LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Airbufo Forspiro

(budesonide, formoterol furoate dihydrate)

SE/H/1690/02/DC
2019-1490

This module reflects the scientific discussion for the approval of Airbufo Forspiro. The procedure was finalised on 2021-01-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sandoz A/S has applied for a marketing authorisation for Airbufo Forspiro 320 microgram/9 microgram inhalation powder, pre-dispensed. The active substances budesonide and formoterol furoate dihydrate are the same as in Airbufo Forspiro 160 microgram/4.5 microgram inhalation powder, pre-dispensed, registered to Sandoz A/S since 2018-05-24.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC 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

III.1 Introduction

The medical products contain two active pharmaceutical ingredients (API): the glucocorticosteroid budesonide and the long-acting beta-2 adrenoceptor agonist (LABA) formoterol fumarate dihydrate.

The pharmacodynamic, pharmacokinetic and toxicological properties of budesonide and formoterol fumarate dihydrate are well known. A short summary is shown below.

III.2 Pharmacology

III.2.1 Budesonide

Budesonide is a synthetic glucocorticosteroid with weak mineralocorticoid activity. It binds with high affinity to the glucocorticoid receptor. Many of the immunosuppressive actions of glucocorticoids are mediated by interference with signalling by the key inflammatory transcriptional regulators nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1). The therapeutic effects of orally inhaled budesonide are thought to result from local actions of the deposited inhaled dose on the respiratory tract rather than from the systemic actions of the swallowed portion of the dose.

III.2.2 Formoterol

Formoterol (formoterol fumarate dihydrate) is a synthetic phenylethanolamine-derivative. It is a long-acting beta-2 adrenoceptor agonist (LABA). Beta-2 receptors are the predominant adrenergic receptors in bronchial smooth muscle. There are also beta-2 receptors in the human heart comprising 10-50% of the total beta-adrenergic receptors. Formoterol acts as a bronchodilatory drug that functions via direct relaxation of airway smooth muscle. The exact mechanism by which formoterol exerts prolonged effects on lung function in patients with asthma is unknown.

III.2.3 Budesonide and Formoterol

The complementary mechanisms of action of budesonide and formoterol mean that different aspects of asthma and COPD pathology, i.e. chronic inflammation and airflow obstruction, are targeted. Pharmacological studies indicate that the combination of budesonide and formoterol acts complementarily (additively or synergistically).

III.3 Pharmacokinetics

III.3.1 Budesonide

A pharmacokinetics (PK) study in rats showed that after inhalation the half-life of budesonide was longer in trachea (8.2 hours) than in plasma (3.7 h). Some placental transfer was demonstrated in the mouse, but it is not known for humans.

III.3.2 Formoterol

In orally exposed rats, formoterol seems to be mainly absorbed from the small intestine. The highest concentrations of radioactivity were measured in the kidneys and liver, followed by the plasma, trachea (33% of plasma levels), lungs (50% of plasma levels) and heart. Only 1-3% of radioactivity was present as unchanged drug in rat plasma. The elimination half-life was 1.7h. In dogs, oral exposure, unchanged formoterol accounted for more than 60% of the radioactivity in plasma immediately after dosage. After 12 hours, ~20% was attributable to unchanged drug. The elimination half-life was 4-6h in dogs. Formoterol is extensively metabolised to formoterol glucuronide in both rats and dogs. The conjugated metabolite excreted in the urine and bile of rats has been identified as the 2-O-glucuronide.

III.3.3 Budesonide and Formoterol

Studies in rats and dogs showed that for both species, there was no evidence of altered exposure to or kinetics of budesonide and formoterol fumarate dihydrate as a result of the combined inhalation of the substances. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide

III.4 Toxicology

A short summary of genotoxicity, carcinogenicity and developmental/reproductive toxicity ("CMR" properties) is provided below.

III.4.1 Budesonide

Genotoxicity and carcinogenicity: Budesonide has been assessed with various genotoxicity tests (including Ames test and micronucleus tests) and not been reported to be mutagenic or clastogenic. There are indications of carcinogenicity in mice (oral exposure for 91 with doses up to 200µg/kg/day). In rat, budesonide caused an increase in gliomas (oral exposure for 104w at 50µg/kg/day). The glioma findings were not repeated in additional rat carcinogenicity studies, although hepatocellular tumours were found at an oral dose of 50µg/kg. The relevance of these findings to human use is unknown.

Developmental and reproductive toxicity: In rats, budesonide had no effect on fertility up to 80µg/kg (s.c.). At 20µg/kg/day (s.c.), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed (NOAEL at 5µg/kg). Budesonide is teratogenic (skeletal malformation, foetal loss) and embryocidal in rabbits (at 25ug/kg s.c.) and rats (500ug/kg s.c.).

