



Public Assessment Report

National Procedure

**Luforbec 200/6 micrograms per actuation
pressurised inhalation solution**

**(beclometasone dipropionate,
formoterol fumarate dihydrate)**

PL 35507/0205

Lupin Healthcare (UK) Limited

LAY SUMMARY

Luforbec 200/6 micrograms per actuation pressurised inhalation solution formoterol fumarate dihydrate

This is a summary of the Public Assessment Report (PAR) for Luforbec 200/6 micrograms per actuation pressurised inhalation solution. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Luforbec in this lay summary for ease of reading.

For practical information about using Luforbec, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Luforbec and what is it used for?

This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised, called Fostair 200/6 micrograms per actuation pressurised inhalation solution.

Luforbec is used to treat asthma in adults.

When Luforbec is prescribed it is likely for:

- situations where asthma is not adequately controlled by using inhaled corticosteroids and “as needed” short-acting bronchodilators

or,

- in cases where asthma responds well to both corticosteroids and long-acting bronchodilators.

How does Luforbec work?

Luforbec is a pressurised inhalation solution containing two active substances which are inhaled through the mouth and delivered directly into the lungs.

The two active substances are: beclometasone dipropionate and formoterol fumarate dihydrate. Beclometasone dipropionate belongs to a group of medicines called corticosteroids which have an anti-inflammatory action reducing the swelling and irritation in the lungs.

Formoterol fumarate dihydrate belongs to a group of medicines called long-acting bronchodilators which relax the muscles in the airways and helps with breathing.

Together, these two active substances make breathing easier. They also help to prevent the symptoms of asthma such as shortness of breath, wheezing and coughing.

How is Luforbec used?

The pharmaceutical form of this medicine is pressurised inhalation solution and the route of administration is inhaled into the lungs.

Dose in adults and the elderly:

The recommended dose is two actuations twice daily. The maximum daily dose is 4 actuations.

The patient should always have their quick-acting “reliever” inhaler with them at all times to treat worsening symptoms of asthma or a sudden asthma attack.

At-risk patients

There is no need for dose adjustment in older patients. No information is available regarding the use of Luforbec in people with liver or kidney problems.

Children and adolescents aged less than 18 years must NOT take this medicine.

Luforbec is effective for the treatment of asthma in a dose of beclometasone dipropionate which may be lower than that of some other inhalers containing beclometasone dipropionate. If the patient has been using a different inhaler containing beclometasone dipropionate previously, the patient's doctor will advise them on the exact dose of Luforbec that the patient should take for their asthma.

For further information on how Luforbec is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare product Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Luforbec have been shown in studies?

Because Luforbec is a hybrid medicine, studies in healthy volunteers consist of tests to determine that it is therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that this product can be approved for use.

What are the possible side effects of Luforbec?

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Luforbec is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why was Luforbec approved?

It was concluded that Luforbec has been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Luforbec?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Luforbec. The RMP details the important risks of Luforbec, how these risks can be minimised, any uncertainties about Luforbec (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Luforbec:

Summary of safety concerns	
Important identified risks	1. Hypokalaemia 2. Adrenal suppression 3. Hyperglycaemia 4. Asthmatic crisis/Paradoxical bronchospasm 5. ECG QTc prolongation, tachycardia, tachyarrhythmia 6. Glaucoma 7. Cataract 8. Atrial fibrillation 9. Granulocytopenia 10. Thrombocytopenia 11. Angina pectoris 12. Psychiatric disorders [Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)] 13. Bone density decreased 14. Cushing's syndrome 15. Angioedema 16. Tremor 17. Pneumonia in patient with COPD
Important potential risks	1. Growth retardation (in children and adolescents) 2. Foetal malformation, tocolytic effect
Missing information	1. Effects in the breast-fed baby 2. Safety in children and adolescent below 17 years of age 3. Use in hepatic/renal impaired patients

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Luforbec are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Luforbec

A Marketing Authorisation for Luforbec was granted in the United Kingdom (UK) on 20 July 2022

The full PAR for Luforbec follows this summary.

