LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bufori Easyhaler
(budesonide, formoterol fumarate dihydrate)

SE/H/1595/01-03/DC

This module reflects the scientific discussion for the approval of Bufori Easyhaler. The procedure was finalised on 2016-10-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Bufori Easyhaler, inhalation powder, 80 micrograms/4.5 micrograms, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Symbicort mite Turbuhaler, inhalation powder, 80 micrograms/4.5 micrograms per inhalation, Symbicort Turbuhaler, inhalation powder, 160 micrograms/4.5 micrograms per inhalation and Symbicort forte Turbuhaler, inhalation powder, 320 micrograms/9 micrograms per inhalation, authorised in SE since 2000 (2001, Symbicort forte Turbuhaler), with AstraZeneca AB as marketing authorisation holder.

It should be noted that in some countries Symbicort Turbuhaler is labelled according to delivered dose, as stated above, and in some countries according to the metered dose (100 microgram/6 microgram/inhalation, 200 microgram/6 microgram/inhalation and 400 microgram/12 microgram/inhalation).

The reference products used in in vitro, pharmacokinetic and clinical studies to demonstrate therapeutic equivalence are Symbicort Turbuhaler forte, 320 microgram/9 microgram/inhalation, inhalation powder from FI with AstraZeneca Oy as MAH and Symbicort forte Turbuhaler, 320 microgram/9 microgram/inhalation, inhalation powder from SE with AstraZeneca AB as MAH.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of budesonide and formoterol fumarate are well known. As budesonide and formoterol fumarate are widely used, well-known active substances, no further studies are required.

Since the product is a hybrid and is intended to replace already marketed fixed-dose combination products containing the same active substances, no increased exposure to the environment is expected.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

In this application the aim of the Applicant has been to demonstrate therapeutic equivalence using pharmacokinetic data in support of efficacy and safety in accordance with the step-wise approach recommended in CPMP/EWP/4151/00 rev 1 guideline; “OIP guideline”.

One pilot study and three pivotal studies have been performed with the final Budesonide/formoterol Easyhaler formulation. The studies were conducted both with and without charcoal blockade and hence both lung deposition and total systemic exposure have been evaluated. Since bioequivalence could not be demonstrated for all parameters in the first two parallel studies (PAX-PILOT and REPECO), two additional studies were conducted in parallel (REFLI and TRIPECO). In these studies bioequivalence was demonstrated for budesonide, but not for all parameters for formoterol.

All studies were conducted with the 320 μg/9 μg strength. Dose proportionality in vitro has been shown for both budesonide and formoterol fumarate dihydrate. It is therefore considered acceptable to extrapolate data from the studies with the highest strength to the lower strengths of 80 μg/4.5 μg and 160 μg/4.5 μg. The study population comprised of healthy volunteers. This is acceptable given the similarity in flow rate dependency between the test and the reference product. In all studies a single dose of 2 inhalations of Bufomix EH 320 μg/9 μg or Symbicort TH 320 μg/9 μg were administered in each period. Blood-samples were collected pre-dose and up to 12 h (budesonide) and 24 h (formoterol) post-dose. The overall design of the studies is acceptable. Plasma concentrations of budesonide and formoterol were determined with adequately validated LC/MS/MS methods.

The results from all studies are summarized and discussed below. See also Table 1 (summary of pharmacokinetic results).

PAX-PILOT (with charcoal):
This was a small study (n=16), not sufficiently powered to draw firm conclusions regarding bioequivalence. The reference batch used in the study was the same as in the parallel REPECO study, and the results were largely in agreement with the results from the REPECO study.

REPECO (with and without charcoal):
In REPECO (and PAX-PILOT) a reference batch with a FPD at the lower end of the representative range was used.

For budesonide, the exposure of the test product was higher compared to the reference product and bioequivalence was not demonstrated in the lung deposition part of the study (with charcoal blockade). Non-inferiority with regard to safety (i.e. not higher systemic exposure of the test product) when administered without charcoal blockade, could not be shown either.

