

Public Assessment Report

Scientific discussion

Bufomix Easyhaler **(budesonide, formoterol fumarate dihydrate)**

SE/H/1213/02-03/DC

This module reflects the scientific discussion for the approval of Bufomix Easyhaler. The procedure was finalised on 2014-03-19. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

The application for Bufomix 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, applied through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, BG, CY, CZ, DK, EE, EL, ES, FI, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SI, SK as concerned member states (CMS). Before day 106 the application was withdrawn in AT, DE, FR, NL and UK.

The strength 80 micrograms/4.5 micrograms was also part of the initial application, but this strength was withdrawn on day 197 of the procedure.

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.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Bufomix Easyhaler is presented in the form of inhalation powder containing 160 or 320 micrograms of budesonide and 4.5 or 9 micrograms of formoterol fumarate dihydrate. The only excipient is lactose monohydrate. The inhalation powder is filled in a multidose inhaler device, Easyhaler.

II.2 Drug Substance

Both budesonide and formoterol fumarate dihydrate has monographs in the Ph Eur.

Budesonide is a white or almost white crystalline powder, practically insoluble in water. Formoterol fumarate dihydrate is a white, almost white or slightly yellow powder, slightly soluble in water. The structures of budesonide and formoterol fumarate dihydrate have been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities 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

Bufomix Easyhaler, inhalation powder is formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with 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 the aerodynamic particle size distribution.

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, with no special storage precautions. After first opening the laminate bag, the inhaler should not be stored above 25°C and should be protected from moisture.

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.

III.1 Ecotoxicity/environmental risk assessment

Bufomix 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 Bufomix 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 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 µg/4.5 µg 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 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.

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 reference batches were used. All reference batches are considered representative regarding FPD, using a limit of median $\pm$ 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 C_{max} 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

Study	PK-parameter	Budesonide Ratio (90% CI or 95% upper CL)	Formoterol Ratio (90% CI or 95% upper CL)
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)
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	0.914 (0.833-1.002)	0.761 (0.698-0.830)
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)
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)

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 Pharmacodynamics

The drug product contains formoterol and budesonide which have differing modes of action. Formoterol is a selective long-acting beta-2-adrenoceptor agonist which produces a longer duration of bronchodilation. Budesonide given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically. Both active substances are considered well known.

IV.4 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.

The Applicant was initially seeking the same indication and dose recommendation as for the originator product, i.e. all three strength as for the originator. However, the strength 80 micrograms/4.5 micrograms was withdrawn at day 197 of the procedure and at the same time the indication in children under 12 years of age was also withdrawn.

To conclude, since therapeutic equivalence has been demonstrated based on pharmacokinetic data, characterisation of flow rate dependency in all relevant patient groups has been explored, there is a similar flow rate dependency for the test and reference product and the Easyhaler device is already approved in children and adolescents with a number of active substances (budesonide, formoterol, salbutamol and beclomethasone, respectively), the inclusion of both adolescents and adults is supported.

IV.5 Discussion on the clinical aspects

The Applicant was initially seeking the same indication and dose recommendation as for the originator product, i.e. all three strength as for the originator. However, the strength 80 micrograms/4.5 micrograms was withdrawn at day 197 of the procedure and at the same time the indication in children under 12 years of age was also withdrawn. Since therapeutic equivalence has been demonstrated based on pharmacokinetic data, characterisation of flow rate dependency in all relevant patients groups has been explored, there is a similar flow rate dependency for the test and reference product and the Easyhaler device is already approved in children and adolescents with a number of active substances (budesonide, formoterol, salbutamol and beclomethasone, respectively), the inclusion of both adolescents and adults is supported.

To conclude, the product is recommended for approval.

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 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 Bufomix Easyhaler, inhalation powder, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation, is recommended for approval.

Commitments

Area	Description
Product information	A variation application to update the SmPC in accordance with the SmPC of the reference product, Symbicort Turbuhaler, will be submitted following the outcome of the pending renewal procedure for the reference product.

VI. APPROVAL

The decentralised procedure for Bufomix Easyhaler, inhalation powder, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation was successfully finalised on 2014-03-19.

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)