

Public Assessment Report Scientific discussion

**Symbicort Turbuhaler, 160 micrograms/4.5
micrograms/inhalation, Symbicort mite
Turbuhaler, 80 micrograms/4.5
micrograms/inhalation, Symbicort forte
Turbuhaler, 320 micrograms/9
micrograms/inhalation, inhalation powder
(Budesonide/Formoterol)**

SE/H/229/01/E02

SE/H/230/01/E01

SE/H/229/02/E02

This module reflects the scientific discussion for the approval of Symbicort Turbuhaler, Symbicort mite Turbuhaler, and Symbicort forte Turbuhaler. The procedures were finalised at August 3, 2010 (day 90). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

AstraZeneca has applied for a Repeat Use Mutual Recognition Procedure (MRP), following on from the initial MRP application with approval in RMS Sweden, August 25, 2000, for Symbicort mite Turbuhaler 80 micrograms/4.5 micrograms/inhalation, Symbicort Turbuhaler 160 micrograms/4.5 micrograms/inhalation, and Symbicort forte Turbuhaler 320 micrograms/9 micrograms/inhalations. The repeat use MRP application aims to incorporate 12 Member States into the existing MRP license in the European Union (EU). The product Symbicort Turbuhaler is presently approved in all of these Member States via the National procedure in respective country. The active substances are the steroid budesonide and the long-acting beta-2-agonist formoterol fumarate dihydrate. For approved indications, see the Summary of Product Characteristics.

This Marketing Authorisation Application concerns Symbicort Turbuhaler via Repeat Use Mutual Recognition Procedure for the following countries: Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia and Slovenia.

II. QUALITY ASPECTS

II.1 Introduction

Symbicort Turbuhaler, 80 micrograms/4.5 micrograms/inhalation, 160 micrograms/4.5 micrograms/inhalation, and 320 micrograms/9 micrograms/inhalation, inhalation powder is presented in the form of device-dry powder inhaler. The products contain a reservoir of powder which is measured into individual inhalation doses by the delivery device. Each delivered dose (the dose that leaves the mouthpiece) contains: budesonide 80 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms /inhalation, or budesonide 160 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms /inhalation, or budesonide 320 micrograms/inhalation and formoterol fumarate dihydrate 9 micrograms/inhalation. The excipient is lactose monohydrate. The inhalation powder is packed in the dry powder inhaler Turbuhaler.

II.2 Drug Substance

The drug substances budesonide and formoterol fumarate dihydrate have monographs in the Ph Eur.

Budesonide is a white, crystalline powder which is poorly soluble in water. The structure of budesonide has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Formoterol fumarate dihydrate is a white to off-white or slightly yellow powder, crystalline powder which is freely soluble in water. The structure of formoterol fumarate dihydrate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specifications include relevant tests, and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Symbicort mite Turbuhaler 80 micrograms/4.5 micrograms/inhalation, Symbicort Turbuhaler 160 micrograms/4.5 micrograms/inhalation, and Symbicort forte Turbuhaler 320 micrograms/9 micrograms/inhalations are formulated using excipients described in the current Ph Eur. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility, hygroscopic properties, polymorphism, and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored up to 30 °C.

III. NON-CLINICAL ASPECTS

Since budesonide and formoterol have been extensively and safely used in humans in an identical or very similar combination, the investigations of potential toxicological interactions in 3-month toxicity studies including toxicokinetics in rats and dogs are considered sufficient. The relevance of a potential improvement of the anti-inflammatory activity of budesonide by co-administration with formoterol remains to be proven in clinical trials. Pharmacokinetic and toxicological data from toxicity studies on the combination of budesonide and formoterol in rats and dogs have not indicated any influence on the profiles of the compounds given separately.

New data was submitted in a type II variation (SE/H/229/01-02/II/36). The results from the performed inhalation embryo-fetal development study in rats with a Symbicort HFA pMDI formulation containing budesonide, formoterol and excipients showed that there is no evidence of any additional effect from the combination formulation or evidence of any effects due to the excipients. In addition, a study conducted by the MAH indicated that the systemic exposure of budesonide in breast-feeding infants is negligible and that adverse effects in nursing infants are unlikely. Relevant sections of the SPC were updated.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

During multiple-dose conditions, the exposure of formoterol after administration of Symbicort Turbuhaler is similar to what is obtained after administration of Oxis (formoterol) Turbuhaler alone or in combination with Pulmicort (budesonide) Turbuhaler.

The plasma concentrations of budesonide were slightly higher after administration of Symbicort Turbuhaler than after given either alone or in combination with Oxis Turbuhaler. The formulations were equivalent with respect to AUC_{0-12h} but not to C_{max}. The differences in exposure are probably caused by differences in the two devices. The differences in exposure of budesonide resulted in a slightly more marked suppression of serum cortisol. The alterations in cortisol suppression probably lack clinical relevance.

IV.2 Clinical efficacy and safety

The studies submitted for Symbicort Turbuhaler support the investigated dosing range targeting children (from age 6) and adults with asthma not well controlled on inhaled GCS alone and adults with severe chronic obstructive pulmonary disease (COPD) and a history of exacerbations. Symbicort Turbuhaler has a well-established safety profile that is comparable to that observed with concurrent therapy, i.e. the monoproducts used together or budesonide alone.

A once to twice daily regimen in symptomatic asthmatic adults would be acceptable in accordance with the approved dosage recommendations for the monoproducts. Patients with predominantly daytime or nocturnal asthma symptoms may be given Symbicort Turbuhaler once daily in the morning or evening.

In the case of a worsening of asthma in adults, the combination product has not been studied. The monoproducts are individually allowed to be temporarily increased to 1600 microgram and 36 microgram of budesonide and formoterol, respectively. Hence, the safety margin for each component has been assessed previously and considered acceptable. However, it could be questioned whether the suggested dose increase (above the investigated doses and to the maximum dose of the individual components) with the combination product could be directly extrapolated to the experience of the monoproducts. In a combination product the flexibility is lost for the exact dosing of the components. A possible risk of an unnecessary increased consumption of one of the components due to an increased need of the other and thereby unnecessary side effects cannot be neglected and has been addressed in an RMP (see below).

An additional posology concerning the use of Symbicort Turbuhaler as both maintenance and as-needed therapy in asthmatic patients was approved in 2006 (SE/H/229/01-02/II/30).

Symbicort is not recommended for children under 6 years of age.

Risk Management Plan

Non-clinical and clinical safety specifications

The MAH submits an updated MAA that is intended for a Repeat Use MRP following on from the initial MRP with approval in RMS 2000-08-25. The Risk Management Plan (RMP) for Symbicort maintenance and reliever therapy is identical as the updated and approved (2009-02-24) Type II variation (SE/H/230/01/II/32, SE/H/229/01/II/40) for Gardette / Symbicort Turbuhaler. In addition to routine pharmacovigilance, the MAH has ongoing observational and

simplified clinical studies to elucidate the potential risks of over/underuse and off-label use in children and high-strength use.

The identified risks associated with Symbicort as maintenance treatment are disclosed in the current SmPC. These risks have been previously assessed, are well understood, and do not require further characterisation or evaluation.

Important potential risks identified for the Symbicort maintenance and reliever therapy posology are:

- Potential risk for overuse: Inappropriately high number of as-needed inhalations over a long-term could result in an increased risk for GCS-related adverse events.
- Potential risk for underuse: Patients could fail to receive adequate dose of medication, resulting in an increased risk for treatment failures.
- Potential for off-label use of Symbicort maintenance and reliever therapy among children under 18 years of age.
- Potential for off-label use of the 320/9 µg/inhalation strength inhaler. High dose inhaler is not appropriate for as-needed use as this could result in a high Symbicort dose and an increased risk for drug-related adverse events.

There are no further safety issues to amend the RMP.

Pharmacovigilance Plan

The MAH's routine pharmacovigilance practices include the elements outlined in the ICH E2E guidance document.

The planned and ongoing actions for the safety concerns is summarised below.

Summary of planned pharmacovigilance actions		
Important potential risks	Overuse and under-use	Enhanced post-marketing surveillance
		Real-life monitoring observational studies
		Simplified clinical trials
Potential for off-label use	Off-label use among children and off-label use of the 320/9 µg/inhalation strength inhaler as maintenance treatment.	Real-life monitoring observational studies

Observational studies

General Practice Research Database registry study (GPRD) (D5890C00017)

The aim of this currently ongoing descriptive pharmacoepidemiological study is to further describe how patients in normal clinical settings use Symbicort when prescribed Symbicort maintenance and reliever therapy.

Patient Follow-up Programme (PFUP) (D5890C00018)

The primary objective of this currently ongoing, 12-month, observational, non-comparative, follow-up programme is to investigate the extent of Symbicort use in patients prescribed Symbicort as maintenance and reliever therapy.

Simplified clinical trials

CHAMPION study programme

The CHAMPION study programme is a set of clinical studies closely following a core protocol “A comparison of Symbicort Single inhaler Therapy (Symbicort Turbuhaler 160/4.5 µg, 1 inhalation twice daily plus as needed) and conventional best practice for the treatment of persistent asthma in adolescents and adults - a 26-week, randomised, open-label, parallel-group, multicentre study”.

The EUROSMART Study

EUROSMART is an ongoing study in 14 European countries, aiming to include 8000 patients for a 26-week treatment period. The study is an open-label, two-armed study in adult patients with asthma currently on treatment with inhaled GCSs and not adequately controlled.

Overview of study protocols

Study	Protocol version	Date for submission of interim data	Planned date for submission of final data
Observational			
GPRD study (D5890C00017)	Final	-	Q4 2009
Patient Follow-up Programme (D5890C00018)	Final	Q2 2008 ^a	Q1 2011
Simplified clinical trials			
CHAMPION study programme (8 studies)	Final	-	Individual studies: Q4 2007 - Q1 2009 Complete safety data: Q2 2009
SHARE (D5890L00001)	Final	-	Completed Q2 2008
EUROSMART (D5890L00022)	Final	-	Q2 2009

^a Interim report is included in [Annex 5](#)

The MAH should provide the final results from ongoing trials when available to the RMS.

Risk Minimisation Plan

Risk minimisation activities have been chosen to introduce additional limitations and recommendations for Symbicort use and to ensure that this information is effectively communicated to doctors and patients so that use of Symbicort is appropriate. The extent to which these risk minimisation activities are successful will be confirmed through enhanced pharmacovigilance, the GPRD study, and the PFUP.

Summary of pharmacovigilance plan and risk minimisation activities for Symbicort maintenance and reliever therapy.

	Pharmacovigilance		Risk Minimisation	
	Routine	Additional	Routine	Additional
Previously identified risks associated with Symbicort Turbuhaler as maintenance therapy				
Systemic GCS effects	√	Enhanced Pharmacovigilance	-	-
Cardiac LABA effects	√	Enhanced Pharmacovigilance	-	-
Life-threatening and fatal asthma events	√	Enhanced Pharmacovigilance	-	-
Potential risks with Symbicort maintenance and reliever therapy				
Overuse	-	GPRD study, PFUP	Information and warnings in SmPC and Patient Information Leaflet	Education activities, consultation with physician groups and patient associations, training of AZ staff
Underuse	-	GPRD study, PFUP	Information and warnings in SmPC and Patient Information Leaflet	Education activities, consultation with physician groups and patient associations, training of AZ staff
Off-label use in children and adolescents	-	GPRD study	Information and warnings in SmPC and Patient Information Leaflet	Education activities, consultation with physician groups and patient associations, training of AZ staff
Off-label high-strength use	-	GPRD study	Information and warnings in SmPC and Patient Information Leaflet	Education activities, consultation with physician groups and patient associations, training of AZ staff

Pharmacovigilance System

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Periodic Safety Update Report (PSUR)

The PSUR submission scheme should follow 1-yearly PSUR cycle and follow the Data Lock Point that is found on Heads of Medicines Agencies website. The next PSUR should have a DLP in August 2010.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The user test was acceptable in procedure SE/H/229/01-02/II/35, SE/H/230/01/II/027.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Symbicort mite Turbuhaler 80 micrograms/4.5 micrograms/inhalation, Symbicort Turbuhaler 160 micrograms/4.5 micrograms/inhalation, and Symbicort forte Turbuhaler 320 micrograms/9 micrograms/inhalation are recommended for approval.

VI. APPROVAL

For Symbicort mite Turbuhaler (budesonide/formoterol 80 micrograms/4.5 micrograms) and Symbicort Turbuhaler (160 micrograms/4.5 micrograms) national approval was granted in Sweden on 2000-08-25. A mutual recognition procedure with AT, BE, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NL, NO, PT, and UK was finalised in December 2000. Symbicort forte Turbuhaler (budesonide/formoterol 320 micrograms/9 micrograms) was approved nationally in 2001-12-28. An MRP was finalised in June 2002 with AT, BE, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NL, NO, PT, and UK. The application was withdrawn in Italy, but approved through a repeat use MPR in July 2004.

The Mutual recognition procedure for Symbicort mite Turbuhaler 80 micrograms/4.5 micrograms/inhalation, Symbicort Turbuhaler 160 micrograms/4.5 micrograms/inhalations, and Symbicort forte Turbuhaler 320 micrograms/9 micrograms/inhalations with BG, CY, CZ, EE, HU, LT, LV, MT, PL, RO, SI, and SK as CMS was successfully finalised on 2010-08-03.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)