CBG MEB

Public Assessment Report

Scientific discussion

Pulentia 100/6, 200/6 and 400/12 microgram/ dose inhalation powder, pre-dispensed

(budesonide/formoterol fumarate dihydrate)

NL/H/3165/001-003/DC

Date: 23 November 2015

This module reflects the scientific discussion for the approval of Pulentia 100/6, 200/6 and 400/12 microgram/dose inhalation powder, pre-dispensed. The procedure was finalised on 2 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t hours
BDP	Beclometasone Dipropionate
CEP	Certificate of Suitability
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
COPD	Chronic Obstructive Pulmonary Disease
DD	Delivered Dose
DPI	Dry Powder Inhaler
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
EU	European Union
EWP	Efficacy Working Party
FDC	Fixed Dose Combination
FPD	Fine Particle Dose
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board of the Netherlands
NNT(h)	Number Needed to Treat to harm
OIP	Orally Inhaled Products
OR	Overall Risk
Ph.Eur.	European Pharmacopoeia
PIFR	Peak Inspiratory Flow Rates
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product information
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
$t_{1/2}$	Half-life

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pulentia 100/6, 200/6 and 400/12 microgram/dose inhalation powder, pre-dispensed from Elpen Pharmaceutical Co. Inc.

Pulentia 100/6, 200/6 and 400/12 microgram/dose are indicated in:

Asthma
The regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting β2 adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting β2 adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

Additionally, *Pulentia 200/6 and 400/12 microgram/dose* are indicated in:

COPD
Symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application with reference to the innovator product Symbicort Turbuhaler (delivered dose strengths: 80/4.5, 160/4.5 and 320/9 µg/inhalation, dry powder inhaler) which has been registered in Germany by AstraZeneca GmbH since 2001 (80/4.5 and 160/4.5 µg/inhalation) and 2002 (320/9 µg/inhalation), respectively.
The Dutch reference product is Symbicort Turbuhaler 100/6, 200/6 and 400/12 µg/inhalation, dry powder (NL License RVG 25886, 25887 and 27690), and has been registered by AstraZeneca BV through procedure SE/H/0230/MR.

The concerned member states (CMS) involved in this procedure were Germany, Hungary, Iceland, Italy, Portugal and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Pulentia is a white, pre-dispensed inhalation powder.

100/6 microgram: Each single dose blister strip contains 100 micrograms of budesonide and 6 micrograms of formoterol fumarate dihydrate, which corresponds to an inhaled dose of 97 micrograms budesonide and 5.5 micrograms formoterol fumarate dihydrate.

200/6 microgram: each single dose blister strip contains 200 micrograms of budesonide and 6 micrograms of formoterol fumarate dihydrate, which corresponds to an inhaled dose of 194 micrograms budesonide and 5.5 micrograms formoterol fumarate dihydrate.

400/12 microgram: each single dose blister strip contains 400 micrograms of budesonide and 12 micrograms of formoterol fumarate dihydrate, which corresponds to an inhaled dose of 380 micrograms budesonide and 11 micrograms formoterol fumarate dihydrate.

The powder is packed in Alu-alu blisters. 60 blisters are packed in the two-tone colored plastic Elpenhaler inhalation device.

The only excipient is lactose monohydrate.

II.2 Drug Substances

Budesonide
The active substance budesonide is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is insoluble in water. It is manufactured as one crystalline form. The molecule contains 6 chiral centres.

The CEP procedure is used for budesonide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH is in line with the Ph.Eur. and CEP. Absence of a test for microbiological purity has been justified. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on budesonide have been provided for three full-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). All results are within specification. The proposed retest period of 60 months is acceptable. The substance is stored protected from light, although the substance was not photosensitive in the photostability study according to ICH Q1B.

Formoterol fumarate dihydrate
The active substance formoterol fumarate dihydrate is an established active substances described in the Ph.Eur. It is slightly soluble in water. No polymorphs are known. The molecule contains two chiral centres. The CEP procedure is used.

Manufacturing process
No details on the manufacturing process have been included, as a CEP is presented.

Quality control of drug substance
The drug substance specification of the MAH is in line with the Ph.Eur. and CEP. Absence of a test for microbiological purity has been justified. Batch analytical data demonstrating compliance with the drug substance specification have been provided for several production-scale batches.

