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1. PRODUCT DEVELOPMENT RATIONALE

1.1. Introduction

Lupin Healthcare (UK) Limited has developed Luforbec 100/6 micrograms [redacted] per actuation pressurised inhalation solution formulations, containing beclometasone dipropionate (BDP) and formoterol fumarate dihydrate (FFD).

A Marketing Authorisation Application (MAA) has been submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) via a National Procedure. The MAA is made under Article 10.3 (hybrid) of European Directive 2001/83/EC (as amended), with Fostair® pressurised inhalation solution (marketed by Chiesi UK Limited) as the reference product.

Each metered dose (ex-valve) of Luforbec 100/6 micrograms contains 100 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of 84.6 micrograms of beclometasone dipropionate and 5.0 micrograms of formoterol fumarate dihydrate.

[redacted]

he Lupin BDP/FFD pressurised inhalation solution was developed to meet all the criteria required to demonstrate therapeutic equivalence to the reference product Fostair®, through comparative *in vitro* and Pharmacokinetic (PK) data, as listed in Section 5.2 of CHMP guideline (CPMP/EWP/4151/00 Rev. 1).

1.2. Pharmacological Class

BDP belongs to the corticosteroids class of medicines.

Inhaled corticosteroids (ICS) like BDP exhibit glucocorticoid local anti-inflammatory and immune suppressive effects within the lungs. These effects are intended to reduce symptoms and exacerbations of asthma with fewer adverse effects than when corticosteroids are given orally. Inhaled glucocorticoids reduce the number of inflammatory cells and restore airway epithelial integrity in bronchial biopsy specimens obtained from mild asthmatic patients. These effects are likely to result from inhibition of transcription of several cytokines that are overexpressed in asthma (Dollery, 1999). Glucocorticoids also inhibit plasma exudation through the endothelial barrier of the bronchial vasculature and therefore lead to a reduction in airway oedema (Dollery, 1999).

FFD belongs to the class of long-acting β2-adrenoceptor agonists (LABAs) and acts by relaxing airway smooth muscles and consequent bronchodilation.

LABAs like FFD are selective β2-adrenergic agonists which bind to the G-protein coupled β2-adrenoreceptor and induce a cAMP/protein kinase A signaling cascade, which results in smooth muscle relaxation, and possible anti-inflammatory effects. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation and has a duration of 12 hours after a single dose (Goodman and Gilman, 12th Edition, 2011; Faulds et al., 1991).

1.3. Indication

As Luforbec has been developed to be therapeutically equivalent to the reference product Fostair®, the Applicant proposes to mirror the approved indications for the reference product:

Luforbec 100/6 micrograms per actuation pressurised inhalation solution

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.

COPD (Chronic obstructive pulmonary disease)

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.

[redacted]

1.4. Scientific background

1.4.1. Disease background: Asthma and COPD

Asthma:

As a common chronic disease that substantially burdens both patients' lives and health economics, asthma has 339 million sufferers worldwide (Asthma UK, 2020). It is estimated that an additional 100 million people will be affected by 2025 (Yildiz, 2013).

Asthma is the most common chronic condition to affect children, and in the UK approximately 5.4 million people (1.1 million children and 4.3 million adults) currently get treatment for asthma (Asthma UK, 2020). The analysis of official figures from the Office for National Statistics, released by the charity Asthma UK, shows that more than 1400 adults and children died from asthma attacks in 2018, an 8% increase since 2017 (Iacobucci, 2019).

Asthma UK's current (2020) analysis, of the most recent Europe-wide figures from 2011 to 2015 found that the UK has one of the worst asthma death rates in Europe, with the rate of people dying from an asthma attack increasing by more than 20% in five years (Asthma UK, 2020)

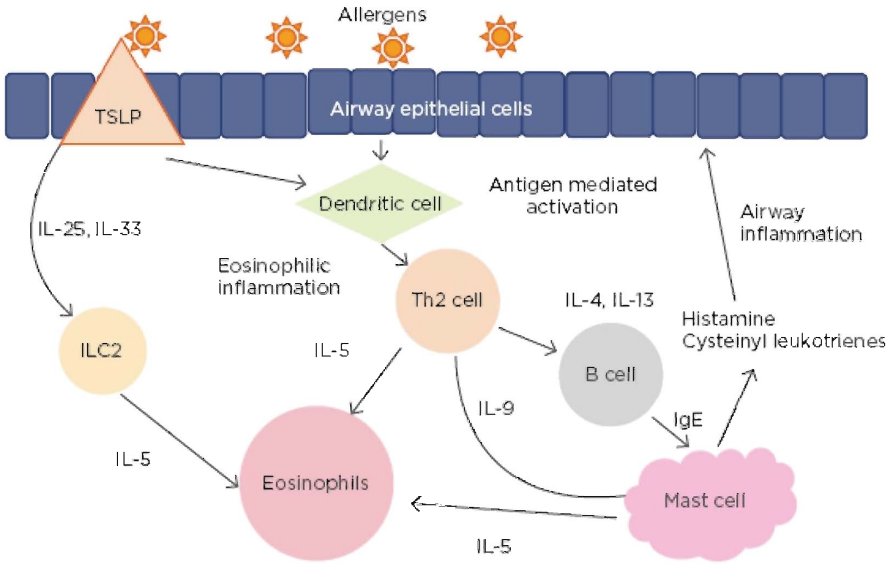
Asthma is a chronic inflammatory disease that exhibits complex pathophysiology characterized by activation of mast cells, infiltration of eosinophils, and T helper 2 (TH2) lymphocytes. During an acute asthma exacerbation, a stimulus or a trigger initiates an airway response that stimulates inflammation, airway hyperactivity, bronchospasm, and increased mucous production. Triggers vary from person to person but may include cold air, pollen, dust, pet dander, cigarette smoke, exercise, infection, medications, bacteria, foods, pollution, coughing, and laughing (Sims, 2006).

When the airways of an asthmatic patient are exposed to a trigger, at first there is an acute inflammatory response in the mast cells that line the airways. Complex cytokine networks, including chemokines and growth factors, play important roles in orchestrating the inflammation process (Barnes, 2008).

The inflammation may be directed by dendritic cells that regulate TH2 cells that drive eosinophilic inflammation and IgE formation by B lymphocytes (

Figure 1). Airways epithelium plays an important role through the release of multiple inflammatory mediators and through the release of growth factors to repair the damage caused by inflammation.

Figure 1: The pathogenesis of asthma



(Source: Jennifer Y et al., 2018)

[ILC2: Type 2 innate lymphoid cells; TSLP: thymic stromal lymphopoietin]

The release of other mediators cause circulating inflammatory cells to travel to the lungs, which cause bronchoconstriction, microvascular leakage and plasma exudation (Goodman and Gilman, 12th Edition, 2011). Hypersecretion then leads to an increase in mucous production and an increased permeability in the airways. The mucous narrows the constricted airways even further, which impairs gas exchange (Sims, 2006). One process leads to another which sets up a vicious cycle in which there is impaired gas exchange.

COPD:

COPD is a condition characterised by poorly reversible airflow limitation that is generally progressive and causes serious disability. Exacerbations and co-morbidities contribute to the overall severity in individual patients.

As part of the Global Burden of Disease (GBD) study for 1990 Murray and Lopez, in collaboration with the World Health Organization, prepared projections of mortality and burden of disease by cause out to 2000, 2010, and 2020. According to this study, COPD was projected to be the 5th most prevalent disease worldwide and 3rd most common cause of death by 2020 (Lopez and Murray, 1998).

Updated projections on global mortality and burden of disease indicates that by 2030, COPD is projected to become the fourth most common cause of death (Mathers and Loncar, 2006).

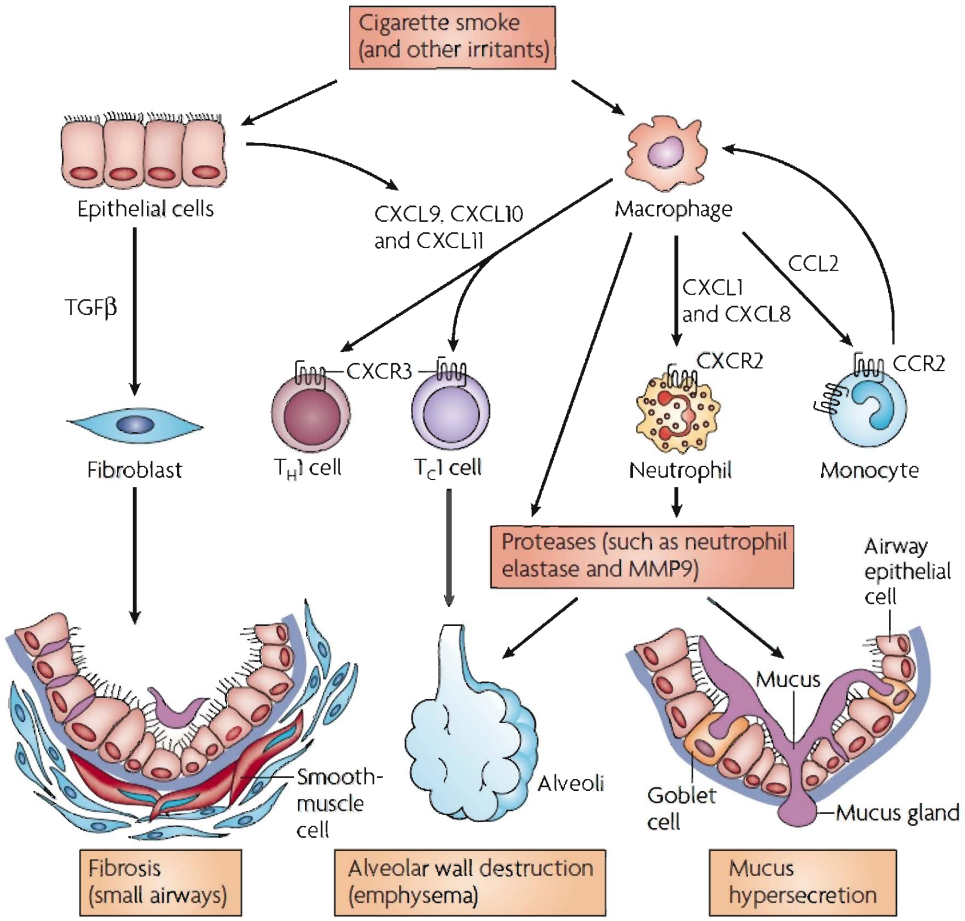
The UK is among the top 20 countries for COPD mortality worldwide and third in Europe, just after Denmark and Hungary (COPD statistics, 2020).

An estimated 1.2 million people in the UK are living with diagnosed COPD – considerably more than the 835,000 estimated by the Department of Health in 2011. COPD is the second most common lung disease in the UK, after asthma. Around 2% of the population over 16 years old – 4.5% of all people aged over 40 – live with diagnosed COPD (COPD statistics, 2020).

COPD is characterized by chronic inflammation of the airways, although there are marked differences in inflammatory mechanisms and response to therapy between asthma and COPD (Goodman and Gilman,12th Edition, 2011; Barnes, 2008).