III.4.2 Formoterol

Genotoxicity and carcinogenicity: Formoterol has been assessed with various genotoxicity tests (including Ames test and micronucleus tests) and not been reported to be mutagenic or clastogenic. In a 24-month inhalation study in rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma was observed at the inhaled dose of 130µg/kg. Uterine leiomyomas were also generated in mice at 0.1mg/kg oral exposure. It can be noted that increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs. At higher exposures (drinking, 69mg/kg), mice demonstrated adrenal subcapsular adenomas and carcinomas. From dietary exposure (NOAEL 5mg/kg, LOAEL 20-50mg/kg), mice manifested hepatocarcinomas. The relevance of these findings to human use is unknown.

Developmental and reproductive toxicity: A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15mg/kg. In a separate study with male rats treated with an oral dose of 15mg/kg, there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides (NOAEL 3mg/kg). In an inhalation study in rats, no teratogenic effects were seen at doses up to 1.2mg/kg/day or at inhaled deposited doses up to 91µg/kg/day. Oral exposure to formoterol fumarate gave teratogenic (e.g. umbilical hernia, brachygnathia), embryocidal and neonatal/postnatal pup-loss effects in rats at 3mg/kg/day and above. In a peri/postnatal and cross fostering study (oral exposure GD17 to PND21) in rats, there was an increase of stillborn offspring at 6 and 30mg/kg, and the surviving pups showed less viability and experienced a suppression of body weight gain after birth. No other effects of formoterol on the functional development or reproductive capacities of either newborns (F1) or the next generation (F2) were observed.

III.5 Ecotoxicity/environmental risk assessment

Since the active substances are part of generic products, it is expected that they will not lead to an increased exposure to the environment based on the stipulation that it will substitute parts of the prescriptions of the currently marketed original drug.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of budesonide and formoterol fumarate dihydrate are well known. As such, non-clinical data are largely superseded by clinical data/experience (both for individual and combined active substances), no further experimental studies are required, and non-clinical overviews based on literature review are appropriate. With regard to the environmental risk assessment, since the active substances are part of products used in/intended for generic substitution, it is not likely that there will be an increased exposure to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

To support the application, the applicant has submitted one pharmacokinetic study which was performed to assess the lung deposition (with charcoal) and the systemic safety (without charcoal) of the concerned product Budesonide/Formoterol in comparison with the reference product Symbicort Turbuhaler.

Pharmacokinetic properties of the active substance

Budesonide
Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. The systemic bioavailability is approximately 49% of the delivered dose. The oral bioavailability is approximately 10%, reflecting extensive first-pass metabolism. The elimination half-life averages 4 hours.

Formoterol
Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. The systemic bioavailability is about 61% of the delivered dose. The terminal elimination half-life averages 17 hours.

Linearity/Non-linearity Budesonide and Formoterol
Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered dose.

Study 2019-08-PWDI-2
This study was an open label, randomised, four-treatment, four-period, two-sequence single-dose crossover study conducted in 68 healthy volunteers under fasting conditions with and without activated charcoal. The following treatments were given in the study:

A: Test product with activated charcoal.
B: Test product without activated charcoal.

C: Reference product with activated charcoal.
D: Reference product without activated charcoal.

In each period, subjects were administered 2 oral inhalations of the test formulation (total dose Budesonide/formoterol fumarate dihydrate 640 mcg/18 mcg DPI) or the reference formulation (total dose Symbicort® Turbuhaler 640 mcg/18 mcg DPI), with and without activated charcoal suspension in order to exclude the gastrointestinal absorption. Blood samples for concentration analysis were collected pre-dose and up to 18 hours (budesonide and formoterol) 24 hours (formoterol only) post-dose. The study periods were separated by a wash-out period of 7 days.

Plasma concentrations of budesonide and formoterol were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} both with and without charcoal.

Results
The results for test and reference product with and without activated charcoal are presented in Tables below.

Table 12 Summary of study results for treatment A vs. treatment C (bioequivalence evaluation with charcoal administration) (Study 2019-08-PWDI-2)

Parameter	Treatment	Geometric Mean	Ratio [%]	90% CI	Intra-subject CV [%]
BUDESONIDE					
C_{max} [pg/ml]	A (n = 66)	1,931.67	98.05	93.00 – 103.38	18
	C (n = 65)	1,970.11			
AUC_t [pg*h/ml]	A (n = 66)	4,725.76	103.61	99.78 – 107.60	13
	C (n = 65)	4,560.90			
AUC_{inf} [pg*h/ml]	A (n = 66)	4,934.99	103.75	99.91 – 107.72	13
	C (n = 65)	4,756.82			
FORMOTEROL					
C_{max} [pg/ml]	A (n = 66)	42.911	99.76	94.18 – 105.67	20
	C (n = 65)	43.014			
AUC_t [pg*h/ml]	A (n = 66)	115.358	102.22	97.79 – 106.86	15
	C (n = 65)	112.850			
AUC_{inf} [pg*h/ml]	A (n = 65)	130.428	103.51	99.14 – 108.07	15
	C (n = 65)	126.005			