Stability of drug substance
Stability data on formoterol fumarate dihydrate have been provided for three full-scale batches stored at 25°C/60% RH (66 months) and 40°C/75% RH (6 months). All results are within specification. In view of these results, the proposed re-test period of 2 years is acceptable. The storage condition ‘protect from light’ is justified, although the results of the photostability study do not show degradation upon exposure to light.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The test product shows a flow-rate dependency regarding fine particle dose (FPD) and delivered dose (DD), although this is smaller than the reference product. The flow rate effect on FPD and DD is not the same for all three strengths. Results of FPD and DD of flow rates of 30 to 90 L/min have been provided. It has been stated that the flow-rate at which a pressure drop of 4 kPa was achieved, was 37 L/min. The device is therefore characterized as a device of high resistance. The FPD and the DD of the batches used in the PK study have been determined at the flow rate at which a pressure drop of 4 kPa is achieved (37-40 L/min).

The reference product and the product at issue differ in the way the dose is metered: in the reference product this is a device metered dose in which a multi-dose reservoir of powder is part of the device, whereas the test product is a single-dose pre-metered dose (one dose per blister). The difference is mechanism is acceptable from a quality point of view.

The mono-compartment Elpenhaler consists of a mouthpiece and its cover, a surface on which the blister strip is placed and a storage compartment which houses the single dose blister strips (60). This mono-compartment Elpenhaler intended to administer one metered dose of the dry powder blend consisting of lactose and both active substances. The nomenclature of the dose is the metered dose and not the delivered dose.

A comparison has been performed per impactor stage, according to the orally inhaled products guideline (OIP) CPMP/EWP/4151/00Rev.1 which shows that the *in vitro* characteristics are not the same for test and reference product. Moreover, in view of the large difference in airflow resistance, an application solely based on *in-vitro* data is not possible for the proposed products

The bioequivalence study has been performed on the highest strength of test and reference product. A waiver for the lower strengths is justified from a chemical-pharmaceutical perspective. Linearity (dose-proportionality) of the FPD of the test product has been shown.

Manufacturing process

The manufacturing process consists of mixing pre-sieved lactose, budesonide and formoterol, filling this into blisters and sealing the blisters. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques, but is considered a non-standard process based on the low amounts of drug substances. Process validation data on the product has been presented for three full-scale batches of each strength and an additional three batches for the 400/12 and 200/6 microgram strengths.

Control of excipients

The excipient lactose complies with the Ph.Eur. This specification is acceptable.

Quality control of drug product

The product specification includes tests for description, identity, assay, uniformity of delivered dose, fine particle dose, water content, related substances and microbiological test. The release and shelf-life requirements/limits are the same except for related substances and assay of formoterol. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on six batches of 100/6 mcg/blister, three batches of 200/6 mcg/blister and four batches of 400/12 mcg/blister (one of these a pilot-scale batch). The results demonstrate compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full-scale batches of each strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (3 months). Updated stability results (6 months long-term and intermediate storage conditions) have been submitted, yet in these studies FPD at the correct flow (37 L/min) was not tested at all time points. At accelerated conditions a rapid deterioration of formoterol was observed of increase of impurities and decrease of assay and fine particle dose with several results already out of specification after 3 months. The studies at accelerated conditions have been discontinued and the studies at intermediate conditions will be continued up to 12 months. In view of the limited data provided, a shelf-life of 6 months can be approved for all three strengths.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data has been provided on the use of lactose and compliance with the 'Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products' has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pulentia 100/6, 200/6 and 400/12 microgram/dose has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pulentia is intended for substitution of other products available on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Symbicort, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Budesonide and formoterol fumarate dihydrate are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

The clinical development programme was in line with the applicable guideline (CHMP Guideline on orally inhaled products, CHMP/EWP/4151/00 Rev. 1) assuming that equivalence through pharmacokinetic studies would be established. For this hybrid application one pilot bioequivalence study, and two pivotal 2-stage bioequivalence studies using the 400/12 mcg strength were submitted. These studies are discussed below.

IV.2 Pharmacokinetics

The combination of budesonide and formoterol is used in the treatment of asthma and COPD. Formoterol fumarate is a long-acting selective β2-adrenoceptor agonist. It acts locally in the lungs as a bronchodilator. *In vitro* studies have shown that formoterol has 200-fold greater activity at β2-receptors than β1-receptors. Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol.