This summary was last updated in April 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare product Regulatory Agency (MHRA) considered that the application for Luforbec 200/6 micrograms per actuation pressurised inhalation solution (PL 35507/0205) could be approved.

The product is approved for the following indication:

Asthma

Luforbec is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta2-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting beta2-agonist or
- patients already adequately controlled on both inhaled corticosteroids and long-acting beta2-agonists.

Luforbec is indicated in adults

This product includes two active substances:

Beclometasone dipropionate

Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid antiinflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol

Formoterol is a selective beta2-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

This application was approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Fostair 200/6 micrograms per actuation pressurised inhalation solution that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

Data from three pharmacokinetic studies were submitted with this application. The studies were conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 23 January 2020 and as a result of its consideration was of the opinion that on grounds relating to quality, safety and efficacy it may be unable to advise the licensing authority to grant the authorisation. In response, the Applicant submitted further quality, safety, and efficacy data for the medicinal product addressing these concerns, the additional information was deemed to resolve the concerns and a marketing authorisation was granted on 20 July 2022.

II QUALITY ASPECTS

II.1 Introduction

Each actuation/metered dose from the inhaler contains 200 micrograms of beclomethasone dipropionate and 6 micrograms of formoterol fumarate dihydrate. This corresponds to a delivered dose of 177.7 micrograms of beclomethasone dipropionate and 5.1 micrograms of formoterol fumarate dihydrate.

In addition to beclomethasone dipropionate and formoterol fumarate dihydrate, this product contains ethanol anhydrous, maleic acid, water for injections and the CFC-free propellant-norflurane (HFA -134a).

The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve and fitted into a white polypropylene plastic actuator which incorporates a mouthpiece and is provided with a green plastic protective cap. The actuator has an integrated dose indicator which indicates the number of actuations (puffs) remaining. Each pack contains 1 pressurised container which provides 120 actuations.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCES

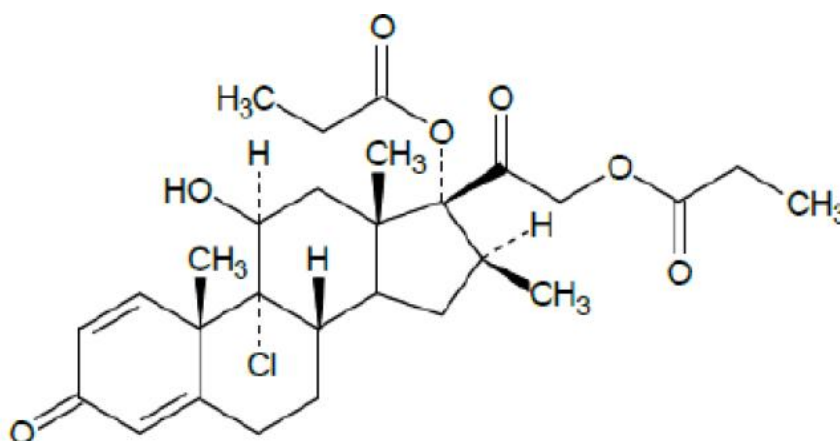
rINN: Beclomethasone dipropionate

Chemical Names: Pregna-1,4-diene-3,20-dione, 9-chloro-21-(2,2-dimethyl-1-oxopropoxy)-6-fluoro-11-hydroxy-16-methyl-, (6 α ,11 β ,16 α)-;
9-Chloro-6 α -fluoro-11 β ,21-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 21-pivalate;

[2-[(6S,9R,16R)-9-chloro-6-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-7,8,11,12,14,15,16,17-octahydro-6H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] 2,2-dimethylpropanoate (IUPAC)

Molecular Formula: C₂₈H₃₇Cl O₇

Chemical Structure:



Molecular Weight: 521.1 g/mol

Appearance: A white or almost white, crystalline powder.

Solubility: Practically insoluble in water, freely soluble in acetone, and sparingly soluble in alcohol. It is slightly hygroscopic (increase in mass lower than 0.2%).

