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.

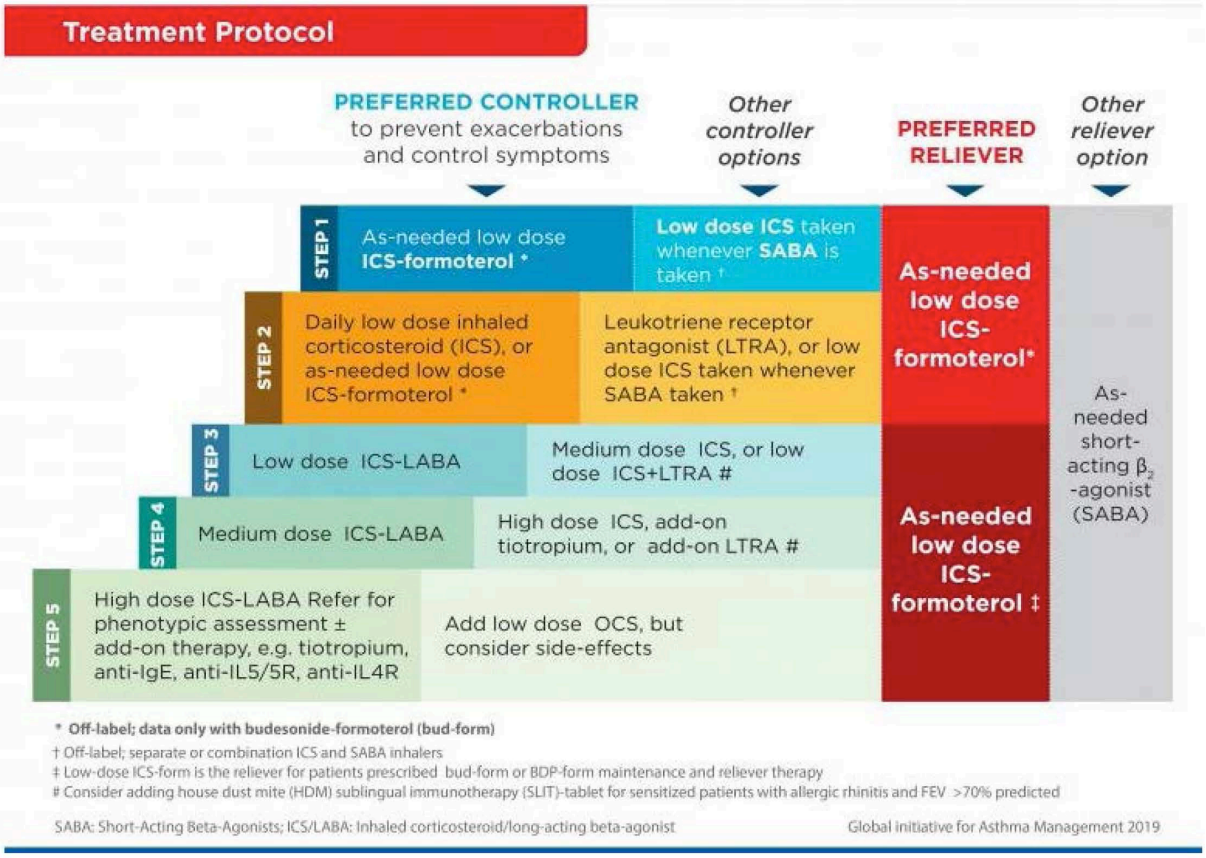
The general approach to management of asthma is to start treatment at the level most appropriate to initial severity, achieve early control and maintain control by increasing treatment as necessary and decreasing treatment when control is good.