To support this hybrid application, the MAH has submitted 3 bioequivalence studies, i.e.

- one pilot four-way bioequivalence study of Pulentia 400 + 12 mcg/inhalation fixed dose combination dry powder inhaler (FDC DPI), in healthy volunteers (study FMBD-PBE-01-ELP/09)
- one pivotal bioequivalence study of Pulentia 400 + 12 mcg/inhalation FDC DPI, in patients with controlled or partly controlled asthma (Study FMBD-PKES-INH-02-EPP/11)
- one pivotal replicate design single dose bioequivalence study without charcoal blockade of Pulentia 400 + 12 mcg/inhalation FDC DPI, in healthy volunteers (Study FMBD-PKES-INH-03-EPP/11).

The reference product used in the studies was Symbicort Turbohaler 400 + 12 mcg/inhalation DPI (Astra Zeneca, Sweden) from the German market. Bioequivalence was assessed both with and without charcoal. The number and type of studies is in accordance with the Guideline on the requirements for clinical documentation for orally inhaled products (OIP).

The pilot study FMBD-PBE-01-ELP/09 is not discussed in this report, as its purpose was mainly to aid in the design of the two pivotal bioequivalence studies.

Biowaiver

The studies were conducted with the highest strength of test and reference product. A biowaiver for additional strengths for this OIP has been granted, based on the conditions in Guideline on the 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).

Bioequivalence studies

- **Pharmacokinetic study FMBD-PKES-INH-02-EPP/11 – with charcoal blockade**

Design

This was a two stage, two period, two sequences, cross-over, block randomized bioavailability study on controlled and partly controlled asthma patients in fasting conditions with charcoal blockade.
One hundred subjects (29 males and 71 females, aged 19-65 years) were enrolled in the first stage as per study protocol. Since bioequivalence was reached after the first stage, the second stage was not required to be performed and no further patients were enrolled. The study medication consisted of one single dose of Pulentia Elpenhaler 400 + 12 microgram/inhalation (budesonide + formoterol test) or one single dose of Symbicort Turbohaler 400 + 12 mcg/inhalation, dry powder for inhalation (reference). Subjects were hospitalised until 24 hours post administration. Then subjects continued the study by visiting the study centre at scheduled time intervals, for the last samples. In each study period all patients swallowed 5 g of activated charcoal suspended in 50 ml of water 2 minutes before study medication administration, 5 g in 50 ml of water 2 minutes after dosing, and 10 g in 100 ml of water at 60, 120 and 180 minutes after dosing.

Plasma samples in tubes containing heparin as anticoagulant for formoterol and budesonide determinations were taken before the administration and at 1 min, 3 min, 5 min, 10 min, 15 min, 30 min, 45 min, 1.0; 1.33; 1.67; 2.0; 2.33; 2.67; 3.0; 4.0; 5.0; 6.0; 8.0; 12.0; 16.0 and 24.0 hours post dose, after each administration. For formoterol determination only additional samples were drawn at 36.0 and 48.0 hours from dosing. Budesonide was not quantified in these samples. The washout period was 5 to 6 days.

The design of the study is adequate. Considering the $t_{1/2}$ of approximately 5 hours for budesonide and of approximately 17 hours for formoterol, the sampling period of 24 hours for budesonide is sufficiently long. For formoterol a sampling period of 48 hours may be short, as formoterol pharmacokinetics is characterised by a slow, terminal elimination. In that respect the blood sampling could have been more opitimised by sampling at a later time point. The MAH conducted a sensitivity analysis by evaluation of partial AUC values over different time periods. The results were very consistent with respect to point estimate and CI. The MAH adequately discussed that in this study the large

extrapolated fraction had no consequences for the reliability of the outcome of the study. Also the washout period of 5-6 days is sufficient.

Analytical/statistical methods
Initially, the statistical analysis did not take into account the multiple testing that is performed in a 2 stage design study. For such a design, the analysis of the first stage data should be treated as an interim analysis and both analyses (first and second stage) should be conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). The MAH was asked to re-analyse the data using a 94.12% CI (as applied in study FMBD-PKES-INH-03-EPP/11 without charcoal). These data have been provided (see below).