Beclometasone dipropionate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

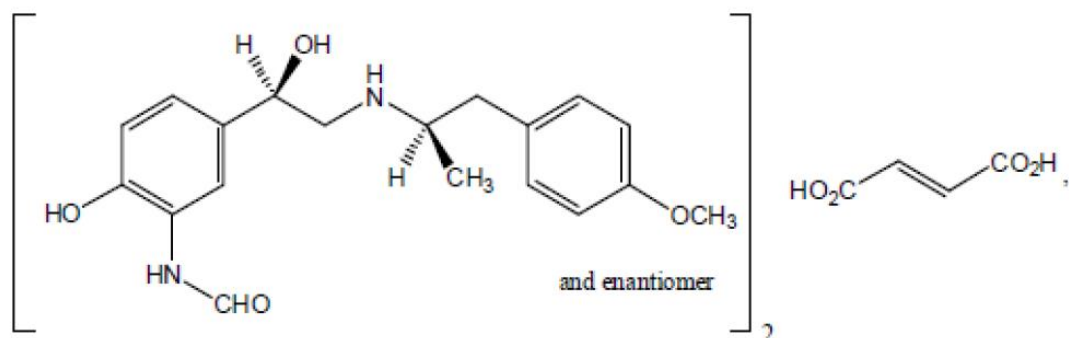
rINN: Formoterol fumarate

Chemical Names: (±)-2'-Hydroxy-5'-[(*R**)-1-hydroxy-2-[(*R**)-*p*-methoxy- α -ethylphenethyl] amino]ethyl] formanilide fumarate (2:1) (salt), dihydrate

N-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino] ethyl]phenyl] formamide, (*E*)-2-butenedioate dihydrate

Molecular Formula: (C₁₉H₂₄N₂O₄)₂ C₄H₄O₄ · 2H₂O
C₄₂H₅₂N₄O₁₂ · 2H₂O

Chemical Structure:



Molecular Weight: 840.91

Appearance: A white or almost white or slightly yellow powder.

Solubility Slightly soluble in water, freely soluble dimethyl sulfoxide and in acetic acid, soluble in methanol, slightly soluble in 2-propanol and in ethanol; practically insoluble in acetonitrile, acetone, ethyl acetate and in diethyl ether.

Formoterol fumarate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 21 months, with the storage conditions:

Prior to dispensing to the patient:

Must be stored in upright position in a refrigerator (2-8°C) for a maximum of 18 months.

After dispensing:

The storage conditions are “do not store above 25°C (for a maximum of 3 months).

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister”.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of beclometasone dipropionate and formoterol fumarate dihydrate are well-known, no new non-clinical studies

are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

Additional data were provided in relation to the excipient maleic acid. Aside from these data, no new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology

No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In accordance with the regulatory requirements, data from three pharmacokinetic (PK) studies have been submitted with this application. These studies were conducted in-line with current Good Clinical Practice (GCP).

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following.

Study BDPFF-AS-101

A single centre, open label, randomised, single-dose, four-period, four treatment cross-over study comparing Luforbec 200/6 micrograms per actuation pressurised inhalation solution to the reference product Fostair 200/6 micrograms per actuation pressurised inhalation solution **with and without the use of a charcoal block** in healthy volunteers under fasting conditions.

Both treatments were administered without a spacer and 2 actuations were inhaled in each treatment period. Treatment periods were separated by a 20 (+3) day washout period between treatment administrations. Blood samples were obtained pre-dose and up to 36.0 hours post-dose.

17-BMP

Table 14: Summary of Statistical Comparisons of Plasma 17-BMP Pharmacokinetic Parameters C_{max} , AUC_{0-4} , and $AUC_{0-\infty}$ (PK Analysis Set)				
Parameter (unit)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	GMR (90% CI) A vs B	Intrasubject CV% A vs B
	GLSM	GLSM		
C_{max} (pg/mL)	534.3078	521.5587	102.44 (96.47, 108.79)	25.38
AUC_{0-4} (pg×hr/mL)	2304.7341	2301.7928	100.13 (95.10, 105.42)	21.66
$AUC_{0-\infty}$ (pg×hr/mL)	2623.5814	2603.3801	100.78 (96.18, 105.60)	18.99

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects 007, 008, 011, 031, 033, 035, 047, 053, 054, 067, 069, 074, 098, 102, and 103.
Source: Table 14.2.1.13.