For formoterol non-inferiority with regard to safety was shown (without charcoal blockade), but bioequivalence was not demonstrated when the products were administered with charcoal due to a higher Cmax for the test product compared to the reference.

The use of a reference batch with a FPD at the lower end of the representative range could be one explanation of the results. An additional explanation presented by the applicant is that the higher exposure of the test product could have been caused by a technical issue in the filling process, causing an approximately 3% higher delivered dose from the Easyhaler. This introduces some uncertainty regarding the results, but the impact on the overall results is expected to be minor.

REFLI (with charcoal):
In the REFLI study two different reference batches and one test batch were compared. The reference batch A was slightly lower in FPD compared to a median batch, while the reference batch B had a FPD close to the higher end of the representative range.

The primary objective was to evaluate bioequivalence between the two reference batches. Bioequivalence between the two reference batches could not be demonstrated due to a lower exposure of batch A compared to batch B. Given the difference in FPD between the two reference batches, differences in pharmacokinetics are expected. Thus, it is not completely unlikely that the two reference batches would not be bioequivalent when conventional acceptance limits of 80-125% are used.

The secondary objective of the REFLI study was to compare the test batch with the two reference batches. Regarding budesonide, the test batch was shown to be bioequivalent with both reference batches. For formoterol, bioequivalence was demonstrated when the test batch was compared to reference batch A (with a slightly lower FPD compared to the median), but not with batch B (with a FPD higher than the median).

TRIPECO (with and without charcoal):
In this study a reference batch with a FPD slightly higher than the median batch was used. Bioequivalence was again shown for budesonide. The exposure of formoterol was however lower with the test formulation compared to the reference, and bioequivalence could not be demonstrated for AUC when administered with charcoal. The pharmacokinetic results appear

to be in agreement with the fact that the FPD of the reference batch was slightly higher than the median batch.

Overall results
The results differ between the different studies. In some studies the exposure was too high and in others too low. Bioequivalence for all parameters was show in study REFLI (ref batch THa) with active charcoal and in TRIPECO without charcoal. The results are summarised below. Confidence intervals outside the acceptance range are highlighted.

Table 1: Summary of pharmacokinetic results.

Study	**PK-parameter**	**Budesoneide Ratio (90% CI or 95% upper CL)**	**Formoterol Ratio (90% CI or 95% upper CL)**
PAX PILOT - with charcoal	**AUC**	1.222 **(1.108-1.348)**	0.991 (0.875-1.121)
	Cmax	1.348 **(1.184-1.536)**	1.140 **(0.989-1.314)**
REPECO - with charcoal	**AUC**	1.254 **(1.184-1.328)**	1.100 (1.032-1.173)
	Cmax	1.281 **(1.166-1.408)**	1.241 **(1.155-1.333)**
REPECO - without charcoal	**AUC**	1.224 **(1.280)**	1.070 (1.117)
	Cmax	1.266 **(1.354)**	1.185 (1.243)
REFLI - with charcoal Ref batch A	**AUC**	1.094 (1.023-1.170)	0.904 (0.814-1.005)
	Cmax	1.054 (0.961-1.156)	0.899 (0.824-0.982)
REFLI - with charcoal Ref batch B	**AUC**	0.977 (0.914-1.044)	0.708 **(0.693-0.785)**
	Cmax	0.941 (0.833-1.002)	0.761 **(0.698-0.830)**
TRIPECO - with charcoal	**AUC**	0.979 (0.932-1.028)	0.800 **(0.757-0.845)**
	Cmax	0.941 (0.872-1.017)	0.861 (0.809-0.917)
TRIPECO - without charcoal	**AUC**	1.034 (1.082)	0.925 (0.969)
	Cmax	1.049 (1.135)	0.929 (0.982)

A likely explanation of the results is the batch-to-batch variability in FPD of the reference product. It is well known that variability in particle-size distribution between batches can be significant for orally inhaled products. Given that PK is a sensitive tool; such differences may result in failure to show bioequivalence at some occasions, although bioequivalence may be shown at other occasions in studies with different batches of the same product. This is evident from the REFLI study in which it was not possible to show bioequivalence between two reference batches.

Four different reference batches were used in the PK-studies. All reference batches are considered to be representative of the batches on the market, based on median values ±15%. However, within the range considered as representative, there was variability in FPD between the reference batches which may explain the outcome of the PK-studies.

The FPD of the reference batch used in the REPECO study, the PAX-PILOT study and of reference A used in the REFLI study was lower than the median FPD values for both budesonide and formoterol. The FPD of the reference batch used in the TRIPECO study and of reference B used in the REFLI study was on the other hand higher than the median FPD values for both active substances.

The difference in FPD is reflected in the PK-results, with a rank order correlation between FPD and PK. In REPECO and PAX-PILOT, in which the reference batch with the lowest FPD was used, the T/R-ratio were higher and bioequivalence could not be demonstrated for budesonide AUC and Cmax (with and without charcoal) or for formoterol Cmax when administered with charcoal. On the contrary the T/R-ratios were in the lower end in TRIPECO and REFLI (ref batch B). Consequently, bioequivalence could not be demonstrated for formoterol AUC (with charcoal) in the TRIPECO study and for budesonide Cmax and formoterol AUC and Cmax in the REFLI study (ref batch B). When the test product was compared to reference batch A in the REFLI study bioequivalence was demonstrated for both budesonide and formoterol, which is in accordance with an FPD rather close to the median.

Although all reference batches could be considered as representative there is a clear trend that when a reference batch with a FPD in the higher end of the range was used the T/R-ratios were lower and when a reference batch with a FPD in the lower range was used the T/R-ratios were higher. The FPD of the reference batches used in the TRIPECO and REFLI (ref batch A) studies are closest to the median FPD values. While the reference batches used in the REPECO, PAX-PILOT and REFLI (ref batch B) studies deviate more from the median FPD values.

To further evaluate the relationship between FPD and the pharmacokinetic parameters an in vitro-in vivo correlation (IVIVC) was developed. When the relationship obtained in the IVIVC was used to predict the outcome of a bioequivalence study comparing the test batch used in the pivotal pharmacokinetic studies with a reference batch with a median FPD the AUC and Cmax T/R-ratios and 90% CIs fell within the bioequivalence acceptance limits for both budesonide and formoterol.

Considering all data together, the test product will most likely be bioequivalent to a reference batch with a FPD close to the median value.

Overall Summary and Conclusion

The results from the pharmacokinetic studies are likely dependent on the variability in FPD of the reference product. The overall results indicate that the test product is bioequivalent to a median batch of the reference product. Bioequivalence and hence equivalence regarding both safety and efficacy has been sufficiently shown for both budesonide and formoterol.

IV.2 Clinical efficacy and safety

Therapeutic equivalence was established based on pharmacokinetics where it was concluded from an IVIVC analysis based on several kinetic studies the test product is bioequivalent to a median batch of the reference product. Nevertheless, there was an individual study indicated lower exposure for formoterol for test versus reference in subjects administered with charcoal (the surrogate endpoint for efficacy).

To address the specific concern about possibly lower efficacy of the test product for formoterol, the applicant has conducted a pharmacodynamic study (BUFODIL 3103013) comparing the bronchodilating effect of the test and reference products. This was a single dose, randomised, double-blind, double-dummy, multicentre, 4-treatment, 4-period crossover study aiming to confirm equivalent bronchodilator efficacy of Budesonide/formoterol Easyhaler compared to the reference product Symbicort Turbuhaler. The subjects enrolled (n=72) in the study were adult asthmatics with pre-bronchodilator FEV1 was 45-90% (inclusive) of the predicted value measured on screening visit and they had reversible airway obstruction: ($\geq$ 12% and $\geq$ 200 ml improvement in FEV1 after inhalation of short-acting β2-agonist (SABA). The primary efficacy variable was average 12-h FEV1. The model based

estimated difference in average 12-h FEV1 between the treatments (Easyhaler-Turbuhaler) was 0.013 l at the 9 μg dose (95% CI -0.047 to 0.073), and -0.028 l (95% CI -0.087 to 0.032) at the 36 μg dose. The primary objective of this study was met.