There is also increased elastolysis and evidence for involvement of several elastolytic enzymes, including serine proteases, cathepsins and matrix metalloproteinases. The inflammation and proteolysis in COPD is an amplification of the normal inflammatory response to cigarette smoke as represented in Figure 2 (Barnes et al., 2003).

Figure 2: Cellular mechanism of the COPD

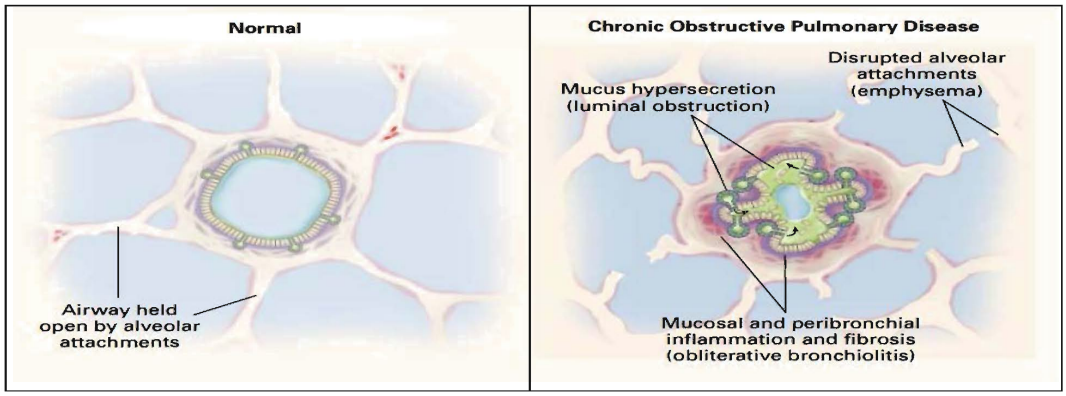


(Source: Barnes et al., 2008)

In COPD, the inflammation predominantly affects small airways, resulting in progressive small airway narrowing and fibrosis (chronic obstructive bronchiolitis) and destruction of the lung parenchyma with destruction of the alveolar walls (emphysema). Figure 3 represents the airways of a COPD patient with air trapping due to emphysema.

The inflammation is characterised by increased numbers of alveolar macrophages, neutrophils and cytotoxic T-lymphocytes, and the release of multiple inflammatory mediators (lipids, chemokines, cytokines, growth factors). A high level of oxidative stress may amplify this inflammation (Barnes, 2000).

Figure 3: Airways of a COPD patient with air trapping due to emphysema



Source: Barnes, 2000

In addition to inflammation and/or alterations in repair mechanisms, presence of inflammatory mediators in the circulation may result in systemic manifestations such as skeletal muscle wasting and cachexia. Systemic inflammation may also initiate or worsen comorbid diseases, such as ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes (Barnes and Celli, 2009).

Assessment of COPD requires assessment of symptoms, degree of airflow limitation, risk of exacerbations and comorbidities. Combined assessment forms the basis of pharmacological and nonpharmacological management of COPD. In addition to being non-invasive and a readily available test, the spirometry test is the most reproducible and objective measurement of airflow limitation. Presence of post bronchodilator $FEV_1/FVC < 70\%$ confirms the presence of persistent airflow limitation and thus of COPD. The criteria of FEV_1/FVC ratio is simple, independent of reference values and has been used on numerous clinical trials that forms the evidence base from which most treatment recommendations are drawn (GOLD 2020 Report).

The global initiative for Chronic Obstructive Lung Disease (GOLD) classifies COPD based on the impairment of lung function i.e. post bronchodilator FEV_1/FVC in the following stages:

Table 1: Classification of airflow limitation severity in COPD

Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1)		
In patients with $FEV_1/FVC < 70\%$		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted

Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1)		
GOLD 4:	Very Severe	FEV_1 < 30% predicted

(Source: GOLD 2020 Report)

1.4.2. Management of asthma and COPD

Management of Asthma:

All guidelines for the management of asthma are based on asthma severity. Disease is graded based on clinical features such as frequency and severity of acute exacerbations and nocturnal symptoms, peak expiratory flow rates (PEFR) or forced expiratory volumes in 1 second (FEV_1).

Asthma self-care management includes optimizing the goals of therapy; these include: maintaining (near) normal pulmonary function tests, maintaining normal activity levels, including exercise, preventing chronic and nocturnal symptoms, preventing recurrent exacerbations, minimizing the effects of medications, identifying and avoiding triggers, upper respiratory infections, sinusitis, and otitis, educating patients to manage their condition, minimize use of emergency visits and hospitalizations (Sims, 2003; Holcomb, 2004).

The aim of asthma management is control of the disease. Complete control is defined as (SIGN158, 2019):

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV_1 and/or PEF >80% predicted or best)
- minimal side effects from medication.

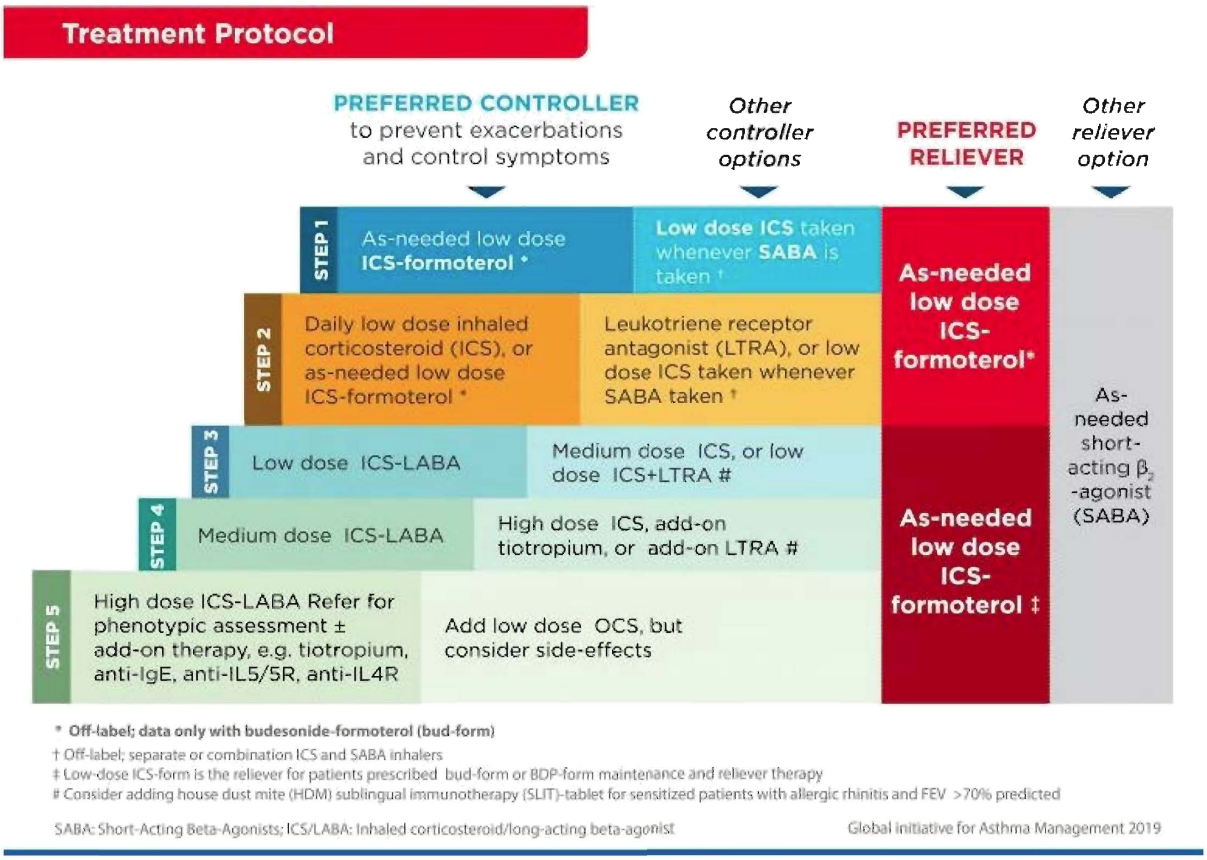
The general approach to management of asthma is to start treatment at the level most appropriate to initial severity, achieve early control and maintain control by increasing treatment as necessary and decreasing treatment when control is good.

On a global level, the Global Initiative of Asthma (GINA) provides a comprehensive and integrated approach to asthma management by providing tools for feasible implementation in clinical practice. Once asthma treatment has been started, ongoing assessment of the patient should continue to adjust pharmacological and nonpharmacological treatment for individual patients need.

Conventionally, ICS treatment is recommended for patients with symptoms on more than 2 days per week, but this criterion has scant evidence. In 2014, with a focus on risk reduction and absence of evidence for safety of treating asthma with short acting beta-agonist (SABA) alone, the Global Initiative for Asthma (GINA) suggested low-dose ICS should be considered as a Step 1 option.

With major advances in asthma management GINA no longer recommends SABA-only treatment for Step 1, see Figure 4 below (GINA, 2019). This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk. GINA now recommends that all adults and adolescents with asthma should receive symptom-driven or regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations and to control symptoms. (Global Initiative for Asthma, www.ginasthma.org)

Figure 4: Asthma Treatment Protocol



(Source: GINA, 2019)

Consistent with international recommendations, there have been recent updates to the UK asthma treatment guidelines (such as BTS/SIGN) which includes a complete revision of the section on

monitoring, and updates to sections including supported self-management, nonpharmacological management of asthma, pharmacological management of asthma, inhaler devices and management of acute asthma.

For better monitoring of asthma, the UK guideline recommends assessment of risk of future asthma attacks at every asthma review by asking about history of previous attacks, objectively assessing current asthma control, and reviewing reliever use. Nonpharmacological management related recommendation as per the UK guideline includes avoiding triggers, asthma education and regular assessment to ensure adherence to the asthma treatment.

From a pharmacological management perspective, the UK guideline recommends using inhaled corticosteroids as a preventer drug for adults for achieving overall treatment goals. It is recommended to initiate treatment with low-dose ICS and make it explicit that patients should not be given short-acting beta-agonists (SABA) alone, except in the few with very occasional short-lived wheeze (SIGN158, 2019).

β2- adrenoceptor agonists play a major role in treatment of bronchoconstriction in treatment of asthma. Delivery of β2- adrenoceptor agonists in the lungs leads to effective activation of β2-receptors in bronchi and very low systemic drug concentrations and less potential for side effects.

The β2- adrenoceptor agonists can be classified as short-acting and long-acting. Formoterol fumarate dihydrate is a long-acting β2 agonist with rapid onset of action and its action may persist for up to 12 hours (Goodman & Gilman, 12th edition, 2011; Faulds et al, 1991).

International guidelines recommend the combination therapy of inhaled corticosteroids (ICS) and long-acting-beta2-agonists (LABA) in a large proportion of asthmatic patients (Crisafulli et al., 2016).

The UK guideline recommends that before considering increasing the dose of inhaled corticosteroids the clinician should check adherence to treatment, inhaler technique and elimination of triggers and treatment and use a long-acting β2 agonist as first line add-on therapy. In the event, asthma control remains sub optimal after addition of long-acting β2 agonist, increasing the dose of inhaled corticosteroids from low dose to medium dose in adults is recommended (SIGN158, 2019).

Management of COPD:

COPD is a common, treatable (but not curable) and largely preventable lung condition. It is characterised by persistent respiratory symptoms and airflow obstruction which is usually progressive and not fully reversible (NICE, 2019).

Current treatment strategies for COPD are aimed at treating both the symptoms and the pulmonary inflammation underlying the complex pathophysiology of COPD.

Pharmacological therapy for COPD is used to reduce the frequency and exacerbations and improve exercise tolerance and health status.

The classes of medicines commonly used to treat COPD are β2-agonists-short acting (SABA) and long-acting (LABA), anticholinergics short-acting (SAMA) and long acting (LAMA), Combinations of SABA/SAMA,LABA/LAMA, triple combination in one device (LABA/LAMA/ICS), methylxanthines, phosphodiesterase inhibitors, mucolytic agents (GOLD 2020).

As per the NICE guideline, as initial inhaled therapy for COPD, a short-acting bronchodilator (SABA), or short-acting muscarinic antagonist (SAMA) for use as needed (to relieve breathlessness and improve exercise tolerance) should be offered. If symptoms are not controlled, long-acting bronchodilators (LABAs), long-acting muscarinic antagonists (LAMAs), or inhaled corticosteroids (ICSs), and add on therapies may be considered in a stepwise approach — choice of treatment depends on the specific clinical situation. ICSs should be prescribed in combination with a long-acting bronchodilator (NICE, 2019).

The NICE guideline recommends that before starting LAMA+LABA+ICS, a clinical review is conducted to ensure that the patient has been offered supportive non-pharmacological management and relevant vaccinations. When considering use of inhaled corticosteroids, the risk of side effects (including pneumonia) in people who take inhaled corticosteroids for COPD should be discussed with the patient. The NICE guideline also recommends to minimise the number of inhalers and the number of different types of inhaler used by each person as far as possible.

The Global Initiative for the Management of Chronic Obstructive Lung Disease (GOLD) report is revised annually and has been used worldwide by healthcare professionals as a strategy document tool to implement effective management programs based on local healthcare systems.

The GOLD report recommends that the assessment of disease severity should be multidimensional. It should take account of symptoms, the degree of airflow limitations and the risk of exacerbations when considering management of COPD. This multidimensional severity assessment divides patients into four categories – A, B, C and D. However, the "ABCD" tool does not perform better than spirometric grades for mortality prediction or other important health outcomes. In the GOLD 2019 revision, initial treatment (based on ABCD) was separated from follow-up treatment [patient's major treatable trait(s) and currently used drug(s)] agents (GOLD, 2020).

The ABCD grouping is considered suitable to decide on appropriate ***initial*** pharmacological treatment but ***should not be used*** for patients who are already on maintenance treatment (Singh, et al., 2019; GOLD, 2020).

The gradation of severity of COPD according to the NICE guideline [NG115] and GOLD 2019 are comparable and summarized in Table 2:

Table 2: Gradation of severity of airflow obstruction

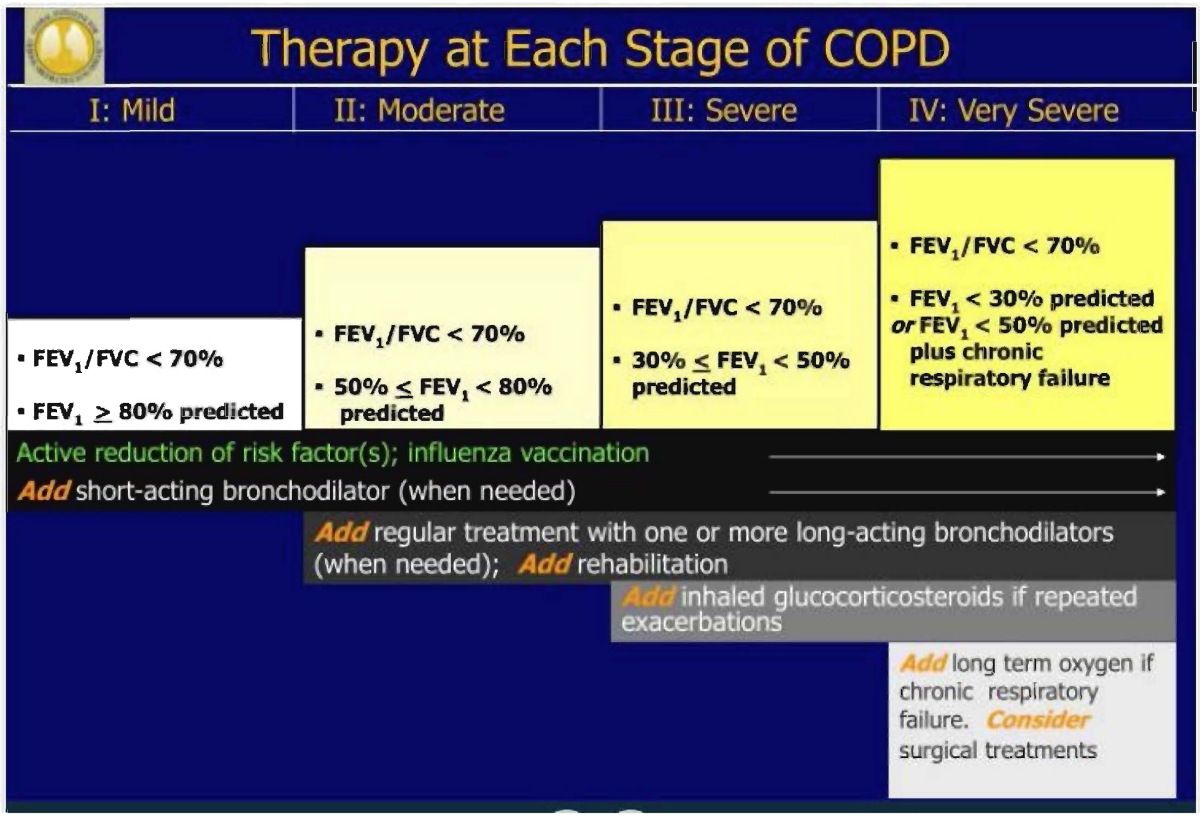
		NICE guideline [NG115], 2019	GOLD 2019
Post-bronchodilator FEV1/FVC	**FEV1 % predicted**	**Severity of airflow obstruction**	
		Post-bronchodilator	Post-bronchodilator
< 0.7	≥ 80%	Stage 1 – Mild	Stage 1 – Mild
< 0.7	50–79%	Stage 2 – Moderate	Stage 2 – Moderate
< 0.7	30–49%	Stage 3 – Severe	Stage 3 – Severe
< 0.7	< 30%	Stage 4 – Very severe	Stage 4 – Very severe*

* Or FEV1 below 50% predicted with respiratory failure.

(Source: NICE, 2019; GOLD, 2020)

The treatment regimen recommended by GOLD for each stage of COPD is as presented in Figure 5.

Figure 5: Therapy at each stages of COPD (GOLD, 2019)



The treatment regimen recommended by the NICE guideline is aligned with GOLD, 2019. Use of short-acting bronchodilators such as short-acting β2-agonists (SABAs) and short-acting muscarinic agents (SAMAs) is considered as initial empirical treatment to relieve breathlessness and exercise limitation. It is advised to check the effectiveness of bronchodilators by assessing a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. In patients at risk of exacerbations, fixed combinations of inhaled steroids and long-acting β_2-agonsits are recommended as a first choice treatment.

2. OVERVIEW OF BIOPHARMACEUTICS

2.1. Overview of different formulations

Module 3.2.P.2 provides details of the pharmaceutical development of Luforbec 100/6 micrograms [redacted] per actuation pressurised inhalation solution.

The objective of the development programme was to formulate a safe and efficacious pressurised inhalation solution equivalent to Fostair®. Drug substance and drug product manufacturing and packaging all comply with Good Manufacturing Practices (GMP).

Beclometasone dipropionate drug substance is monographed in the Ph. Eur. The quality attributes are controlled in line with EDQM Certificate of suitability [redacted]

Formoterol fumarate dihydrate drug substance is monographed in the Ph. Eur. The quality attributes are controlled in line with EDQM Certificate of suitability [redacted]

The need to replace chlorofluorocarbon (CFC) propellants as a result of the 1987 Montreal protocol, which banned substances that deplete the ozone layer, led to the evolution of the non-CFC based formulations. In accordance with Montreal initiative HFA-134a has been used as a propellant in Luforbec formulations.

HFA-134a is considered a safe alternative to CFCs for use in pharmaceutical metered-dose inhalers. The pharmacology and toxicology of HFA-134a have been extensively investigated and its safety and tolerability confirmed in a series of single- and multi-dose studies in healthy individuals (Chopra, 2005; Harrison et al.,1996; Ventresca,1995).

HFA-134a has also been demonstrated to be at least as safe and well tolerated as the CFC propellants (Hawksworth, 2002). An extensive review of the literature on HFA-134a has been undertaken and is discussed in nonclinical overview.

All excipients [Ethanol anhydrous, Water for injections, Maleic acid] comply with their respective Ph. Eur. Monographs.

No materials of animal origin and no genetically modified organisms (GMO) are used in the manufacture of the medicinal product.

The pharmaceutical form is a pressurised inhalation, solution. The description of each is as follows:

Luforbec 100/6 micrograms per actuation pressurised inhalation solution

Pressurised aluminium multidose canister containing a colourless to yellowish solution sealed with a metering valve and fitted into white polypropylene actuator with a dose indicator and a purple polypropylene dust cap.

[redacted]

[redacted]

The information and knowledge gained from the pharmaceutical development studies and manufacturing experience have provided a scientific understanding to support the establishment of specifications and manufacturing controls as detailed in Module 3.

2.2. Dosage-form proportionality

[redacted]

Each metered dose (ex-valve) of Luforbec 100/6 micrograms contains 100 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of 84.6 micrograms of beclometasone dipropionate and 5.0 micrograms of formoterol fumarate dihydrate.

[redacted]

2.3. Effect of food on bioavailability

Not applicable for an inhaled product.

2.4. Comparative bioavailability/bioequivalence

2.4.1. Comparison with reference product

The 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 (2009) (CPMP/EWP/4151/00 Rev. 1), describes the requirements for abridged applications to demonstrate therapeutic equivalence to a reference medicinal product.

The Lupin BDP/FFD pressurized inhalation solution was developed to meet all the criteria required to demonstrate therapeutic equivalence to the reference product, Fostair® as listed in Section 5.2 of CHMP guideline[1].

Both formulations contain the same concentrations of the two active ingredients [redacted] in [redacted] ethanol and propellant HFA-134a presented as pressurised metered dose inhalers (pMDIs) with the same metered and delivered doses for each drug substance per actuation.

[redacted]

The only difference between Lupin's BDP/FFD (Luforbec) formulations and the reference product, Fostair® is the type of acid [redacted] Fostair® formulations use an inorganic acid (hydrochloric acid), whilst Lupin BDP/FFD formulations contain an organic acid (maleic acid) used [redacted] in the presence of [redacted] water.

The presence of maleic acid does not raise any new safety concerns. Extensive literature review of products containing maleic acid or maleate salt are provided in the non-clinical overview (refer to section 3.7.3 of the non-clinical overview) and based on available literature, use of maleic acid instead of hydrochloric acid in the Lupin formulation does not change the safety profile of the product relative to the reference product .

[redacted]

Therefore, the handling of the Lupin device to release the required amount of active substance is no different than that of the reference product.

In order to demonstrate *in vitro* equivalence, a study comparing delivered dose uniformity (DDU) aerodynamic particle size distribution (APSD), and spray pattern and plume geometry profiles of the Test (Luforbec) and Reference Product (Fostair®) was conducted on three consecutive batches (report provided in Module 5, Section 5.3.1.2).

Delivered Dose Uniformity analysis was carried out using 5 inhalers from each batch of each products. The Test Product (TP) product at [redacted] the 100/6 mcg [redacted] met the pre-defined DDU acceptance criteria. The Reference Product (RP) was also compared against the specification criteria but for information purposes only. All inhaler means for the 100/6 mcg

[1] CPMP/EWP/4151/00 Rev. 1

RP were within 85-115% of the respective product label claims (BDP: 93% - 108%, FFD: 91% - 108%). The target delivered dose of BDP/FF is within ±15% of that from the corresponding strength of Fostair®, meeting the requirements of the Guideline on clinical documentation for Orally Inhaled Products (OIP).

Aerodynamic Particle Size Distribution by Next Generation Impactor analysis was carried out using 10 inhalers from each of the products. Group data for both APIs were comparable for the TP and RP with overlapping ranges. In addition, all groups showed similar means across the two products for both APIs, as seen in the narrow range of TP/RP ratios observed for each group. The TP/RP ratios were calculated separately (100/6 mcg, API (BDP, FFD) and Group. Ratios for BDP were within the acceptance range of 85% -115% (observed range: 95% -106%) and are considered equivalent. Ratios for FFD were within the acceptance range of 80-120% (observed range: 94% - 106%) and are also considered equivalent.

All evaluated parameters, for both DDU and APSD, met the pre-defined acceptance criteria hence demonstrating *in-vitro* equivalency between the reference marketed product Fostair® and BDP/FFD Pressurised Inhalation Solution

Lupin also conducted a comparative in vivo bioavailability and bioequivalence study to demonstrate PK bioequivalence, both with and without activated charcoal. The purpose was to establish that the inclusion of maleic acid instead of hydrochloric acid in the Test formulation did not affect the relative bioavailability between Test and Reference products, as well as to establish that the safety profile in healthy volunteers did not suggest any new safety concerns. This study, BDPFF-AS-101 demonstrated that the test formulation of Lupin BDP/FF 200/6 mcg without oral charcoal (Treatment A) resulted in a similar rate and extent of absorption for 17-BMP and formoterol compared to the reference product FOSTAIR 200/6 mcg without oral charcoal (Treatment B).

The test formulation of Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) resulted in a similar rate and extent of absorption for formoterol compared to the reference product FOSTAIR 200/6 mcg with oral charcoal (Treatment D).

The 90% CI for the GMRs of AUC_{0-t} and C_{max} for 17-BMP (without charcoal) and formoterol (with and without charcoal) are all contained within 80.00–125.00%. Therefore, Lupin BDP/FF 200/6 mcg is bioequivalent to FOSTAIR 200/6 mcg. In terms of safety, single orally inhaled doses (2 inhalations, total dose = 400/12 mcg) of the test product Lupin BDP/FF 200/6 mcg and the reference product FOSTAIR 200/6 mcg manufactured by Chiesi Limited, were safe and well tolerated in healthy male and female subjects, ages 18–45 years.

The overall safety profile of 2 inhalations of Lupin BDP/FF 200/6 mcg was similar and consistent with the prescribing information for 2 inhalations for FOSTAIR 200/6 mcg. No new safety concerns were identified following treatment.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

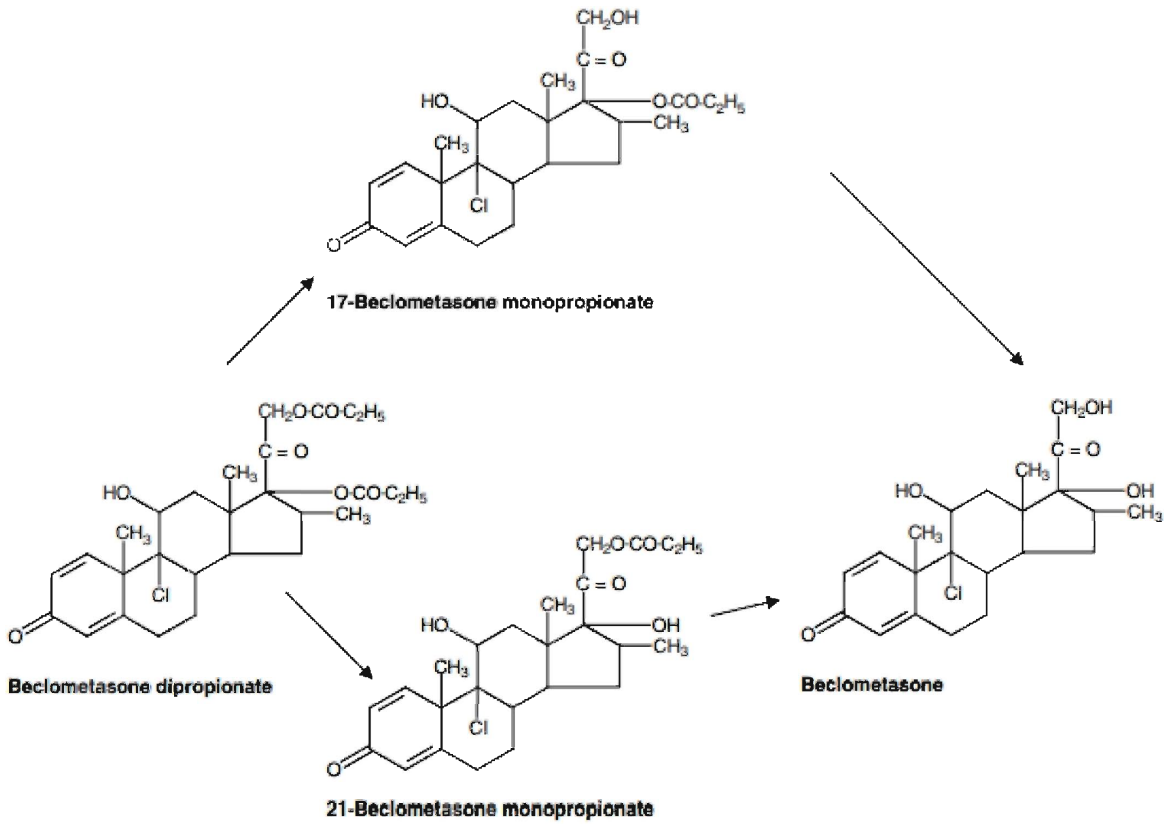
This Clinical Overview section details information on pharmacodynamics and pharmacokinetics pertaining to the use of beclometasone dipropionate and formoterol in human subjects.

3.1. Pharmacokinetics

3.1.1. Absorption

Absorption pharmacokinetics of inhaled drugs depends on their biopharmaceutical properties. Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to its active metabolite beclometasone-17-monopropionate via esterase enzymes that are found in most tissues. Minor inactive metabolites, beclomethasone 21-monopropionate (B-21-MP) and beclomethasone (BOH), are also formed (Derom and Pauwels, 2005; Würthwei and Rohdewald, 1990).

Figure 6: Metabolites of Beclometasone



Source: Derom and Pauwels, 2005

Three different studies showed very rapid absorption in adults when beclomethasone was inhaled via an HFA-pMDI. Maximal concentration of serum beclometasone esters or 17-BMP occurred 0.6–1 hour after inhalation, compared with 2 hours after inhalation from the reference CFC-inhaler (Derom and Pauwels, 2005; Harrison et al., 2002).

Absorption of formoterol is linear following inhalation of 12 to 96 µg of formoterol fumarate. Upon inhalation, formoterol is absorbed both from the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler (MDI) may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract

3.1.2. Distribution

For beclometasone, there is an approximately linear increase in systemic exposure with increasing inhaled dose. The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone-17-monopropionate respectively.

For formoterol, peak plasma concentrations of unchanged drug occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours.

Since extrafine particles are expected to improve drug delivery to the respiratory tree (also expected to improve efficacy, see section 4.1), the lung deposition and distribution pattern of BDP/FFD have been recently assessed using a gamma-scintigraphic technique (De Backer et al., 2010). The average lung deposition was 34% relative to the nominal dose in healthy subjects and 31% in patients with asthma, suggesting that good delivery to the lung can be achieved regardless of the underlying pathophysiological condition.

The objectives of the study were to compare the systemic exposure to BDP, to its active metabolite beclometasone-17-monopropionate (17-BMP) and to formoterol after administration of BDP/FFD HFA pMDI versus separate administration of BDP CFC and formoterol HFA. The study showed that BDP plasma exposure was not significantly different after the administration of BDP extra-fine (100 mg · 4 inhalations) through the fixed combination compared with BDP CFC (250 mg · 4 inhalations) administered through the separate components. Total systemic exposure to the active metabolite 17-BMP was significantly lower (about 35%) with the fixed combination; however, 17-BMP plasma concentrations during the first 30 minutes after administration (AUC_{30} min), was indicative of pulmonary absorption, were significantly higher (86%) with BDP/F than with the separate components (353 vs 190 pgh/mL; p = 0.003) and the corresponding median t_{max} was reached more rapidly (0.5 vs 2 hours). This finding is in line with

the lower dose of corticosteroid in the fixed combination, which was possibly due to the optimized lung deposition and a reduced swallowed dose with the extra-fine formulation.

This study showed that, in line with the reduced ICS systemic exposure, a significantly lower reduction in 24-hour serum cortisol concentrations was observed with the fixed combination compared with the separate components (Bousquet et al., 2009).

A study was conducted to assess the lung deposition and lung distribution of beclomethasone dipropionate (BDP)=formoterol (100/6 mg), both dissolved in hydrofluoroalkane (HFA) and delivered by pressurized metered dose inhaler (pMDI) in healthy subjects, asthmatic, and chronic obstructive pulmonary disease (COPD) patients, to investigate how the *in vitro* characteristics of the formulation translate into the *in vivo* performance in diseases with different airway obstruction. The correlation between particle size distribution of radioactivity and of the drugs in the radiolabeled formulation was validated. Intra- and extrapulmonary deposition, amount of exhaled drug, and the central to peripheral ratio (C=P) were calculated immediately after inhalation. This study showed that a large amount of the inhaled BDP+formoterol extrafine HFA fixed combination was deposited into the lungs (31–34%), with a low variability between healthy subjects, asthmatic, and COPD patients, confirming efficient lung delivery regardless of pathophysiological condition. Drug distribution was observed throughout the lung, including the peripheral airways, where at least one-third of the drug was deposited (41% in healthy subjects and 34% in asthmatic and COPD patients), indicating that the increased airway obstruction in patients had a moderate impact on the pattern of deposition (C=P ratio, VAR) (De Backer et al., 2010).

3.1.3. Metabolism

BDP is rapidly metabolized to 17-BMP (also refer to section 3.2.1), and so was not detectable in plasma 1.5 h after dosing. The mean maximum plasma concentration of 17-BMP was reached at median t_{max} of 0.5 h in healthy subjects and asthmatics and 0.37 h in COPD patients.

Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

The formoterol maximum plasma concentration for healthy and asthmatics is similar and slightly lower for COPD patients. The median t_{max} of formoterol was observed as 0.25 h in healthy subjects and asthmatics and 0.75 h in patients with COPD (De Backer et al., 2010).

3.1.4. Excretion

Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 h and 2.7 h for beclometasone dipropionate and beclometasone-17-monopropionate respectively.

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 – 96 µg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 µg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

After oral administration (40 to 80 µg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.

A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 ml/min. (Fostair® SPC)

3.2. Pharmacodynamics

3.2.1. Mechanism of action

Luforbec is a combination of corticosteroid (beclometasone dipropionate 100 or 200 micrograms (µg)) and long acting beta$_2$ agonist inhaler (formoterol 6 µg). The beclometasone is characterised by extra-fine particle size distribution resulting in a more potent effect than beclometasone in other CFC-free preparations.

The rationale for developing an extrafine formulation lies in the fact that asthma is characterized by airway inflammation and remodeling in all parts of the airways, including small airways (Tulic et al., 2001). Therefore, the optimized drug deposition from using a reduced particle size should result in improved clinical benefits (as described in section 3.1.2). The extrafine formulation optimises small particle deposition throughout the bronchial tree.

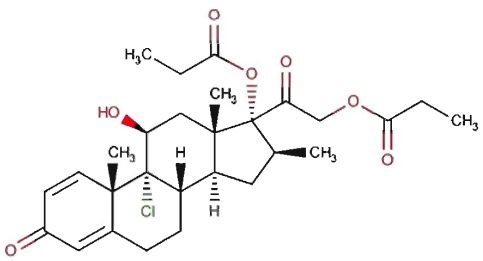
Inhaled beclometasone has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of COPD with less adverse effects than when corticosteroids are administered systemically.

Beclomethasone dipropionate is a second-generation synthetic corticosteroid agent and a diester of beclomethasone, which is structurally similar to dexamethasone. It is a prodrug of an active metabolite beclomethasone 17-monopropionate (17-BMP), which acts on the glucocorticoid

receptor to mediates its therapeutic action. Beclomethasone dipropionate itself possesses weak glucocorticoid receptor binding affinity and is rapidly converted into 17-BMP upon administration (Daley-Yates et al., 2001).

Due to its anti-inflammatory, antipruritic, and anti-allergy properties, beclomethasone dipropionate is used in various inflammatory conditions, such as asthma, allergic rhinitis, and dermatoses to reduce symptoms. When inhaled, it is proposed that beclomethasone dipropionate remains active locally in the lung without causing significant side effects associated with systemic corticosteroids (Wilcox and Avery, 1973).

Figure 7: Structural formula of beclomethasone dipropionate

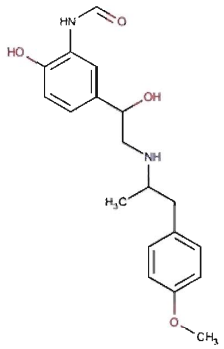


BDP is rapidly metabolized to 17-BMP. 17-BMP has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone and 25 times that of beclomethasone dipropionate. The glucocorticoid receptors dimerize and translocate into the nucleus upon binding of the ligand, where they then bind to glucocorticoid response elements on glucocorticoid-responsive genes, leading to changes in transcription. There are several proposed mechanisms for the anti-inflammatory action of corticosteroids. Corticosteroids may work by increasing the transcription of genes coding for anti-inflammatory proteins, including lipocortin-1 and interleukin-10 (Barnes, 1998). Corticosteroids were also shown to inhibit the expression of multiple genes that encode pro-inflammatory factors, such as cytokines, chemokines, and adhesion molecules that are activated during the chronic inflammatory process (Barnes, 2006). This may be due to the direct inhibitory interaction between activated glucocorticoid receptors and activated pro-inflammatory transcription factors, such as nuclear factor-kappa B and activator protein-1 (Barnes, 1998). Chronic inflammation is often characterized by enhanced expression of these transcription factors that bind to and activate coactivator molecules, which then acetylate core histones to switch on gene transcription to further amplify the inflammatory process. Corticosteroids

suppress the multiple inflammatory gene expression by promoting histone deacetylation, resulting in tighter coiling of DNA and reduced access of transcription factors to their binding sites (Barnes, 1998).

Formoterol is an inhaled beta$_2$-agonist. It acts on bronchial smooth muscle to dilate and relax airways, and is administered as a racemic mixture of its active (R;R)- and inactive (S;S)-enantiomers (Zhang et al., 2002).

Figure 8: Structural formula of formoterol



Formoterol is a relatively selective long-acting agonist of beta$_2$-adrenergic receptors, although it does carry some degree of activity at beta$_1$ and beta$_3$ receptors (Hoffmann et al., 2004). Beta$_2$ receptors are found predominantly in bronchial smooth muscle (there is a minor amount in cardiac tissue) whereas beta$_1$ receptors are the predominant adrenergic receptors found in the heart - hence, selectivity for beta$_2$ receptors is desirable in the treatment of pulmonary diseases such as COPD and asthma. Formoterol has demonstrated an approximately 200-fold greater activity at beta$_2$ receptors over beta$_1$ receptors (FDA Approved Drug Products: Perforomist® inhalation solution).

On a molecular level, activation of beta receptors by agonists like formoterol stimulates intracellular adenylyl cyclase, an enzyme responsible for the conversion of ATP to cyclic AMP (cAMP). The increased levels of cAMP in bronchial smooth muscle tissue result in relaxation of these muscles and subsequent dilation of the airways, as well as inhibition of the release of hypersensitivity mediators (e.g. histamine, leukotrienes) from culprit cells, especially mast cells (FDA Approved Drug Products: Perforomist® inhalation solution).

ICS represent the mainstay of persistent asthma therapy and the addition of LABAs is the preferred option for patients whose asthma is not controlled with low doses of ICS alone (GINA 2019). The therapeutic value of ICS/LABA combinations is increased by the evidence suggesting that LABA and ICS mutually potentiate their effects when given in combination (Barnes, 2002; Caramori et al., 2006). Possible mechanisms of synergistic interactions include (i) the increase in expression of beta$_2$ receptors (i.e. adrenergic receptors mediating smooth muscle relaxation in the airways) by increasing gene transcription induced by ICS leading to a greater

number of receptors available for beta$_2$ agonists (Scott et al., 1999), (ii) the increase in the nuclear localization of glucocorticoid receptors induced by beta$_2$ agonists potentiating the antinflammatory mechanisms of ICS (Eickelberg et al., 1999), and (iii) the direct synergic action of both drugs on the release of inflammatory mediators promoting a more pronounced antiinflammatory effect (Caramori et al., 2006).

The complementary effects of the combination of BDP and FFD on the inflammatory process in patients with asthma were investigated in sputum-derived inflammatory cells *in vitro* (Profita et al., 2005). Antiremodeling and antiproliferative effects were documented in human lung fibroblasts (Descalzi et al., 2008). The findings of these studies indicate that the BDP/F combination induces a favorable pharmacodynamic interaction that can produce added benefits in terms of bronchodilation, anti-inflammatory, anti-remodeling, and anti-proliferative effects.

3.2.2. Interactions

The interactions as outlined within the Fostair® SmPC are those associated with the individual active substances within the product:

Pharmacokinetic interactions

Hypothalamic–pituitary–adrenal axis suppression is frequently identified in patients on inhaled or nasal corticosteroids. CYP3A4 inhibitors such as ritonavir or cobicistat may increase the chance of this adverse effect (Besemer et.al, 2020). Long-term fluticasone and ritonavir should be avoided. If ritonavir is required, another inhaled steroid such as low-dose budesonide or beclomethasone can be used cautiously (Foisy et al., 2008).

Beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes. Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents (Fostair® SmPC).

Pharmacodynamic interactions

The use of beta-blockers in chronic obstructive pulmonary disease (COPD) is controversial, primarily due to concerns that they may worsen lung function and attenuate bronchodilator response. Initiating treatment with beta-blockers requires dose titration and monitoring over a period of weeks, and beta-blockers may be less well tolerated in older patients with COPD who have other comorbidities (Lipworth et al., 2016). There is a growing body of evidence demonstrating the safety of beta-blockers in patients with acute heart failure, acute respiratory failure or sepsis, entities that could occur simultaneously with COPD exacerbations. However, randomized controlled trials are still lacking to confirm these results.

Beta-blockers (including eye drops) should be avoided in asthmatic patients. If beta-blockers are administered for compelling reasons, the effect of formoterol will be reduced or abolished.

Observed hypokalemic and eosinophilic effect caused by combination of formoterol and theophylline are more pronounced compared to single drug administration (Vandenberg et al., 1999).

Concomitant use of other beta-adrenergic drugs can have potentially additive effects, therefore caution is required when theophylline or other beta-adrenergic drugs are prescribed concomitantly with formoterol (Fostair® SmPC).

The most commonly used agents in COPD are β2-adrenergic agonists and anticholinergic agents. β2-Adrenergic agonists such as albuterol, indacaterol, and salmeterol can cause dose-related prolongation of the QT interval and potassium loss. Theoretically, coadministration with some SSRIs (e.g. escitalopram, citalopram or fluoxetine) and tricyclic antidepressants (TCAs) (e.g. nortriptyline or doxepin) that can prolong the QT interval may result in additive effects and an increased risk of ventricular arrhythmias, including torsade de pointes and sudden death. The risk of ventricular arrhythmia related to QT prolongation is unpredictable but may be increased by congenital long-QT syndrome, cardiac disease, hypokalaemia and hypomagnesaemia. TCAs can potentiate the cardiovascular adverse effects of β2-adrenergic agonists, such as hypertension, palpitations and chest pain. In addition, the anticholinergic action of TCAs may be added to that of anticholinergic bronchodilators used in COPD (e.g. tiotropium, ipratropium) and may lead to dry mouth, tachycardia, urinary retention, constipation, mydriasis, blurred vision, heat intolerance, confusion, fever and exacerbation of glaucoma. None of the above interactions constitute absolute contraindications to combining antidepressants with β2-adrenergic agonists and anticholinergic bronchodilators. However, awareness of potential drug interactions, judicious follow-up and appropriate interventions can increase the safety of antidepressant drug therapy in COPD patients (Yohannes et al., 2014).

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias (Fostair® SmPC).

In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta$_2$-sympathomimetics (Fostair® SmPC).

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions (Fostair® SmPC).

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons (Fostair® SmPC).

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of beta2-agonists. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides (Fostair® SmPC).

4. OVERVIEW OF EFFICACY

4.1. Asthma

Currently available drugs for asthma treatment, including short- and long-acting bronchodilators alone or in combination and corticosteroids alone or in combination with bronchodilators, are all effective and reasonably safe (Nicolini et al., 2008). The goal of asthma treatment, as defined in the recent guidelines update (GINA 2019; SIGN158, 2019) is to reach and maintain asthma control, defined as minimal symptoms, no exacerbations, and no limitation of activities, together with normal lung function.

Inhaled corticosteroids (ICSs) are the mainstay of daily controller treatment for persistent and uncontrolled asthma. However, many clinicians are wary of ICSs because of safety concerns. Clinicians need to know the underlying efficacy data that support the use of ICSs to weigh efficacy against safety. Pivotal efficacy trials of ICS in asthma have revealed that ICSs are effective in reducing the risk of exacerbations in both children and adults. ICSs also reduce the risk of hospitalization and asthma-related death, improve asthma symptoms, and improve quality of life. Intermittent therapy may not be as effective as daily therapy, and clinicians should weigh reduced efficacy against reduced risk of adverse effects (Covar, 2016).

A post hoc analysis of data from the START study (Pauwels et al., 2003) found that low-dose ICS leads to substantial risk reduction in mild asthma, both for exacerbations and for decline in lung function, in patients with infrequent baseline symptoms who would not previously have been considered for ICS treatment (Reddel et al., 2017). This analysis supported the potential benefit of using ICS based on population risk reduction rather than only on symptom frequency (Antoniu, 2003).

There is considerable literature available on BDP, covering all relevant outcomes in asthma treatment in both adults and children. In the only available study showing that inhaled corticosteroids (ICS) reduce asthma mortality (Suissa et al., 2000), 93% of the prescribed canisters contained low-dose BDP. Formoterol is the only fast, long-acting bronchodilator with dose-dependent effects (McGavin et al., 2001) and well-documented efficacy and safety in obstructive diseases (Prenner, 2007); it can also be used as a reliever medication in asthma, provided the patient is receiving regular ICS treatment (GINA 2019).

Luforbec 100/6 micrograms [redacted] per actuation pressurised inhalation solution formulations, contain beclometasone dipropionate (BDP) and formoterol fumarate dihydrate (FFD) combination is an extrafine solution formulation in which the BDP dose is lower than the conventional BDP CFC product. The reduction in BDP nominal dose, together with the extrafine particle size, allows a similar dose of the drug to reach the lower airways and less drug to be deposited in the upper airways, potentially improving the efficacy/safety ratio. The formoterol component in BDP/F is not associated with nominal dose reduction (Dhillon and Keating, 2006).

The rationale for developing an extrafine formulation lies in the fact that asthma is characterized by airway inflammation and remodeling in all parts of the airways, including small airways (Tulic et al., 2001). Therefore, the optimized drug deposition that results from reduced particle size may lead to improved clinical benefits.

Most of ICS benefits are achieved in adults in relatively low doses. However, there is marked variability partly due to heterogenicity of airway inflammation. To achieve good asthma control, add-on therapy with another class of controller such as LABA is preferred over increasing dose of ICS (Bateman et al., 2004).

The Gaining Optimal Asthma controL (GOAL) study was a 1-year, randomized, stratified, double-blind, parallel-group study and included 3,421 patients with uncontrolled asthma and compared fluticasone propionate and salmeterol/fluticasone. The patients received stepwise increments in treatment until their asthma was totally controlled or they were receiving the maximum ICS dose of 500 mg b.i.d. Patients were divided into three strata: previously corticosteroid-free, low-dose corticosteroid users, and moderate-dose corticosteroid users. Significantly more patients in each stratum achieved asthma control with ICS/LABA than with ICS alone. Across all strata after dose escalation, a higher proportion of patients treated with ICS/LABA than those treated with ICS exhibited total control (31% vs. 19%, respectively; $p < 0.001$). The corresponding figures at 1 year were 41% and 28%. Across all strata, 68% of patients treated with ICS/LABA and 76% of those treated with ICS ultimately received the highest corticosteroid dose. The GOAL study provides further evidence that ICS/ LABA therapy is more effective than ICS alone for the treatment of asthma (Bateman et al., 2004). Although considering a different ICS/LABA combination, the study confirmed the utility of the principle of this approach to combination therapy.

Controlled studies have shown that delivering ICS and LABA in combination inhaler is as effective as giving each drug separately (Main et al., 2008). Fixed combination inhalers are more convenient for patients, may increase adherence compared with separate inhalers and ensure that LABA is always accompanied by ICS (Stoloff et al., 2004).

The significant synergistic effects of ICS and LABA in one device are well evidenced. A fixed dose combination therapy reduces the daily dosage of ICS and asthma exacerbation. It is safe to use regularly as controller. The efficacy of each individual combination on asthma treatment is generally similar. Clinical experience, ease of use, cost and side effects of medication would guide the clinician's preferences (Chantaphakul and Ruxrungtham, 2016).

An observational study was conducted in 5789 asthmatic patients from Poland in patients treated with ICS/LABA inhalers and to identify factors related to optimal asthma control. Throughout the study period, the rate of patient-reported control of asthma increased from 24.8% to 67.7%, while physician-reported control increased from 22.6% to 66.4%. The incidence of exacerbations decreased from 23.4% to 1.9%. Less than 0.1% of the patients reported adverse drug reactions.

The results confirmed the efficacy and safety of combined ICS/LABA inhalers in a real-life clinical setting (Rogala et al., 2017).

The extrafine fixed combination of 100 µg of BDP and 6 µg of FFD in a pressurized metered dose inhaler (pMDI) provides a medium daily dose of ICS. The efficacy and safety of this combination was proved in clinical studies (Huchon et al., 2009) and its effectiveness was confirmed in real life conditions (Kuna et al., 2015).

[redacted]

4.2. COPD

Recognition that chronic inflammation is also present in COPD provided a rationale for use of inhaled corticosteroids in COPD. Symptoms (dyspnoea and exercise limitation) and exacerbations are still the focus of treatment, and there are separate algorithms for each of these treatable traits (Barnes et al., 2003).

The disease encompasses multiple structural and functional components of which inflammation is at the core of the disease, affecting the lungs and other organs. Pharmacotherapy with bronchodilating agents, including the β_2-agonists, anticholinergics and methylxanthines, is central to the symptomatic management of all stages of COPD (Hanania, 2008).

Several large-scale studies in patients with moderate-to-severe COPD have demonstrated that treatment with LABA/ICS leads to significantly greater improvements in lung function, exacerbations, health status and breathlessness, compared with placebo or monotherapy with the component drugs (Hanania, 2008).

A Cochrane review of fourteen RCTs comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD, showed that combined inhalers reduced the frequency of exacerbations compared with their LABA component alone (Nannini et.al., 2012).

Combination therapy with an inhaled corticosteroid (ICS) and a long-acting β-agonist (LABA) is considered an important approach for treating patients with severe COPD who have frequent exacerbations (Cazzola and Matera, 2017).

Although to date none of the currently available interventions have been shown to halt or slow down the decline in lung function in COPD patients, the results of the TORCH (TOwards a Revolution in COPD Health) trial, a prospective, multicenter, randomized, double-blind, parallel-group study in 6112 COPD patients, suggest that LABA [SFC (50/500 mg)] has a beneficial effect on lung function in the medium term.

According to TORCH study, regular treatment with LABA narrowly missed demonstrating a statistically significant benefit on the reduction in all-cause mortality over 3 years (17.5% reduction in risk, P ¼ 0.052), further emphasizing the clinical usefulness of LABA+ICS therapy in COPD. In view of this increasing evidence for the additional effectiveness of LABA+ICS combinations compared with the individual components, and the potential benefits of LABA+ICS on lung function, disease progression and potentially on all-cause mortality, initiation of LABA+ICS combination treatment early in the COPD disease process may be warranted (Calverley et al., 2007).

The fixed dose combinations of Luforbec 100/6 micrograms [redacted] per actuation pressurised inhalation solution formulations, are characterised by an extrafine (i.e., mean mass aerodynamic diameter (MMAD) < 2.0 μm) formulation of both active components. Small airway inflammation and remodeling are cardinal features of COPD; therefore, the ability of this extrafine formulation to reach the small, as well as the large, airways is likely to be therapeutically important by enabling treatment of inflammatory processes in the whole bronchial tree. The clinical development of extrafine BDP/FFD has demonstrated significant benefits over extrafine FFD in terms of lung function improvement and reduction of the exacerbation rate, thus supporting the beneficial effect of an ICS combined to a LABA in COPD patients (Singh et al., 2016).

The extrafine formulation enables drug delivery [redacted] to both the large and small airways and allows the clinical benefits to be achieved with a lower ICS dose compared with larger-particle ICS/LABA combinations. The clinical studies performed show a benefit of extrafine BDP/FFD over FFD in terms of lung function and the risk of exacerbations that is comparable to the effect sizes observed for other ICS/LABA combinations.

A study investigating the lung deposition profile of a fixed combination ICS+LABA, and correlating this pattern to the lung function at baseline of patients with different obstructive diseases, indicate that BDP+formoterol (100+6 mcg) extrafine formulation is efficiently delivered to the lung, produces high lung deposition, low variability, and homogeneous distribution of BDP and formoterol throughout the airways, regardless of pathophysiological condition and independent of lung function (De Backer et al., 2010).

The FORWARD study was conducted to compare extra fine BDP/FFD 100/6 µg with extra fine FF 6 µg with two co-primary efficacy end points: COPD exacerbation rate over 1year and change in pre-dose morning FEV1 from baseline (randomisation visit) to Week 12. Use of tiotropium as a concomitant medication was permitted, except for a 72-h wash-out period before each clinic visit. Making this study more relevant in 'real-life' setting with a severe COPD population, as a large proportion (50–70%) of severe COPD patients in Western Europe use tiotropium. Outcome of FORWARD study, a 28% reduction of moderate-to-severe exacerbations with extrafine BDP/FFD compared with FFD & the change in pre-dose morning FEV1 from baseline to Week 12 validates superiority of Extrafine BDP/FFD over FFD alone (Wedzicha et al., 2014).

A phase 3, double-blind, double-dummy, randomised, active-controlled, 3-arm parallel-group multicentre study was conducted in 76 centres in 8 countries across Europe (Calverley et al., 2010). Over 48 weeks, beclometasone/formoterol, budesonide/formoterol and formoterol alone improved pre-dose morning FEV1 (the first primary outcome) by 0.077 L, 0.080 L and 0.026 L respectively in 718 people with severe COPD (FEV1 between 30% and 50% of predicted). In the intention-to-treat analysis, beclometasone/formoterol was shown to be non-inferior to budesonide/formoterol (the lower limit of the 97.5% CI was −0.052 L, which is within the pre-specified non-inferiority margin of −0.100 L) and statistically significantly better than formoterol alone (p=0.046).

In this study, the mean rate of COPD exacerbations/patient per year (the second primary outcome) was not statistically significantly different between the treatments (beclometasone/formoterol 0.414, budesonide/formoterol 0.423 and formoterol alone 0.431). The number of patients with exacerbations leading to hospitalisation was statistically significantly higher in the beclometasone/formoterol group compared with the budesonide/formoterol and formoterol alone groups (13 [5.6%] compared with 7 [2.9%, p<0.001] and 8 [3.4%, p=0.008] respectively). However, the numbers of exacerbations were lower than expected and these analyses may have been underpowered. Quality of life and COPD symptoms improved in all groups and use of rescue medication decreased.