Formoterol

Table 18: Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max} , AUC_{0-4} , and $AUC_{0-\infty}$, Without and With Oral Charcoal (PK Analysis Set)

Parameter (unit)	Treatments			
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D)
	GLSM	GLSM	GLSM	GLSM
C_{max} (pg/mL)	16.0682	15.2830	14.6351	13.2526
AUC_{0-4} (pg*hr/mL)	44.1205	42.9461	23.5434	21.0990
$AUC_{0-\infty}$ (pg*hr/mL)	52.4552	51.6675	43.5534	41.5183
Parameter (unit)	GMR (90% CI) Treatment A vs Treatment B (without Oral Charcoal)		GMR (90% CI) Treatment C vs Treatment D (with Oral Charcoal)	Intrasubject CV%
C_{max} (pg/mL)	105.14 (98.67, 112.03)		110.43 (103.48, 117.85)	26.75
AUC_{0-4} (pg*hr/mL)	102.73 (94.21, 112.03)		111.59 (102.12, 121.93)	37.03
$AUC_{0-\infty}$ (pg*hr/mL)	101.52 (95.30, 108.15)		104.90 (98.32, 111.92)	22.00

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):

Subjects 007, 008, 011, 031, 033, 035, 047, 053, 054, 067, 069, 074, 098, 102, and 103.

The following subjects were excluded from the PK Analysis Set for both Treatments C and D (see Section 11.1 for details):

Subjects 003, 008, 015, 025, 026, 030, 031, 033, 035, 042, 054, 055, 057, 058, 060, 067, 068, 075, 084, 098, 103, 106, and 107. Additionally, Subject 038 was excluded from the PK Analysis Set for both Treatments C and D due to the inability to quantify all formoterol samples.

Source: Table 14.2.1.15.

BDP

Table 22: Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max} , AUC_{0-4} , and $AUC_{0-\infty}$ (PK Analysis Set)

Parameter (unit)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	GMR (90% CI) A vs B	Intrasubject CV% A vs B
	GLSM	GLSM		
C_{max} (pg/mL)	2363.9272	2421.7765	97.61 (89.81, 106.09)	35.68
AUC_{0-4} (pg*hr/mL)	235.4247	242.1470	97.22 (90.97, 103.91)	28.19
$AUC_{0-\infty}$ (pg*hr/mL)	245.7612	255.6832	96.12 (89.58, 103.14)	25.88

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):

Subjects 007, 008, 011, 031, 033, 035, 047, 053, 054, 067, 069, 074, 098, 102, and 103.

Source: Table 14.2.1.17.

Based on the results of this PK study, equivalent lung and systemic exposure can be concluded between the 200/6 mcg per actuation strengths of Test and Reference products.

Study BDPFF-AS-102

A single centre, open-label, single-dose, randomised, 2-period, 2-treatment, 2-sequence, crossover study, comparing Luforbec 200/6 micrograms per actuation pressurised inhalation solution without charcoal block and Fostair 200/6 micrograms per actuation pressurised inhalation solution **without charcoal block** in healthy subjects under fasting conditions.

Both treatments were administered with the Aerochamber Plus spacer and 2 actuations were inhaled in each study period. Treatment periods were separated by a 7 (+2) day washout period

between treatment administrations. Blood samples were obtained pre-dose and up to 36.0 hours post-dose.

Study 102: Pharmacokinetic Results Summary

There were a high number of subjects with lack of any measurable plasma concentrations for 17-BMP and formoterol for all timepoints. There were also subjects with very low plasma concentrations, defined as having AUC_{0-t} less than 5% of geometric mean AUC_{0-t} for reference product, calculated without inclusion of data from the outlying subjects for 17-BMP, BDP, and formoterol.