Results
Three subjects were considered drop-outs: one was a drop-out due to consent withdrawal, a second subject was a drop-out because of a positive pregnancy test before study drug administration and a third subject was a drop-out due to an adverse event (fever) before study drug administration. Pharmacokinetic analysis was conducted using data from the 97 volunteers who completed the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of budesonide (+ charcoal)

Treatment N=97	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1502 ± 624	1573 ± 658	696 ± 278	0.167 (0.5-1.0)	--
Reference	1725 ± 750	1803 ± 779	816 ±398	0.167 (0.5-1.0)	--
***Ratio (94.12% CI)**	0.88 (0.80-0.97)	--	0.88 (0.80-0.97)	-	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CI confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of formoterol (+ charcoal)

Treatment N=97	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	63.4 ± 24.9	76.2 ± 28.5	9.97 ± 4.64	0.083 (0.05-0.5)	--
Reference	65.2 ± 24.5	77.1 ± 27.4	10.2 ± 4.85	0.083 (0.05-0.5	--
***Ratio (94.12% CI)**	0.96 (0.92-1.00)	--	0.98 (0.90-1.06)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CI confidence interval

**ln-transformed values*

- **Pharmacokinetic study FMBD-PKES-INH-03-EPP/11 – without charcoal blockade**

Design
This was a two stage, four period, cross-over, block randomized, replicate design, single dose bioavailability study in healthy volunteers without charcoal blockade. Forty-eight healthy volunteers (24 males and 24 females, aged 18-55 years) were enrolled in the first stage according to study protocol. Bioequivalence was reached at the first stage according to protocol; therefore the second stage of the study was not required to be performed. There were four periods in the first stage: both test and reference product were given twice according to a replicated design.

The study medication consisted of one single dose of Pulentia Elpenhaler 400 + 12 microgram/inhalation (budesonide + formoterol test) or one single dose of Symbicort Turbohaler 400 + 12 mcg/inhalation, dry powder for inhalation (reference). Patients received the study drug without charcoal blockade. Subjects were hospitalised until 24 post-administration. Then subjects continued the study by visiting the study centre at scheduled time intervals, for the last samples.

Plasma samples in tubes containing heparin as anticoagulant for formoterol and budesonide determinations were taken before the administration and at 1 min, 3 min, 5 min, 10 min, 15 min, 30 min, 45 min, 1.0; 1.33; 1.67; 2.0; 2.33; 2.67; 3.0; 4.0; 5.0; 6.0; 8.0; 12.0; 16.0 and 24.0 hours post dose, after each administration. For formoterol determination only additional samples at 36.0 and 48.0 hours from dosing were also withdrawn. Budesonide was not quantified in these samples. The washout period was 7 days for stage I.

The replicate design of the study is adequate. Considering the $t_{1/2}$ of approximately 5 hours for budesonide and of approximately 17 hours for formoterol, the sampling period of 24 hours for budesonide is sufficiently long. For formoterol a sampling period of 48 hours may be short. However, it was adequately justified based on a sensitivity analysis. Also the washout period of 7 days is adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Forty-six subjects completed the clinical part. One subject was a drop-out and received only once the test formulation, therefore this subject was excluded from the statistical analysis. A second drop-out received once the reference formulation and once the test formulation - statistics was performed only for period one and period two. Three subjects had only 3 study periods included in the statistic evaluation. These three subjects did not perform the administration 100% correctly in the respective study periods and consequently, in agreement with the study protocol provisions were excluded for this periods from the pharmacokinetic analysis and statistics. A total of forty-seven subjects were included in the statistical analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of budesonide (without charcoal)

Treatment N=47	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2363 ± 702	2425 ± 722	1255 ± 473	0.083 (0.016-0.75)	--
Reference	2446 ± 767	2516 ± 807	1140 ± 397	0.083 (0.016-0.75)	--
***Ratio (94.12% CI)**	1.02 (0.91-1.15)	--	0.91 (0.80-1.04)	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CI	confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of formoterol (without charcoal)

Treatment N=47	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	63.7 ± 41.9	68.7 ± 42.6	25.0 ± 13.0	0.083 (0.05-1.67)	--
Reference	57.4 ± 28.8	62.6 ± 29.6	24.3 ± 11.9	0.083 (0.05-1.33)	--
***Ratio (94.12% CI)**	1.03 (0.86-1.24)	--	1.02 (0.89-1.17)	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CI	confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies

Based on the submitted bioequivalence study without charcoal blockade, Pulentia 400/24 microgram is considered bioequivalent with Symbicort Turbuhaler 400/12 microgram. Correct statistical analysis was conduced. Point estimates and 94.12% CI obtained for AUC_{0-t} and C_{max} were within the bioequivalence acceptance range of 0.80-1.25.