AUC: area under the plasma concentration-time curve; AUC_{inf}: AUC from time zero (0) to infinity; AUC_t: AUC from time zero (0) to the time of the last measurable analyte concentration (t); CI: confidence interval; C_{max}: maximum plasma concentration; n: number of subjects; CV: coefficient of variation; vs.: versus

Treatment A: 2 x **Budesonide/Formoterol 320 µg/9 µg DPI HEXAL**, Lot No. 0905H1/1 (TEST 1) (Sandoz Product Development AEROPHARM GmbH, Germany) + activated charcoal, Lot No. 191190 (Dr. Franz Köhler Chemie GmbH, Germany)

Treatment C: 2 x Symbicort Turbuhaler 320 µg/9 µg DPI, Lot No. PFYS/1 (REFERENCE 1) (AstraZeneca AB, Sweden) + activated charcoal, Lot No. 191190 (Dr. Franz Köhler Chemie GmbH, Germany)

Table 13 Summary of study results for treatment B vs. treatment D (bioequivalence evaluation without charcoal administration) (Study 2019-08-PWDI-2)

Parameter	Treatment	Geometric Mean	Ratio [%]	90% CI	Intra-subject CV [%]
BUDESONIDE					
C_{max} [pg/ml]	B (n = 60)	2,139.85	86.27	80.78 – 92.14	21
	D (n = 66)	2,480.35			
AUC_t [pg*h/ml]	B (n = 60)	5,224.58	91.31	87.10 – 95.73	14
	D (n = 66)	5,721.75			
AUC_{inf} [pg*h/ml]	B (n = 60)	5,511.67	91.46	87.23 – 95.90	14
	D (n = 66)	6,026.35			

Parameter	Treatment	Geometric Mean	Ratio [%]	90% CI	Intra-subject CV [%]
FORMOTEROL					
C_{max} [pg/ml]	B (n = 60)	46.110	90.01	84.47 – 95.92	20
	D (n = 66)	51.226			
AUC_t [pg*h/ml]	B (n = 60)	137.598	90.43	86.20 – 94.87	15
	D (n = 66)	152.160			
AUC_{inf} [pg*h/ml]	B (n = 60)	150.683	88.41	84.30 – 92.71	14
	D (n = 66)	170.445			

AUC: area under the plasma concentration-time curve; AUC_{inf}: AUC from time zero (0) to infinity; AUC_t: AUC from time zero (0) to the time of the last measurable analyte concentration (t); CI: confidence interval; C_{max}: maximum plasma concentration; n: number of subjects; CV: coefficient of variation; vs.: versus

Treatment B: 2 x **Budesonide/Formoterol 320 µg/9 µg DPI HEXAL**, Lot No. 0905H1/2 (TEST 2) (Sandoz Product Development AEROPHARM GmbH, Germany)

Treatment D: 2 x Symbicort Turbuhaler 320 µg/9 µg DPI, Lot No. PFYS/2 (REFERENCE 2) (AstraZeneca AB, Sweden)

Therapeutic equivalence was demonstrated since the 90% confidence interval for the AUC_{0-t} and C_{max} ratio of the test and reference products, for both budesonide and formoterol, with and without charcoal blockade, fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

Therapeutic equivalence, with and without charcoal blockade, between the applied product and the reference product was demonstrated. The performance of the analytical methods was satisfactory. The applied product is recommended for approval, from a pharmacokinetic point of view.

IV.3 Pharmacodynamics

There are no new data.

IV.4 Clinical efficacy and safety

There are no new data.

IV.5 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 Bofunir.

Safety specification

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. All important risks and missing information have been deleted in accordance with the reference product. Version 2.1 with data lock point 28 July 2020 was submitted in response to the first round of questions and is deemed acceptable.

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 an 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 Symbicort Turbuhaler, procedurenumber: SE/H/229/01-02/II/35, SE/H/230/01/II/027. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Bofunir, Budesonide/Formoterol Sandoz and Airbufo Forspiro inhalation powder, is found adequate. There are no objections to approval of Bofunir, Budesonide/Formoterol Sandoz and Airbufo Forspiro inhalation powder, from a non-clinical and clinical point of view. Therapeutic equivalence between the test and reference product has been

adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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 Airbufo Forspiro 320 microgram/9 microgram inhalation powder, pre-dispensed was positively finalised on 2021-01-20.

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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

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

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