The Applicant has submitted two flow rate studies, PIFECO 3103003 and CONPIF 3103009 to support this application. The aim of the study PIFECO 3103003 was primarily to compare inhalation flow rate profiles between the originator inhaler device (Turbuhaler) and the inhaler device of the applicant (Easyhaler) in patients with asthma including children, adults, and the elderly and in patients with chronic obstructive pulmonary disease (COPD). In total 187 subjects were studied. The handling of the devices was assessed in the subpopulation of asthmatic children (6 to 11 years of age, N=54). No active substances were included in the study, thus, only the performance of the devices (empty) was compared. The result show that the peak inspiratory flow (PIF) rates through Easyhaler type B device, which is the device intended for marketing, and Turbuhaler were very similar for all studied subject groups, in asthmatic and COPD patients which included asthmatic children and elderly COPD patients. The incorrect use and acceptability of the devices, investigated in children, was roughly comparable. To conclude, the inhalation rates were comparable between the test and reference devices in each patient/subject group.

Bufori Easyhaler is presented in 3 different strengths, similar to the reference product. All strengths are intended for adolescents (≥ 12 years of age) and adults in contrast to the reference product where the lowest strength is approved for children ≥ 6 years. The pharmacokinetic studies and the clinical study were all conducted in adults. The absence of specific clinical studies in adolescents is deemed acceptable as the flow rate dependency in vitro and the peak inspiratory force in vivo for the different devices is considered similar. In addition there is an extensive experience of the use of Easyhaler in children as the corresponding mono-component products (Giona Easyhaler and Formoterol Easyhaler) are approved in EU from 6 years of age. Together, all information available from children and adolescents, and from extrapolating data from adults gives a clear indication of therapeutic similarity between products in adolescents from 12 years of age. Clinical studies to further support the use of Bufori Easyhaler in this age group are not warranted.

IV.3 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bufori Easyhaler.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns associated with Bufomix Easyhaler maintenance therapy	
Important identified risks	Systemic GCS effects Cardiac LABA effects Life-threatening and fatal asthma events Pneumonia in COPD Hypersensitivity reactions including anaphylactic reactions Bronchospasm
Important potential risks	-
Missing information	Use in patients with hepatic impairment Use in patients with renal impairment Use during pregnancy Use during breastfeeding Effect on fertility

Summary of additional safety concerns associated with Bufomix Easyhaler maintenance and reliever therapy	
Important identified risks	-
Important potential risks	Off-label use
Missing information	-

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Bufomix Easyhaler, SE/H/1213/001-3/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Bufori Easyhaler, inhalation powder, 80 micrograms/4.5 micrograms, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Bufori Easyhaler, inhalation powder, 80 micrograms/4.5 micrograms, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation was positively finalised on 2016-10-12.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1595/01-03/II/25	The MAH would like to propose variation Type II C.I.6.a for the extension of the therapeutic indication for the product Bufori Easyhaler 80/4.5, 160/4.5 and 320/9 micrograms/Inhalation powder to children aged 6 years and older. Currently Bufori Easyhaler is indicated in Adults (18 years and older) and Adolescents (12–17 years). The pursued variation is an extension of indication to include children for the regular treatment of asthma. The claimed indications are: Bufori Easyhaler 80/4.5 µg is indicated in adults, adolescents, and children aged 6 years and older. Bufori Easyhaler 160/4.5 µg and 320/9 µg are indicated in adults, and adolescents aged 12 to 17 years.	Yes	2024-12-18	Approval	Considering that a similar product has been approved with the same age limits since almost a decade the RMS is of the opinion that this variation application can be approved.

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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