Lack of any measurable plasma concentrations or very low plasma concentrations indicates that some subjects may not have received the full test and/or reference dose. In the absence of similar observations in BDPFF-AS-101 (performed using the same product), a likely reason for the observation was thought related to the inhalation technique when using the spacer, where incorrect technique, for example exhaling into the spacer, is expected to lead to poor dose delivery. Consequently, based on the determination that the study results are likely affected by the technique during administration and not the product, the study was invalidated.

Study BDPFF-AS-103

Following invalidation of study 102, the study was repeated under study code 103. This study used the same batch of test product used in the 102 study, however a different reference product batch was used (since it was not possible to procure the original reference product batch from the 102 study). The design of the study was not changed, however several modifications were made with respect to the handling of the spacer device prior to and during the inhalation manoeuvre. Additional subject training was added to the study protocol procedures to ensure proper inhalation technique was achieved using an Aerosol Inhalation Monitor (AIM) at the spacer setting, and training with spacers using placebo inhalers. Additional instructions and retraining on the spacer handling and cleaning procedures, to minimise electronic charge, were implemented for the new study.

The study was a single centre, open-label, 2-period, 2-treatment, 2-sequence cross-over study comparing Luforbec 200/6 micrograms per actuation pressurised inhalation solution and Fostair 200/6 micrograms per actuation pressurised inhalation solution **without charcoal block** in healthy subjects under fasting conditions.

Both treatments were administered with Aerochamber Plus spacer and 2 actuations were inhaled in each study period. No charcoal block was used in the study. Treatment periods were separated by a 7 (+2) day washout period between treatment administrations. Blood samples were obtained pre-dose and up to 36.0 hours post-dose.

A summary of the pharmacokinetic results is presented below.

Formoterol

Table 13: Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max} , AUC_{0-4} , $AUC_{0-\infty}$, and $AUC_{0-30min}$ (PK Analysis Set)

Parameter (unit)	n	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	GMR (90% CI) A vs B	Intra- subject CV%
		GLSM	GLSM		
C_{max} (pg/mL)	93	17.2	16.4	105 (101, 109)	16.9
AUC_{0-4} (pg×hr/mL)	93	35.8	32.2	111 (107, 116)	17.2
$AUC_{0-\infty}$ (pg×hr/mL)	91	40.6	36.9	110 (106, 114)	14.5
$AUC_{0-30min}$ (pg×hr/mL)	93	5.14	4.85	106 (102, 110)	15.8

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects 023 and 088. In addition, Subject 093 was excluded from the analyses since the pre-dose concentration in treatment period 1 (Treatment B) was >5% of C_{max} .

Source: Table 14.2.1.15.

BDP

Table 15: Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max} , AUC_{0-4} , $AUC_{0-\infty}$, and $AUC_{0-30min}$ (PK Analysis Set)

Parameter (unit)	n	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	GMR (90% CI) A vs B	Intra- subject CV%
		GLSM	GLSM		
C_{max} (pg/mL)	94	5200	4980	104 (98.6, 111)	24.1
AUC_{0-4} (pg×hr/mL)	94	523	525	99.6 (95.2, 104)	18.8
$AUC_{0-\infty}$ (pg×hr/mL)	64	511	511	100 (94.1, 106)	20.6
$AUC_{0-30min}$ (pg×hr/mL)	94	488	495	98.7 (94.5, 103)	18.0

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects 023 and 088.

Source: Table 14.2.1.17.

According to the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference products when used with Aerochamber Plus spacer.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety

With the exception of the safety data from the PK studies submitted with this application, no new safety data were submitted. The safety data submitted showed that the product was well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

