Public Assessment Report
Scientific discussion

Orbufox Easyhaler
(budesonide, formoterol fumarate dihydrate)

SE/H/1519/01-02/DC

This module reflects the scientific discussion for the approval of Orbufox Easyhaler. The procedure was finalised on 2015-12-16. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Orbufox Easyhaler, inhalation powder, 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 NL as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is 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.

The reference product used in the bioequivalence studies is 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

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

Orbufox Easyhaler is not considered to pose any risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

According to the guideline “Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents” (CPMP/EWP/4151/00 rev 1 guideline; “OIP guideline”) a step-wise approach should be considered when demonstrating therapeutic equivalence. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data.

The first step in the evaluation is the pharmaceutical properties. The use of only comparative in vitro data may be considered acceptable for approval of a “new inhalation generic product” if the product satisfies all of the criteria (compared with the reference product) as outlined in section 5.2 of the OIP guideline. Several pharmaceutical parameters should be evaluated.

Step 2: If the product does not satisfy all of the pharmaceutical criteria for equivalence, in vivo studies should be performed to substantiate therapeutic equivalence. Thus, a second step, pharmacokinetic documentation may be used to support efficacy and safety.

Step 3: If therapeutic equivalence cannot be demonstrated based on in-vitro and/or pharmacokinetic data, pharmacodynamic/clinical efficacy and safety data are needed to demonstrate therapeutic equivalence.

In this application the aim of the Applicant has been to demonstrate therapeutic equivalence using pharmacokinetic data in support of efficacy and safety.
IV.2 Pharmacokinetics

Pharmacokinetic studies aim at demonstrating similar pulmonary deposition and similar total systemic exposure between a “new inhalation generic product” and the originator. According to the OIP-guideline, pharmacokinetic data may be used to support efficacy and safety. Efficacy is supported by a pulmonary deposition study, which means a bioequivalence study with concomitant active charcoal. For substances that are absorbed after oral administration, like budesonide and formoterol, a bioequivalence study without charcoal is also needed to provide a pharmacokinetic support of safety.

One pilot study and three pivotal studies have been performed with the final Orbufox 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 $\mu$g/9 $\mu$g strength. Dose proportionality 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 160 $\mu$g/4.5 $\mu$g strength based on this in vitro data. The study population comprised of healthy volunteers which 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 Orbufox EH 320 $\mu$g/9 $\mu$g or Symbicort TH 320 $\mu$g/9 $\mu$g 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.

A plausible explanation of the difficulties in demonstrating bioequivalence may be the variability in FPD between different batches of the reference product. Batch to batch variability in FPD for orally inhaled products is a well-recognised problem. To be able to obtain reliable results in the pharmacokinetic studies it is therefore important to test several batches in vitro in order to find a batch representative of the reference product on the market, i.e. with a FPD as close to the median of several tested batches as possible. The same test batch was used in all studies while four different references batches were used. All reference batches are considered representative regarding FPD, using a limit of median ± 15%. The FPD of the different reference batches did however vary from the lower to the higher end within this range.

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 slightly 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.

**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 slightly 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.
Table 1: Summary of pharmacokinetic results

<table>
<thead>
<tr>
<th>Study</th>
<th>PK-parameter</th>
<th>Budesonide Ratio (90% CI or 95% upper CL)</th>
<th>Formoterol Ratio (90% CI or 95% upper CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIPECO - with charcoal</td>
<td>AUC</td>
<td>0.979 (0.932-1.028)</td>
<td>0.800 (0.757-0.845)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>0.941 (0.872-1.017)</td>
<td>0.861 (0.809-0.917)</td>
</tr>
<tr>
<td>TRIPECO - without charcoal</td>
<td>AUC</td>
<td>1.034 (1.082)</td>
<td>0.925 (0.969)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.049 (1.135)</td>
<td>0.929 (0.982)</td>
</tr>
<tr>
<td>REFLI - with charcoal Ref batch A</td>
<td>AUC</td>
<td>1.094 (1.023-1.170)</td>
<td>0.904 (0.814-1.005)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.054 (0.961-1.156)</td>
<td>0.899 (0.824-0.982)</td>
</tr>
<tr>
<td>REFLI - with charcoal Ref batch B</td>
<td>AUC</td>
<td>0.977 (0.914-1.044)</td>
<td>0.708 (0.693-0.785)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>0.914 (0.833-1.002)</td>
<td>0.791 (0.698-0.830)</td>
</tr>
<tr>
<td>REPECO - with charcoal</td>
<td>AUC</td>
<td>1.254 (1.184-1.328)</td>
<td>1.100 (1.082-1.173)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.281 (1.166-1.408)</td>
<td>1.241 (1.155-1.333)</td>
</tr>
<tr>
<td>REPECO - without charcoal</td>
<td>AUC</td>
<td>1.224 (1.280)</td>
<td>1.070 (1.117)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.266 (1.354)</td>
<td>1.185 (1.243)</td>
</tr>
<tr>
<td>PAX PILOT - with charcoal</td>
<td>AUC</td>
<td>1.222 (1.108-1.348)</td>
<td>0.991 (0.875-1.121)</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.348 (1.184-1.536)</td>
<td>1.140 (0.989-1.314)</td>
</tr>
</tbody>
</table>

**Overall results:**

Looking at the overall result, it appears to be a trend where a reference product with a low FPD results in higher PK T/R-ratios and a reference product with a high FPD results in lower PK T/R-ratios.

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 FPD at the median of several tested batches, the AUC and Cmax T/R-ratios and 90% CIs fell within the bioequivalence acceptance limits for both budesonide and formoterol. The predicted results were very similar to the results seen in TRIPECO and REFLI (ref batch A) in which the test batch was compared to a reference batch with a FPD close to the median FPD-values. Hence, the IVIVC supports the conclusion that the test batch will most certainly be bioequivalent with a median reference batch.

**Budesonide**

Regarding budesonide, the test batch had a FPD rather close to the FPD of the median of all 28 tested reference batches and bioequivalence was demonstrated with three of the reference batches (TRIPECO and REFLI studies). Only in the studies including the reference batch with the lowest FPD (used in the REPECO and PAX-PILOT studies) bioequivalence could not be demonstrated. Additional predictions based on the IVIVC-model showed that the test product is likely to be bioequivalent with a reference product with a median FPD.

Taken together, bioequivalence and hence equivalence regarding both safety and efficacy has been sufficiently shown for budesonide in the TRIPECO and REFLI studies.

**Formoterol**

Regarding formoterol, the FPD of the test batch was on the other hand significantly lower than the median reference batch, which seems to be reflected in the pharmacokinetic results.
Bioequivalence could only be demonstrated when a reference batch with a FPD very close or actually slightly lower than the median reference batch was used (REFLI reference batch A). Bioequivalence was not shown in the TRIPECO study in which the reference batch had a FPD slightly higher, but also very close to the median batch. In the studies with the reference product with the lowest FPD, REPECO and PAX-PILOT, the exposure of the test product was similar or slightly higher than the reference product. Also for formoterol, predictions based on the IVIVC-model have shown that the test product is likely to be bioequivalent with a reference product with a median FPD.

Since the exposure of formoterol was at the lower end of the bioequivalence limits in several studies the IVIVC-model was further used to estimate within which range the test and the reference products are expected to be bioequivalent. When these limits were compared with the proposed specification limits, it appears that the bioavailability of the low side batch of the test product is not expected to be lower than a low side reference batch and conversely, that the bioavailability of the high side test batch is not expected to be higher than a high side reference batch. The risk that a test product within the specification will not be bioequivalent to a reference product on the market is therefore expected to be minor.

Taken together, bioequivalence and hence equivalence regarding both safety and efficacy has been sufficiently shown for formoterol.

Overall Summary and Conclusion

The results from the pharmacokinetic studies are likely dependent on the variability in FPD of the reference product. Using the established IVIVC-model the test product is predicted to be bioequivalent to a median batch of the reference product. Furthermore, the risk that a test product within the specification will not be bioequivalent to a reference product on the market is expected to be minor.

Bioequivalence and hence equivalence regarding both safety and efficacy has been sufficiently shown for both budesonide and formoterol.

IV.3 Clinical efficacy and safety

The Applicant has submitted two flow rate studies in patients PIFECO 3103003 (N=187), CONPIF 3103009 (N=60). The aims of the studies were 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 (CONPIF 3103009) and in asthmatic children, adolescents, adults and elderly and in patients with chronic obstructive pulmonary disease (PIFECO 3103003). The PIFECO 3103003 study used empty devices of the Easyhaler and the Turbuhaler and study CONPIF 3103009 was conducted with both empty and placebo devices of the Easyhaler and the Turbuhaler. Similarity in flow rate dependency between the test and the reference product was shown with the flow rate range achievable by the intended patient population. The use of healthy volunteers in the conducted PK studies is considered acceptable based on the presented data. The study CONPIF 3103009 was performed to address a potential concern whether the PIF rate of empty inhalers would be different from that of placebo inhalers. The results show that the PIF rates generated via empty and placebo inhalers were similar for both Easyhaler and Turbuhaler and their 90% CIs were within the predefined CI interval. To conclude, flow rate data using empty or placebo devices are similar. Thus, the results from studies with empty devices are relevant.
To conclude, therapeutic equivalence has been demonstrated based on pharmacokinetic data, characterisation of flow rate dependency in all relevant patient groups has been explored, and there is a similar flow rate dependency for the test and reference product.

IV.4 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 Orbufox Easyhaler

Safety specification

Summary table of safety concerns as approved in RMP

| 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                  | Off-label use, including use in patients under the age of 18 years |
|                                           | |

| Missing information                        | Use in patients with hepatic impairment |
|                                           | Use in patients with renal impairment |
|                                           | Use during pregnancy |
|                                           | Use during breastfeeding |
|                                           | Effect on fertility |

No additional pharmacovigilance activities or risk minimisation measures are proposed. This is endorsed.

Summary of the RMP

The RMP is approved.

V. USER CONSULTATION

The PL is identical to the reference product Bufomix Easyhaler both in content and layout. Bufomix Easyhaler was tested and approved in procedure SE/H/1213/02-03/DC.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns Orbufox Easyhaler, inhalation powder in two different strengths, i.e., 160 microgram/4.5 microgram/inhalation and 320 microgram/9 microgram/inhalation.
Orbufox Easyhaler is a dry powder inhaler containing budesonide and formoterol with the Easyhaler inhalation device.

The application for Orbufox Easyhaler is a hybrid application and evaluated in a step-wise approach according to the guideline CPMP/EWP/4151/00 Rev.1. In this case the quality data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based on in vitro data and in vivo studies are needed for demonstration of therapeutic equivalence. In this application the aim of the Applicant has been to demonstrate therapeutic equivalence using pharmacokinetic data in support of efficacy and safety.

The batches, of both test and reference product, used in the PK studies needs to be representative for the product intended for marketing (test) and the reference product on the market. The reference batches used in the PK studies with the final formulation of the test product are considered representative, within ±15% of the mean and median FPD value. The test product will be representative as the finished product specification should be based on the batches used in the PK studies.

Four pharmacokinetic studies, with and without active charcoal, have been performed with the final Budesonide/formoterol formulation, which is adequate to evaluate similarity in both efficacy and safety. Bioequivalence was not indisputably shown in all studies, which is likely to be caused by the variability in FPD of the reference product. The same test batch was used in all pivotal studies, but different reference batches were used. 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 representative range was used, the PK T/R-ratios were lower and when a reference batch with a FPD in the lower range was used the PK T/R-ratios were higher. The overall results indicate that the test product is bioequivalent to a median batch of the reference product. Furthermore, the risk that a test product within the specification will not be bioequivalent to a reference product on the market is expected to be minor. To conclude, bioequivalence and hence equivalence regarding both safety and efficacy has been sufficiently shown for both budesonide and formoterol.

The Applicant has submitted two flow rate studies in patients PIFECO 3103003 (N=187), CONPIF 3103009 (N=60). The aim of the studies were 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 which included children, adolescents, adults and elderly (PIFECO 3103003, CONPIF 3103009) and in patients with chronic obstructive pulmonary disease (PIFECO 3103003). The PIFECO 3103003 study used empty devices of the Easyhaler and the Turbuhaler and study CONPIF 3103009 was conducted with both empty and placebo devices of the Easyhaler and the Turbuhaler. 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 comparable between the test and reference devices in each patient/subject group. The use of healthy volunteers in the conducted PK studies is considered acceptable based on the presented data. The study CONPIF 3103009 was performed to address a potential concern whether the PIF rate of empty inhalers would be different from that of placebo inhalers. The results show that the PIF rates generated via empty and placebo inhalers were similar for both Easyhaler and Turbuhaler and their 90% CIs were within the predefined CI interval. To conclude, flow rate data using empty or placebo devices are similar. Thus, the results from studies with empty devices are relevant.

To conclude, since therapeutic equivalence has been demonstrated based on pharmacokinetic data, characterisation of flow rate dependency in all relevant patients groups has been explored.
and there is a similar flow rate dependency for the test and reference product. The application is considered approvable.

**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 Orbufox Easyhaler, inhalation powder, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation was positively finalised on 2015-12-16.
## Public Assessment Report – Update

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<th>Product Information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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