AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

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

Study No: NCT01232348

Developmental Phase: post-marketing
Study Completion Date: October 2011
Date of Report: November 2012

OBJECTIVES:

The purpose of this study is to confirm the safety (ADR related to beta stimulant drugs, unexpected ADRs) and efficacy of Symbicort in daily practice and the control status on bronchial asthma and Patient satisfaction.

METHODS: Observational Study

RESULTS:

1.Safety

1) Adverse drug reactions (ADRs) were confirmed in 87 of 3212 safety evaluable patients (2.7%). ADRs reported for more than 5 patients were Dysphonia (18 patients, 0.6%), Palpitations (10 patients, 0.3%), Tremor (8 patients, 0.2%), and Asthma (8 patients, 0.2%), all of which were non-serious. Serious ADRs were reported in 3 patients (0.1%): Pneumonia (1 patient), Pulmonary tuberculosis (1 patient), and Abortion (1 patient), in all of which the causality with Symbicort was unclear.

Unexpected ADRs were Asthma (8 patients), Dysgeusia (4 patients), Cystitis (1 patient), Pulmonary tuberculosis (1 patient), Amnesia (1 patient), Trigeminal neuralgia (1 patient), Tinnitus (1 patient), Sputum increased (1 patient), Cheilitis (1 patient), Stomatitis (1 patient), Buccal mucosal roughening (1 patient), Hyperhidrosis (1 patient), Back pain (1 patient), Abortion (1 patient), Chest discomfort (1 patient), and Blood

cortisol decreased (1 patient). As the causality was suspected for the underlying disease or other factors in all cases, and as the number of reported events were small, no new measures should be taken presently.

2) In the ADR development by patient background factor and by treatment factor, significant difference in the ADR incidence ($p<0.05$) was recognized for age ($p=0.0039$), severity prior to this drug (Fisher's exact probability test: $p=0.0011$, Cochran-Armitage test: $p=0.0002$), with/without concomitant disease ($p=0.0005$), maximum daily dose (Fisher's exact probability test: $p=0.0050$, Cochran-Armitage test: $p=0.0008$) and with/without concomitant drug ($p=0.0005$). As the result of reviewing these factors, no new issue requiring any new measures was found.

3) Regarding ADR development at switching from previous therapeutic drug for asthma (maintenance drug) to Symbicort, it was examined for each previous therapeutic drug by Symbicort administration pattern (switching or addition) and by initiation dose of Symbicort. As the result, no obvious issue was found.

4) The key investigation items were examined: i) ADRs possibly related to the pharmacological action of beta 2 stimulant, ii) systemic ADRs possibly related to steroid.

i) Twenty-six events of ADRs possibly related to the pharmacological action of beta 2 stimulant were reported in 25 patients (0.8%). The ADRs were Palpitations (10 patients, 0.3%), Tremor (8 patients, 0.2%), Muscle spasm (3 patients, 0.1%), Headache (2 patients, 0.1%), Hypoklaemia (1 patient, 0.03%), Supraventricular extrasystoles (1 patient, 0.03%), and Tachycardia (1 patient, 0.03%). All of these ADR events were non-serious, which outcomes were recovery for 21 events, improvement for 3 events, and unknown for 2 events.

The ADR incidences were examined by the maximum daily dose. As the result, it was confirmed that the incidences increased significantly as the dose increased (Fisher's exact probability test: $p=0.0009$, Cochran-Armitage test: $p=0.0002$). However, as the package insert has already included 'Palpitations, Tremor, Muscle spasm, Headache, Extrasystoles, Tachycardia' for attention attracting in the section of 4. Adverse Drug Reactions of Precautions for Use, and as all of the reported events were non-serious, no new measures should be taken.

ii) Thirty-four events of ADRs possibly related to steroid were reported in 32 patients (1.0%). The ADRs were Dysphonia (18 patients, 0.6%), Bronchitis (4 patients, 0.1%), Nasopharyngitis (2 patients, 0.1%), Pharyngitis (2 patients, 0.1%), Pneumonia (2 patients, 0.1%), Oral candidasis (1 patient, 0.03%), Pulmonary tuberculosis (1 patient, 0.03%), Tonsilitis (1 patient, 0.03%), Oropharyngeal candidasis (1 patient, 0.03%), and Blood cortisol decreased (1 patient, 0.03%). The outcomes were recovery for 22 events, improvement for 6 events, and not-recovered or unknown for 3 events. The events of ADRs other than Pneumonia (1 event) and Pulmonary tuberculosis (1 event) were non-serious. Regarding the serious events of pneumonia and pulmonary tuberculosis, the causality with Symbicort was unclear. Therefore, no new measures should be taken for systemic ADRs possibly related to steroid.

2 .Efficacy

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

1) Regarding 1902 patients whose ACQ scores at the start of Symbicort and Week 12 are available, the mean variation of ACQ score from the start to Week 12 was -1.61 +- 1.23, indicating significant decrease of ACQ score at Week 12 compared to that at the start ($p<0.0001$).

Regarding 2739 patients whose ACQ scores at the start and the end (Week 12 or at the time of discontinuation) of Symbicort are available, the mean variation of ACQ score from the start to the end was -1.65 +- 1.25, indicating significant decrease of ACQ score at the end compared to that at the start as same as at Week 12 ($p<0.0001$).

2) As the result of reviewing the mean variation of ACQ scores from the start of Symbicort to Week 12 by patient background factor and by treatment factor, significant difference was recognized for sex ($p=0.0072$), age ($p=0.0009$), severity prior to this drug ($p<0.0001$), smoking history ($p=0.0074$), with/without previous therapeutic drug for asthma ($p<0.0001$), with/without concomitant disease ($p<0.0001$), duration of illness ($p<0.0001$), maximum daily dose ($p<0.0001$), and mean daily dose ($p=0.0112$). However, even in the sub-group with small variation, the ACQ score at Week 12 decreased significantly compared to that at the start ($p<0.0001$), thus there should be no problem.

3) Regarding patient satisfaction, SABA use and its frequency, and peak flow rate, significant improvement was confirmed at Week 12 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 use was confirmed, and no new issue was recognized.