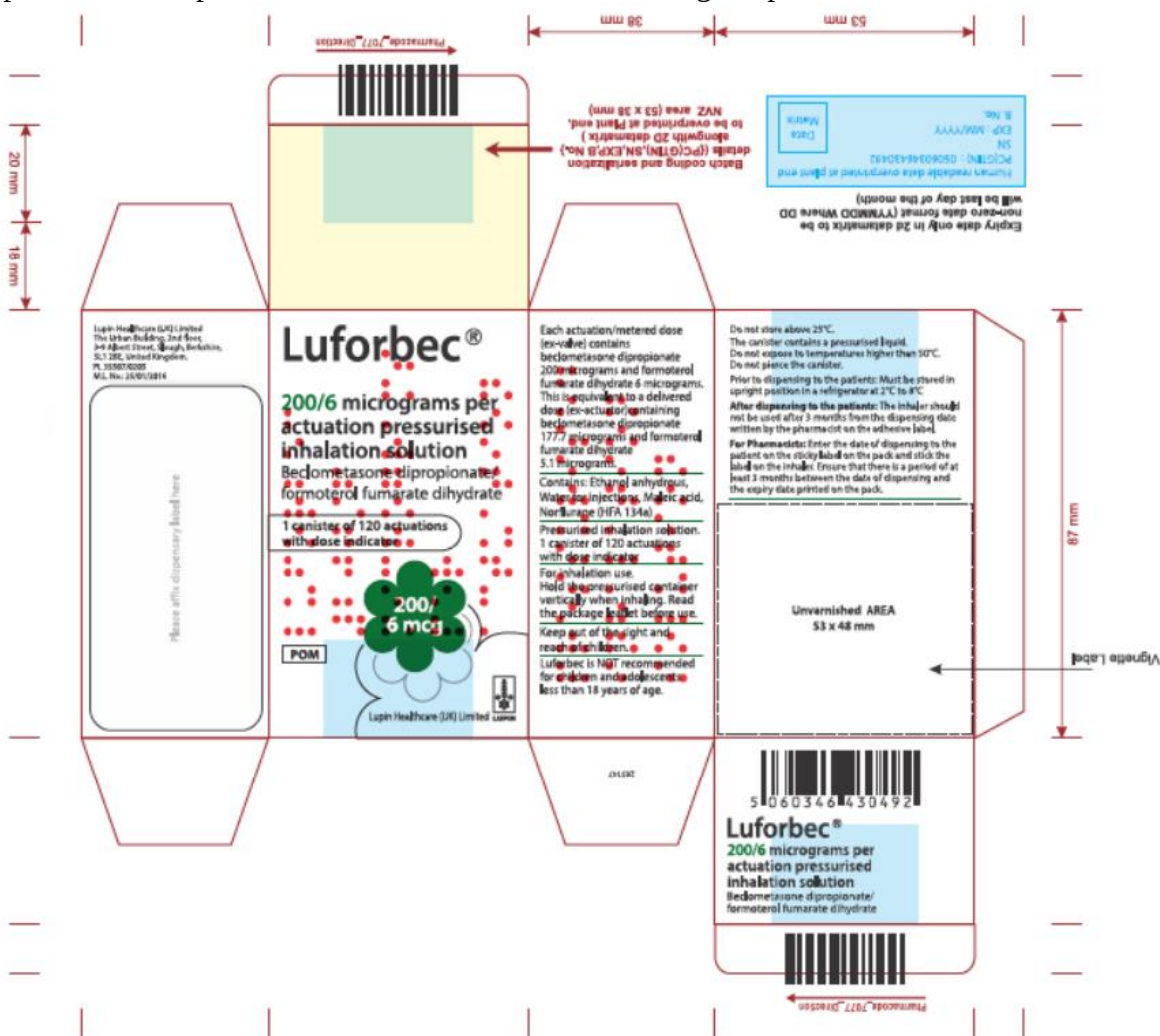
Extensive clinical experience with beclometasone dipropionate and formoterol fumarate dihydrate is considered to have demonstrated the therapeutic value of the product.

The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

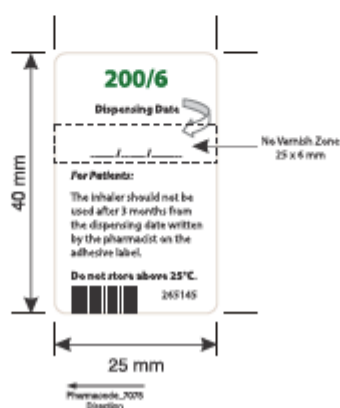
In accordance with legal requirements, the current approved versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.





