



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg

2.5 – Clinical Overview

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1. PRODUCT DEVELOPMENT RATIONALE

1.1. Introduction

Lupin Healthcare (UK) Limited has developed Luforbec 100/6 micrograms 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.

The 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 β 2-adrenoceptor agonists (LABAs) and acts by relaxing airway smooth muscles and consequent bronchodilation.



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LABAs like FFD are selective β_2 -adrenergic agonists which bind to the G-protein coupled β_2 -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 ($FEV_1 < 50\%$ 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:



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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](#)).

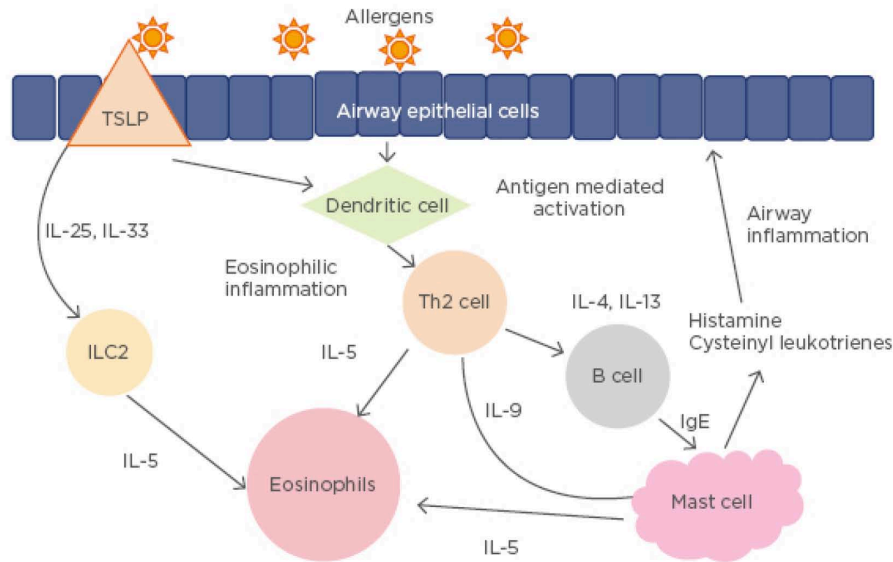
When the airways of an asthmatic patient are exposed to a trigger, at first there is an acute inflammatory response in the mast cells that line the airways. Complex cytokine networks, including chemokines and growth factors, play important roles in orchestrating the inflammation process ([Barnes, 2008](#)).

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](#)).



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

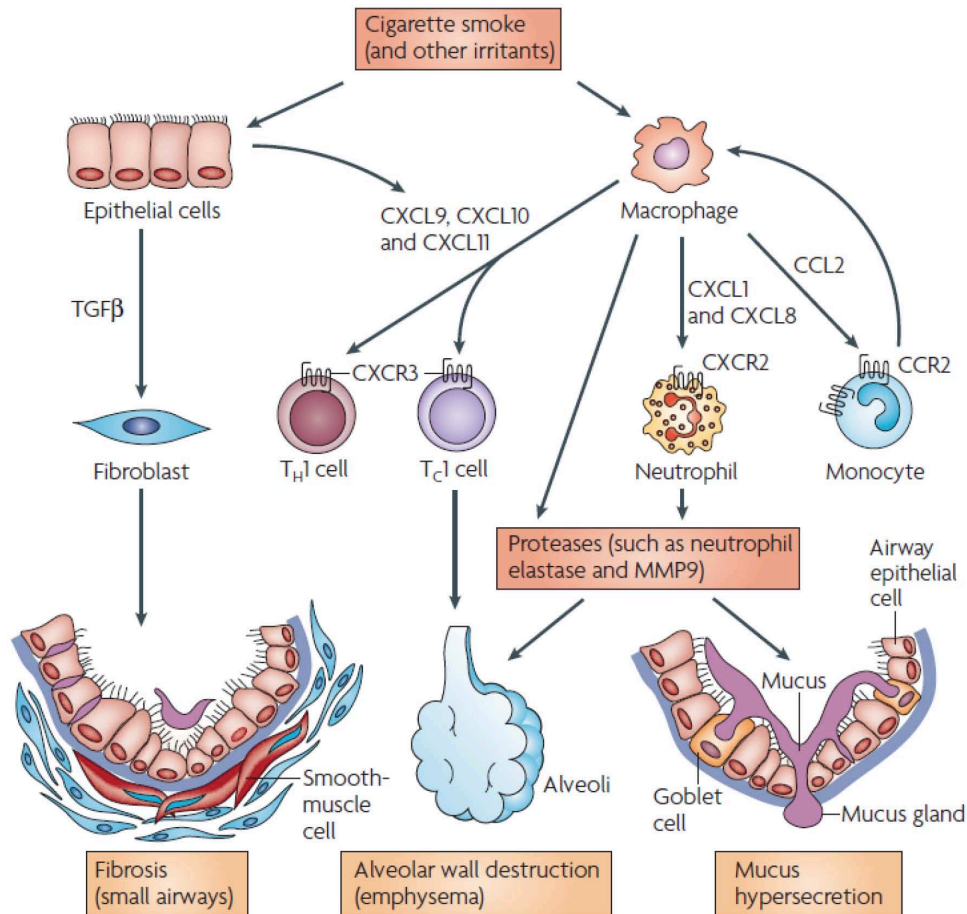
An estimated 1.2 million people in the UK are living with diagnosed COPD – considerably more than the 835,000 estimated by the Department of Health in 2011. COPD is the second most common lung disease in the UK, after asthma. Around 2% of the population over 16 years old – 4.5% of all people aged over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

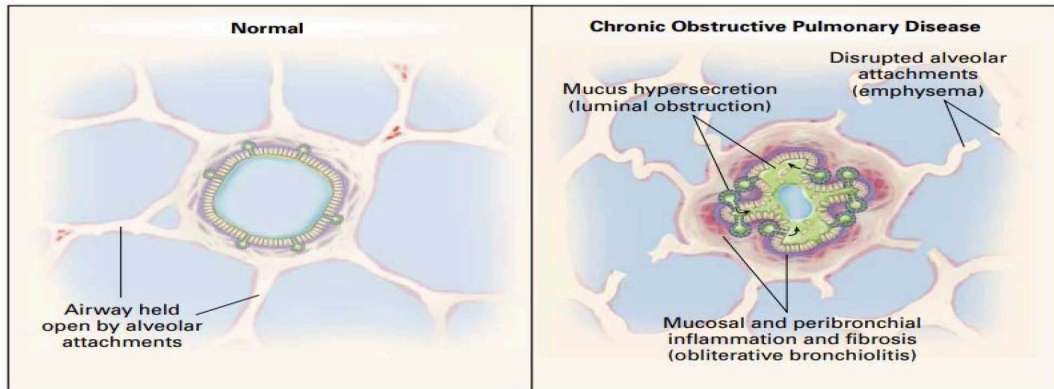


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Figure 3: Airways of a COPD patient with air trapping due to emphysema



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