For the study with charcoal blockade, reanalysis was conducted applying 94.12% CI. Results were within the 0.80-1.25 acceptance range for AUC_{0-t} and C_{max} for both budesonide and formoterol. Therefore, bioequivalence has been demonstrated both with and without charcoal blockade.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics, clinical efficacy and safety

The clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, and is well known.

No other clinical studies than the above described pharmacokinetic studies have been submitted.

As outlined in the quality section of this report, in the *in vitro* studies at normal flow rates, the Fine Particle Dose is in general comparable between Elpenhaler and Symbicort Turbuhaler, but at the low flow rate of 30 L/min FPD is higher for the Elpenhaler than Symbicort Turbuhaler. These values are for the highest strength but the same trend is seen (although to a lesser extent) in the lower strengths.

The MAH has performed pharmacokinetic studies in patients with mild asthma (FMBD-PKES-INH-02-EPP/11) and healthy volunteers (FMBD-PKES-INH-03-EPP/11) as in line with the OIP guideline. Equivalence has been established with these studies. However, as the Elpenhaler is less flow dependent than the Turbuhaler, it would be unclear whether the results can be extrapolated to other populations.

In the recent application for DuoResp Spiromax (EPAR, EMEA/H/C/002348), the same issue of devices with different flow resistance was discussed. In that dossier the results of a comparative study in different patient populations and healthy volunteers investigating peak inspiratory flow rates (PIFRs)

the Turbuhaler and the Spiromax inhaler showed that very few patients had PIFRs below 40 L/min. When PIFRs were less than 40 L/min there appeared to be no clustering by age or disease severity. Malmberg (2010)[1] found that age and gender are more important determinants of inspiratory flow through DPIs than the degree of expiratory airway obstruction, while Weiner (2006)[2] suggests that women with severe COPD are more at risk than others. Altogether, the RMS considers that although the deposition of both budesonide and formoterol would be higher at low flow, this cannot be translated into a potential safety issue for a specific patient population. Further data is considered not necessary.

The deposition of the active substances at the upper respiratory tract is higher for the test product compared to Symbicort Turbuhaler (33%). The higher deposition of budesonide may cause an increase of the frequency of adverse events like oropharyngeal candidiasis (thrush). It has also been suggested that oropharyngeal candidiasis is perhaps a consequence of immunosuppression at the oral mucosal surface. Other frequently reported adverse events concern hoarseness or dysphonia.
However, a recent Cochrane review failed to show a relation between a higher delivered ICS dose and side effects.
The overall risk of oropharyngeal candidiasis was increased among ICS users compared with placebo (OR 2.65, 95% CI 2.03-3.46; 5586 participants). When focussing on participants randomised to less than 1000 µg/day beclometasone dipropionate (BDP) equivalent, this gave a number needed to treat to harm NNT(h) of 37. In studies assessing more than 1000 µg/day BDP equivalent, there was some variation in baseline risk. In participants from the control group of Burge 2000[3] risk was around 7%, and NNT(h) for participants randomised to steroid was 13 (95% CI 7 to 34), whereas in Calverley 2003a[4] the control group event rate was 1.4%, giving a NNT(h) of 57 (95% CI 29 to 156). In another study, the event rate was 11% amongst those randomised to ICS giving a NNT(h) of 13.
There was also an increased risk of hoarseness or dysphonia (OR 1.95, 95%CI 1.41 to 2.70, 3267 participants). There was minimal heterogeneity, implying a consistent effect across the studies.
The difference in OR (active treatment vs. placebo) does not reveal a clinically relevant difference for less than 1000 µg/day BDP equivalent (OR 1.81 [1.16, 2.84]) and more than 1000 µg/day BDP equivalent (OR 2.11, [1.41, 2.70]).
In the medium-term studies (longer than two months and up to six months), pooling showed an increased risk of oropharyngeal candidiasis (OR 5.59, 95% CI 3.58 to 8.74, 2109 participants). Hoarseness and sore throat were more common with very high dose BDP (3000 µg/day) over four weeks fluticasone propionate 880 µg/day increased the risk of hoarseness.