A 12-week multicentre, randomised, double-blind, double dummy study, the FUTURE study, in 419 patients with moderate/severe COPD randomised to BDP/FFD 200/12 µg or FP/S 500/50 µg twice daily was conducted (Singh et al., 2014). The study evaluated the efficacy of beclomethasone dipropionate/formoterol fumarate (BDP/FFD) extrafine combination versus fluticasone propionate/salmeterol (FP/S) combination in COPD patients. The primary objective was to demonstrate the equivalence between treatments in terms of Transition Dyspnoea Index (TDI) score and the superiority of BDP/FFD in terms of change from pre-dose in the first 30 minutes in forced expiratory volume in the first second (FEV1). Secondary endpoints included lung function, symptom scores, symptom-free days and use of rescue medication, St. George's Respiratory Questionnaire, six-minute walking test and COPD exacerbations.

The study found that beclometasone/formoterol and fluticasone/salmeterol statistically significantly improved Transition Dyspnoea Index scores (a measure of breathlessness; the first primary outcome) by 1.32 units respectively and 1.15 units over 12 weeks in 419 people with moderate-to-severe COPD. The full NICE guideline on COPD considers an improvement of 1 unit to be clinically important. The combination treatments were found to be equivalent in the intention-to-treat analysis (the 95% CI for the difference [−0.39 to 0.72] was entirely within the pre-specified ±1 equivalence margins).

As assessed by the change in FEV1 from pre-dose in the first 30 minutes after drug inhalation (the secondary primary outcome), in this study beclometasone/formoterol had a statistically significantly faster onset of action than fluticasone/salmeterol (AUC0-30min adjusted means at 12 weeks 0.18 L compared with 0.11 L respectively, $p<0.001$). It is unclear whether this difference is clinically important.

Overall, the clinical development of extrafine BDP/FFD demonstrates that this extrafine formulation achieves the type of health benefits expected from such a targeted ICS/LABA combination.

Early randomised controlled trials (RCTs) did not show an effect of ICS monotherapy on exacerbations of COPD (ECOPD) rate/severity; although, since they investigated the potential effects of ICS on lung function decline, they were not enriched with patients at increased risk of ECOPD.

Later RCTs of ICS/long-acting β2-agonist (LABA) combinations generally recruited patients with ⩾1 ECOPD in the previous year and showed that ICS/LABA combinations reduce ECOPD rates by approximately 25–35% compared with LABA monotherapy.

In RCTs of ICS/long-acting β2-agonist (LABA) combinations whereby patients with ⩾1 ECOPD in the previous year were recruited, it was shown that ICS/LABA combinations reduce ECOPD rates by approximately 25–35% (Calverley et al., 2003).

Likewise, despite not specifically focusing on patients at increased ECOPD risk, TORCH and SUMMIT were large enough to demonstrate ICS efficacy on ECOPD (Calverley et al., 2007; Vestbo et al., 2016).

In summary, for asthma and chronic obstructive pulmonary disease (COPD), an important step in simplifying management and improving adherence with prescribed therapy is to reduce the dose frequency to the minimum necessary to maintain disease control. Fixed-dose combination therapy is thought to enhance compliance by decreasing the number of medications and/or the number of daily doses (Marceau et al., 2006). Furthermore, they have the potential for enhancing, sensitizing, and prolonging the effects of mono components (Cazzola et al., 2012).

It seems reasonable to postulate that targeting bronchoconstriction through two distinct mechanisms should maximize the bronchodilator response and help to overcome inter- and

intrapatient variability in bronchomotor tone associated with airway obstruction (Bellia et al., 2006).

5. OVERVIEW OF SAFETY

As Luforbec contains beclometasone dipropionate and formoterol fumarate dihydrate, certain adverse reactions of varying type and frequency associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Beclometasone

Glucocorticosteroids have been widely used for asthma management for a long time. Inhaled corticosteroids offer advantage of delivery of drug to the airways in doses that are effective with a much lower risk of systemic side effects. Systemic effects of inhaled corticosteroids (e.g., Beclometasone dipropionate) may occur particularly when administered at high doses or prescribed for prolonged periods (Fostair® SPC; Pandya et al.,2014).

The most common local AEs of ICS are hoarseness and weakness of the voice (dysphonia) due to atrophy of the vocal cords following laryngeal deposition of steroid. Oropharyngeal is observed in ~5% of the patients. The systemic AEs associated with ICS include adrenal suppression and insufficiency, growth suppression, bruising, osteoporosis, cataracts, glaucoma, metabolic abnormalities (glucose, insulin, triglycerides), psychiatric disturbances (euphoria, depression) and pneumonia, the main ones being Adrenal suppression and Growth suppression (Goodman and Gilman, 12th Edition, 2011).

Clinical experience over the past 20 years suggests that the occurrence of adrenal axis suppression with the use of ICS alone is very low. Most of the reported cases generally reflect an excess of dosing or the residual effect of prior oral corticosteroid treatment. Thus, children receiving low to moderate doses of ICS do not require routine monitoring of adrenal axis function unless there is evidence of growth suppression (Colucci et al., 2007).

In a crossover study of asthmatic children not controlled on other medications were commenced on beclomethasone dipropionate (BDP) or budesonide (BUD), both administered at the dose of 200 micrograms twice per day for 2 weeks each in randomized order. Monitoring included twice daily symptom scores recording at home, peak expiratory flow readings, and the use of additional antiasthma medications. Before and after each treatment period the patients were admitted for overnight blood sampling for cortisol, ACTH, and growth hormone, 24-h urine collections for cortisol, and detailed lung function tests. A total of 12 children completed the study. The nocturnal serum cortisol production was significantly reduced by 27 and 35% after 2 and 4 weeks of treatment ($p = 0.005$, $p = 0.004$; Wilcoxon test), and the urinary free cortisol showed a similar reduction of 33 and 48% ($p = 0.023$, $p = 0.005$). Such suppression could be shown on both drugs, BDP and BUD, and there was no significant difference between them. The ACTH and growth hormone values were not significantly changed on any treatment. Lung function tests showed an impressive improvement in FVC, FEV1, FEF50, and FEF25 after 2 weeks of treatment regardless of the medication. Differences in lung function improvements between the two drugs were very small and not of clinical relevance. The observations indicate

that even low-dose inhaled corticosteroids in the form of BDP or BUD have a systemic effect, which emphasizes the importance of using the minimum dose compatible with good control of asthma (Nicolaizik et al.,1994).

Although most respiratory specialists believe that these drugs may induce growth suppression, many have rarely or never observed such an AE in children using ICS. The risk of growth suppression can be influenced by several factors, including total dose, drug delivery device, genetic predisposition, age, and asthma severity (Brand, 2001).

Patients transferring from oral to inhaled corticosteroids may remain at risk of impaired adrenal reserve for a considerable time. Because recovery from impaired adrenocortical function caused by prolonged systemic steroid therapy is usually slow, special care is necessary for the first 9 to 12 months after the transfer, until the HPA axis has sufficiently recovered to enable the patient to cope with any emergencies such as trauma, surgery, severe infections, or an acute attack of asthma (Brogden et al., 1975).

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

The risk of pneumonia in COPD patients using ICS is higher in those with older age, lower body mass index (BMI), greater overall fragility, receiving higher ICS doses and those with blood eosinophils <100 cells·μL−1. All these factors must be carefully considered and balanced in any individual COPD patient before adding ICS to her/his maintenance bronchodilator treatment (Agusti et al., 2018).

Formoterol

The use of a regular LABA is now established in asthma guidelines as the preferred option for second-line controller therapy in addition to inhaled corticosteroids.

Tolerance of human airway smooth muscle to β2 agonists *in vitro* has been demonstrated, although the concentration of agonist necessary is high and the degree of desensitization is variable (Goodman and Gilman, 12th Edition, 2011).

A review was conducted to assess tolerability of short-term use (4–48 hours) of high doses of formoterol (up to 228 μg) in healthy volunteers and patients with stable asthma. In patients with asthma, formoterol had a tolerability profile comparable to that of equivalent doses of albuterol. Potential adverse effects of formoterol on cardiovascular and metabolic parameters, including plasma potassium concentrations, resolved relatively rapidly (within 24 hours), whereas the bronchodilating effects of therapy persisted for 12 hours. Of the studies describing the effects of high-dose formoterol on the QTc interval, the QTc interval returned to baseline within 24 hours in the 2 studies in healthy adults, and the change was similar in magnitude to that with albuterol

but less than that with fenoterol. In one of the studies in adult patients with asthma, the QTc interval was not significantly affected by administration of formoterol doses of 12 to 48 µg. Overall, the range and incidence of adverse effects observed with formoterol did not appear to be significantly different from that of other β2-agonists (Ostrom, 2003).

Excessive doses of formoterol may lead to effects that are typical of β_2-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia, hyperglycaemia (British National Formulary 2020).

Epidemiological evidence has suggested a link between use of β_2-agonists and increased asthma mortality. Much debate has surrounded possible causal links for this association, and whether regular (daily) long-acting β_2-agonists (LABAs) are safe, particularly when used in combination with inhaled corticosteroids (ICSs). The Cochrane Review included data from two large trials including 11,679 adults and 6208 children and author did not find a difference in the risk of death or serious adverse events in either adults or children. The possible risks still have to be weighed against the benefits experienced by people who take combination treatment (Cates et al., 2018).

β2-agonists should be used with caution with patients with diabetes because of the risk of ketoacidosis. β2-AR stimulation in the liver induces glycogenolysis and therefore raises blood sugar levels (Philipson, 2002). β2-agonists stimulate the Na^+, K^+-ATPase driven pump coupled to β2-ARs in skeletal muscle, thus facilitating the release of Na^+ out of the cell and the intracellular accumulation of K^+, thereby lowering K^+ plasma levels and causing hypokalaemia (Matera et al., 2016)

BDP/FF combination

Clinical experience with BDP and FFD is extensive and the adverse effects of the respective components of the drug combination are manageable. As Luforbec contains beclometasone dipropionate and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Inhaled doses of BDP/FFD for up to twelve cumulative actuations (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed (Fostair® SPC).

There have been reports of Takotsubo cardiomyopathy, a transient cardiac dysfunction with a ballooning shape, following medical interventions with ICS/LABA in status asthmaticus (Saito et al., 2016). The pathogenic mechanism of this disease is still unclear but sympathetic

hyperactivity, as well as coronary vasospasm, microcirculatory disorder, and estrogen deficiency, have been considered as one of the most likely pathogenic mechanism (Yoshikawa, 2015).

Calverley et al. (2010) found that the incidence of adverse events did not differ significantly between beclometasone/formoterol, budesonide/formoterol and formoterol alone. The most commonly reported adverse event was exacerbation or worsening of COPD, which occurred in 27–28% of participants. Pneumonia was reported by 5 people (2.1%) in the beclometasone/formoterol group, 7 people (2.9%) in the budesonide/formoterol group and 1 person (0.4%) in the formoterol group (statistical significance of differences not reported).

In Singh et al. (2014), serious adverse events occurred statistically significantly more often in the fluticasone/salmeterol group than the beclometasone/formoterol group (13 people [6.3%] compared with 4 people [1.9%], p=0.024). Pneumonia was reported in 3 people (1.4%) treated with fluticasone/salmeterol and none treated with beclometasone/formoterol.

Safety analyses from Phase 3 study (CT01) conducted on the safety population included 239 patients in the BDP/Form group, 244 patients in the BDP group and 242 in the FP/Salm group. The percentage of patients experiencing treatment-emergent adverse events (TEAEs) during the randomized treatment period was similar among the treatment groups (37.2% with BDP/Form, 38.1% with BDP monotherapy, and 37.2% with FP/Salm), as well as the percentage of patients experiencing adverse drug reactions (ADRs) during the randomized treatment period (8.8% with BDP/Form, 7.8% with BDP monotherapy, and 8.3% with FP/Salm). The incidence of dysphonia was significantly greater in the FP/Salm group (2.9%) than BDP monotherapy group (0.4%). There were no other significant differences between treatment groups for all other ADRs reported; however a higher incidence of oral candidiasis was reported in the BDP group (five cases versus one case in each ICS/LABA combination group) (Corradi et al., 2016).

Safety analysis from another Phase 3 study (FORCE), which included 189 patients in the BDP/Form group and 180 patients in the BDP group, Treatment-emergent ADRs were reported slightly less frequently in the BDP/Form group than in the BDP group: three events in two (1.1%) patients versus five events in five (2.8%) patients, respectively. (Corradi et al., 2016)

Safety of excipients

Lupin is developing a beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FFD) pressurized inhalation solution using a proprietary actuator. Lupin's BDP/FFD formulations contain approximately [redacted] of an organic acid – maleic acid, in the presence of [redacted] water. Once maleic acid is in contact with the water in the formulation or body fluids, such as airway surface liquid, the acid donates its proton and is converted to maleate. This process happens almost instantaneously. The amount of maleic acid delivered to patients through inhalation is small.

Maleic acid, a dicarboxylic acid, can be conjugated to free base compounds/drugs to improve physiochemical properties, including stability, solubility, and dissolution rate. Therefore, maleate

salts are frequently used in pharmaceutical formulations for systemic administration, as well as for cosmetic uses (Cosmetic Ingredient Review, 2018).

A 20% aqueous solution produced mild and reversible skin irritation in humans. Lower concentrations (<5%) are sufficient to produce serious ocular irritation in human subjects. Maleic acid is reported to be an irritant to the mucous membranes of humans. In vitro, maleic acid produced highly significant alterations in the physical state of human erythrocyte membrane proteins (PubChem, 2020).

Although maleic acid itself may be a dermal and/or ocular irritant, its use in cosmetic formulations indicates that most of the acid will be neutralized into various maleate salts. Therefore, the concentration of free maleic acid is expected to be low, and dermal or systemic toxicity is not a significant concern. The safety of maleic acid should be based on the amount of free maleic acid that remains after neutralizing the formulation (Cosmetic Ingredient Review Expert Panel, 2007).

Extensive review of published data has been presented in nonclinical overview.

Based on the available literature, inhaled maleic acid from the Lupin product is not expected to result in any local or systemic safety impact due to the formulation containing a small amount [redacted] of maleic acid which is readily converted to maleate both in the formulation and in body fluids.

Ethanol is an excipient used in Luforbec formulation. Luforbec contains [redacted] alcohol (ethanol) per actuation in the 100/6 mcg per actuation formulation [redacted] The maximum daily dose of Luforbec for asthma is 8 puffs for the 100/6 mcg per actuation formulation [redacted] Therefore, the maximum amount of ethanol inhaled per day would be [redacted] Thus, the amount of ethanol in Luforbec formulations is too low to have any pharmacological effect.

5.1. Use in special situations

5.1.1. Pregnancy

There are no relevant clinical data on the specific use of Luforbec in pregnant women.

A review was conducted to assess the effectiveness and safety of different interventions for managing asthma during pregnancy. The results from five trials in the review assessing pharmacological interventions did not provide clear evidence of benefits or harms to support or refute current practice (Murphy, 2015). While no clear effect on asthma exacerbations was seen with the addition of inhaled beclomethasone to routine asthma therapy in two trials (Caramez, 1998), these trials were also both of unclear methodological quality, and had small sample sizes.

High doses of inhaled corticosteroids during the first trimester of pregnancy, as opposed to low to moderate doses, have been associated with an increased risk of congenital malformations (Blais, 2009; Bain 2014).

While safety data on the use of inhaled short-acting β-agonists in pregnancy have been regarded as reassuring (Busse, 2005- NAEPP Expert Panel Report) a number of epidemiological studies have suggested an increase in the risk of congenital abnormalities with the use of maternal bronchodilators, including short-acting β-agonists, anticholinergic agents and theophylline (Källén, 2007; Lin, 2008).

β2-sympathomimetic agents are known to exhibit tocolytic actions in the run up to delivery. Formoterol should not be recommended for use during pregnancy and particularly at the end of pregnancy or during labour unless there is no other (safer) established alternative.

As such, and in line with the SmPC of Fostair, Luforbec should only be used during pregnancy if the expected benefits outweigh the potential risks.

5.1.2. Lactation

There are no relevant clinical data on the specific use of Luforbec in lactation in humans.

Although not measured, the amounts of inhaled corticosteroids absorbed into the maternal bloodstream and excreted into breastmilk are probably too small to affect a breastfed infant (Drugs and Lactation Database- Beclomethasone (LactMed, 2018).

Although no published data exist on the use of formoterol by inhalation during lactation, data from the related drug, terbutaline, indicate that very little is expected to be excreted into breastmilk (Drugs and Lactation Database- Formoterol (LactMed, 2018).

Consistent with the SmPC for Fostair, administration of Luforbec to women who are breast-feeding should only be considered if the expected benefits outweigh the potential risks.

5.1.3. Children

As described also in the SmPC for Fostair, the safety and efficacy of Luforbec in children and adolescents under 18 years of age have not been established yet. No data are available with ~~Luforbec~~ BDP/FFD in children under 12 years of age. Only limited data are available in children between 5 and 11 years of age and adolescents between 12 and 17 years of age. These are described below, but no recommendation on posology can be made.

Asthmatic adolescents (12 to 17 years of age) are unique in many ways and limited efficacy, safety and pharmacokinetic (PK) data are available on fixed ICS/LABA combinations. Indeed, adolescents in comparison with adults have a lower body size and therefore a lower apparent volume in which the drug can be distributed (volume of distribution) after systemic absorption. Prescription of inhaled corticosteroids to children with asthma is recommended at half the

nominal dose of adults in order to reduce the risk of systemic side effects. However, there is a lack of pharmacokinetic trials supporting such dose reduction regimen (Chawes et al., 2014).

Pharmacokinetic profiles of formoterol and beclometasone-17-monopropionate (17-BMP; active metabolite of BDP) were evaluated over 8 h from two independent studies comprising children (6-11yrs, n =27), adolescents (12-17 yrs, n= 28) and adults (≥18 yrs, n =30) receiving a single, fixed dose of BDP/formoterol (children: 200 mg/24 mg, adolescents and adults: 400 mg/24 mg) via DPI. The systemic exposure (AUC) for children versus adults was almost doubled for formoterol and similar for 17-BMP despite the halved BDP dose administered in children. In adolescents the AUC for formoterol and 17-BMP were approximately one third higher than in adults for both compounds. Upon normalization for the BDP/formoterol dose in the three populations, the AUC and peak concentration (C_{max}) correlated inversely with age and body surface area of the patients.Therefore, it is important that the patient is reviewed regularly, and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained (Chawes BL et al., 2014).

5.1.4. Hepatic & Renal impairment

Beclometasone dipropionate

The pharmacokinetics of beclometasone dipropionate in patients with renal or hepatic impairment has not been studied; however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver, to originate the more polar products beclometasone-21-monopropionate, beclometasone-17-monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.

As beclometasone dipropionate or its metabolites were not traced in the urine, an increase in systemic exposure is not envisaged in patients with renal impairment (Fostair® SPC).

Formoterol

The pharmacokinetics of formoterol has not been studied in patients with hepatic or renal impairment however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis (Fostair® SPC).

5.2. Effects on ability to drive/operate machinery

Luforbec is not expected to affect the ability to drive a car or operate machinery. Certain side effects (such as dizziness) that have been reported with LABAs may affect some patients' ability to drive or operate machinery (British National Formulary, 2020).

5.3. Overdose

Inhaled doses of the drug up to 12 cumulative actuations (total Beclometasone dipropionate 1200 mcg, Formoterol 72 mcg) have been studied in asthmatic patients (Fostair® SmPC). The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed.

Excessive doses of formoterol may lead to effects that are typical of β2-adrenergic agonists: Nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalemia and hyperglycemia.

In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardio selective beta-adrenergic blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

Acute inhalation of beclometasone dipropionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function recovers in a few days, as verified by plasma cortisol measurements. In these patients, treatment should be continued at a dose sufficient to control asthma.

Chronic overdose of inhaled beclometasone dipropionate may be associated with the risk of adrenal suppression. Monitoring of adrenal reserve may be necessary. Treatment should be continued at a dose sufficient to control asthma (Fostair® SPC).

6. BENEFITS AND RISKS CONCLUSIONS

Lupin has developed Luforbec 100/6 micrograms [redacted] per actuation pressurised inhalation solution formulation containing beclometasone dipropionate/formoterol fumarate dihydrate.

This clinical overview has been presented to support Marketing Authorisation Application (MAA) via a National Procedure to the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA).

Luforbec 100/6 mcg per actuation pressurised inhalation solution will be indicated for the regular treatment of asthma in adult patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists, or adult patients already adequately controlled on both inhaled corticosteroids and long acting β2 adrenoceptor agonists. It will also be indicated for symptomatic treatment of patients with severe COPD (FEV_1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

[redacted]

As this is a hybrid, abridged license application claiming essential similarity to a currently marketed product, no new or additional clinical testing, apart from the in vitro bioequivalence testing (Module 5, Section 5.3.1.2) and the in vivo bioequivalence study BDPFF-AS-101, was carried out by the applicant. This submission relies solely on information from the public domain.

Beclometasone dipropionate and formoterol fumarate are well-known active substances with established efficacy and tolerability.

GINA guideline recommends combining an ICS with a LABA as cornerstone for the treatment of adult patients with asthma symptoms when a medium dose of ICS alone fails to achieve control of asthma. The addition of long-acting beta-agonist (LABA) therapy with ICS increases the efficacy of ICS effects in moderate-to-severe asthma.

Use of ICS has also been established in the treatment of COPD, particularly symptomatic patients, who experience useful gains in quality of life, likely from an improvement in symptoms such as breathlessness and in reduction in exacerbations, and an attenuation of the yearly rate of deterioration in lung function.

The incidence of adverse events related to ICS varies among the studies and seems to be dose dependent, with recent well-designed, large studies on low-dose ICS reporting similar safety profiles in ICS and non-ICS groups. The benefits of ICS in COPD continue to outweigh the risks, especially when lower ICS doses are administered

The Global initiative for the management of chronic Obstructive Lung Disease (GOLD) recommends use of ICS in combination with bronchodilators such as LABA/LAMAs.

The clinical experience with BDP and FFD is extensive and long established, such that their adverse effects are avoidable and manageable.

The literature search also supports the safe use of maleic acid and ethanol as excipients and HFA-134a as the propellant.

The Applicant proposes to mirror the current SmPC for the innovator product, Fostair thus capturing the current knowledge on benefits and risks for this fixed dose combination product.

Overall, the benefit of using the ICS/LABA combination in management of Asthma and COPD in adult patients outweighs risk posed providing the product is used in accordance with the proposed SmPC.

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