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

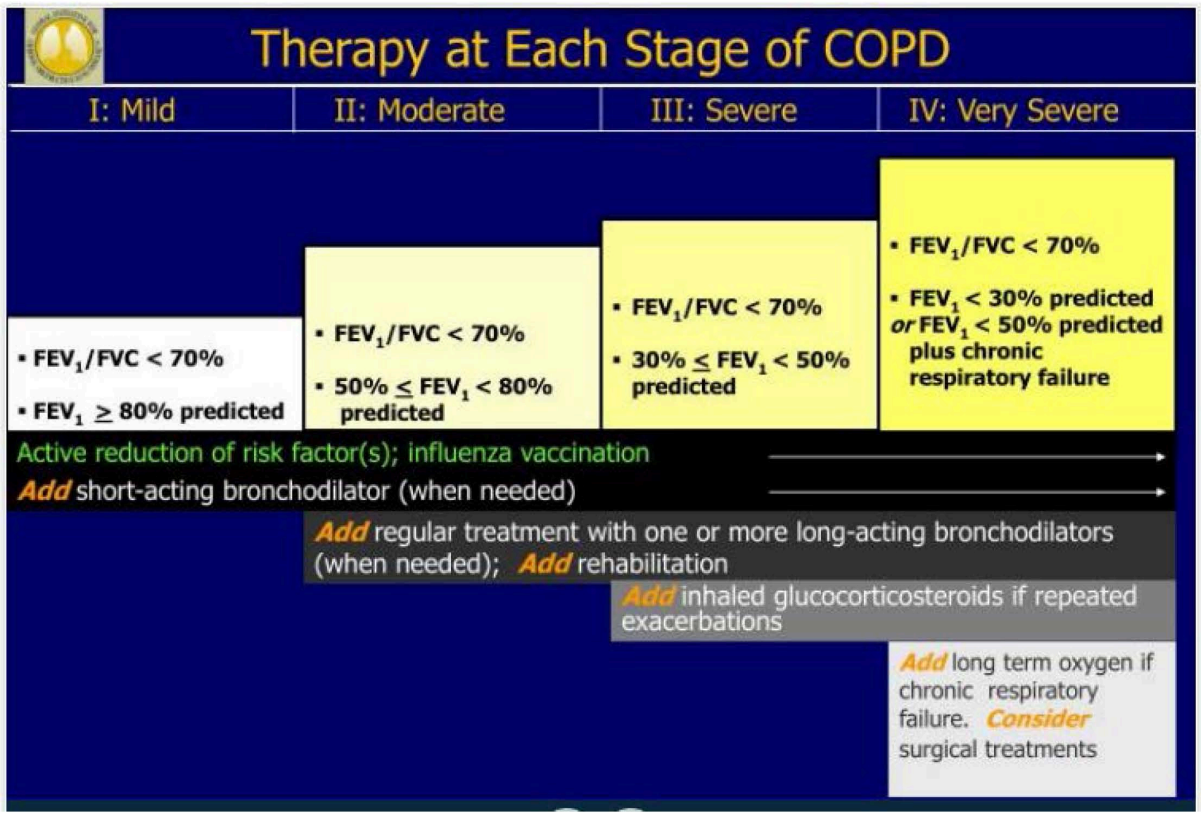
		NICE guideline [NG115], 2019	GOLD 2019
Post-bronchodilator FEV1/FVC	**FEV1 % predicted**	**Severity of airflow obstruction**	
		Post-bronchodilator	Post-bronchodilator
< 0.7	≥ 80%	Stage 1 – Mild	Stage 1 – Mild
< 0.7	50–79%	Stage 2 – Moderate	Stage 2 – Moderate
< 0.7	30–49%	Stage 3 – Severe	Stage 3 – 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 demonstrated that the test formulation of Lupin BDP/FF 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 without oral charcoal (Treatment B).

The test formulation of Lupin BDP/FF with oral charcoal (Treatment C) resulted in a similar rate and extent of absorption for formoterol compared to the reference product FOSTAIR 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 is bioequivalent to FOSTAIR In terms of safety, single orally inhaled doses of the test product Lupin BDP/FF and the reference product FOSTAIR 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 was similar and consistent with the prescribing information for 2 inhalations for FOSTAIR No new safety concerns were identified following treatment.