300% enlarged



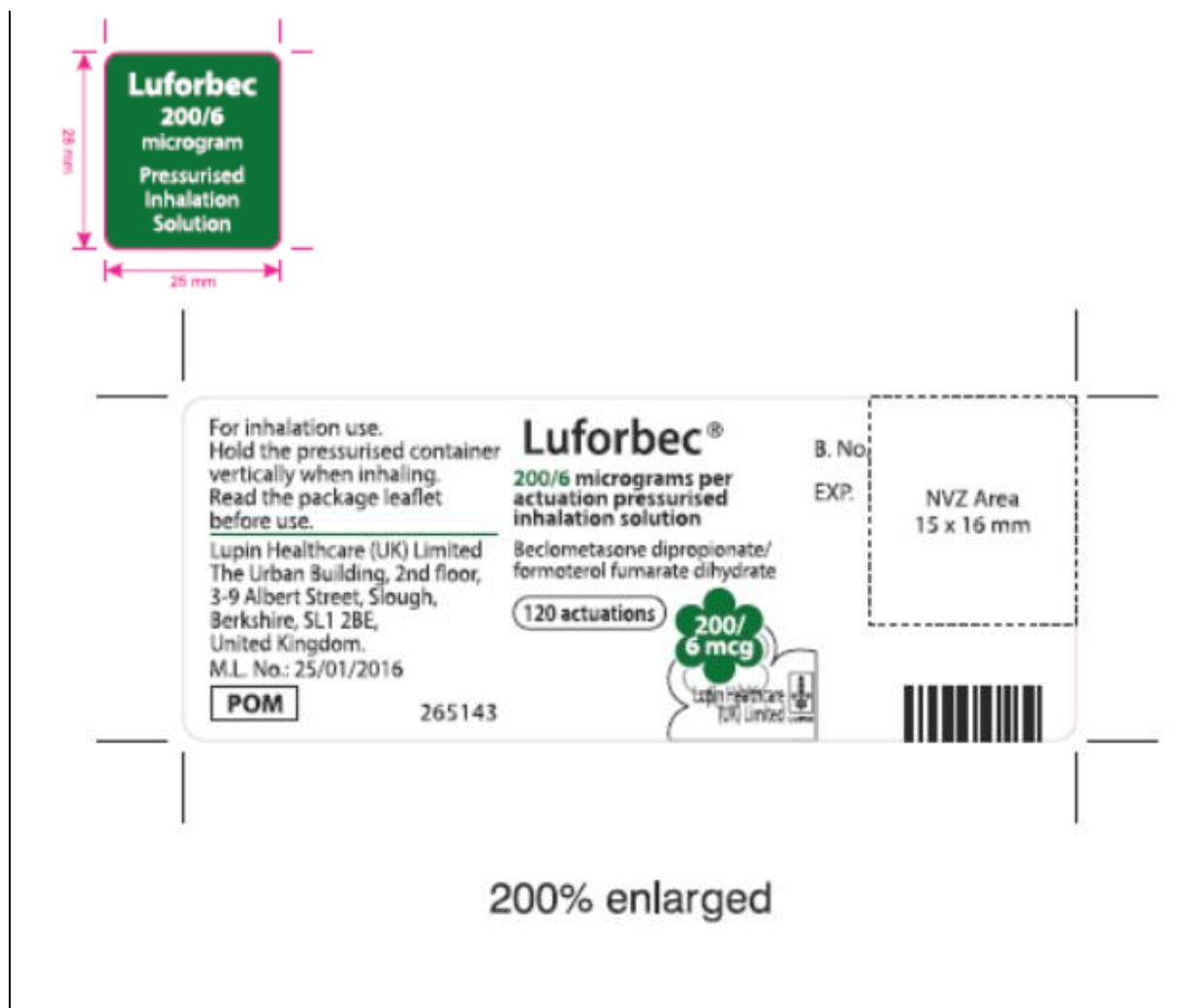


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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N