ score at Year 1 compared to that at the start ($p<0.0001$). The same result was obtained for the mean variation of ACQ score from the start of Symbicort to Week 24/the end of the drug.
2) As the result of reviewing the mean variation of ACQ scores from the start of Symbicort to Year 1 by patient background factor and by treatment factor, significant difference was recognized for age ($p=0.0460$), severity prior to this drug ($p=0.0084$), smoking history ($p=0.0025$), with/without previous therapeutic drug for asthma ($p<0.0001$), with/without concomitant disease ($p<0.0474$), duration of illness ($p=0.0405$), maximum daily dose ($p=0.0002$), and mean daily dose ($p=0.0293$). However, in the all sub-groups with small variation, the ACQ score at Year 1 decreased significantly compared to that at the start ($p<0.05$), thus there should be no problem.
3) Regarding SABA use and its frequency, and peak flow rate, significant improvement was confirmed at Week 24, Year 1, or at the end of treatment compared to the start of Symbicort, as same as the change of mean variation of ACQ score.

As the results of the investigation stated above, the safety and efficacy of Symbicort under actual long-term use was confirmed, and no new issue was recognized.