The application for Pulentia does not concern the paediatric and adolescent population, while the reference product includes adolescents. A restriction to the adult population is acceptable. Moreover, there is already a precedent of accepting a product for only adults: Flusaterol (salmeterol xinafoate/fluticasone propionate) inhalation powder, pre-dispensed, registered through procedure SE/H/1190/002-003/DC.

The presentation of two observational studies was submitted during the procedure (Opinion study and Critical Steps study) following questions from the member states. In the Opinion study out of the 4312 patients who participated in the study 1152 (26.7%) pointed out advantages and 331 (7.7%) pointed out disadvantages. 106 found the device difficult to use (2.46% of the total of patients recruited and 32% of the subgroup that reported a disadvantage) and 140 inconvenient to use (3.25% of the total of patients recruited and 42.3% of the subgroup that reported a disadvantage). In this study both the mono-compartment and duo-compartment Elpenhaler were investigated.
In the second study (Critical Steps) the target was to measure the critical errors that patients do when using their devices. Preliminary results of the study were submitted. The final report of the study will be submitted once available.

[1] L Pekka Malmberg., Paula Rytilä, Pertti Happonen, Tari Haahtela. Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters. International Journal of Chronic Obstructive Pulmonary Disease 2010:5 257–262
[2] Paltiel Weiner, Margalit Weiner. Inspiratory Muscle Training May Increase Peak Inspiratory Flow in Chronic Obstructive Pulmonary Disease. Clinical Investigations. Respiration 2006;73:151–156.
[3] Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.
[4] Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003a;22:912-9.

IV.4 Risk Management Plan

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 Pulentia.

Summary table of safety concerns as approved in RMP

Important identified risks	• Risk of cardiovascular undesirable effects • Paradoxical bronchospasm • Hypersensitivity reactions (e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction)
Important potential risks	• Asthma related mortality and morbidity • Off-label use in patients under the age of 18 years • Off-label use of the high strength formulation • Off-label use in COPD patients • Systemic effects of steroid (including Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children)
Missing information	• None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Symbicort Turbuhaler. No new clinical studies were conducted. The MAH demonstrated bioequivalence based on *in vitro* data and pharmacokinetic studies, with and without charcoal blockade. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questionnaire contained 17 questions addressing the key safety issues and presentation of information. Four additional, solicited questions were asked to complete the questionnaire with regards to positive, negative and stylistic feedback about the readability of the PL. Both rounds of testing showed that, for each question, 100% of participants were able to find the correct information, and all of them were able to answer the questions correctly.
The user testing results indicate that the leaflet is well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the PL is readable and patients/users are able to act upon the information that it contains. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pulentia 100/6, 200/6 and 400/12 microgram/dose inhalation powder, pre-dispensed has a proven chemical-pharmaceutical quality and is a hybrid form of Symbicort Turbuhaler. Symbicort is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence between Pulentia Elpenhaler and the reference formulation Symbicort Turbohaler has been established, both with and without charcoal blockade.

On 30 August 2014 and 30 April 2015, the application was discussed in the Board meetings of the RMS. Concerns were raised regarding the statistical methods applied in the bioequivalence study with charcoal blockade. Also dose proportionality of Fine Particle Dose (FPC) between strengths was discussed. The MAH adequately addressed these matters. An appropriate reanalysis was submitted, using 94.12% confidence intervals, which demonstrated bioequivalence between test and reference product with charcoal blockade. Regarding the difference in deposition between Elpenhaler and Turbuhaler, the Board considered that the higher delivery of the Elpenhaler at low inspiratory flow would not present a potential safety issue for a specific patient population. Overall, a positive conclusion was reached in the Board meeting of 30 April 2015.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that therapeutic equivalence has been demonstrated for Pulentia 100/6, 200/6 and 400/12 microgram/dose with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 June 2015.

The following post-approval commitment has been made during the procedure:

- The MAH committed to provide the study report of the usability study (‘Opinion’ - study code: 2014-HAL-EL-45) once the report has been finalised

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached