3. OVERVIEW OF CLINICAL PHARMACOLOGY

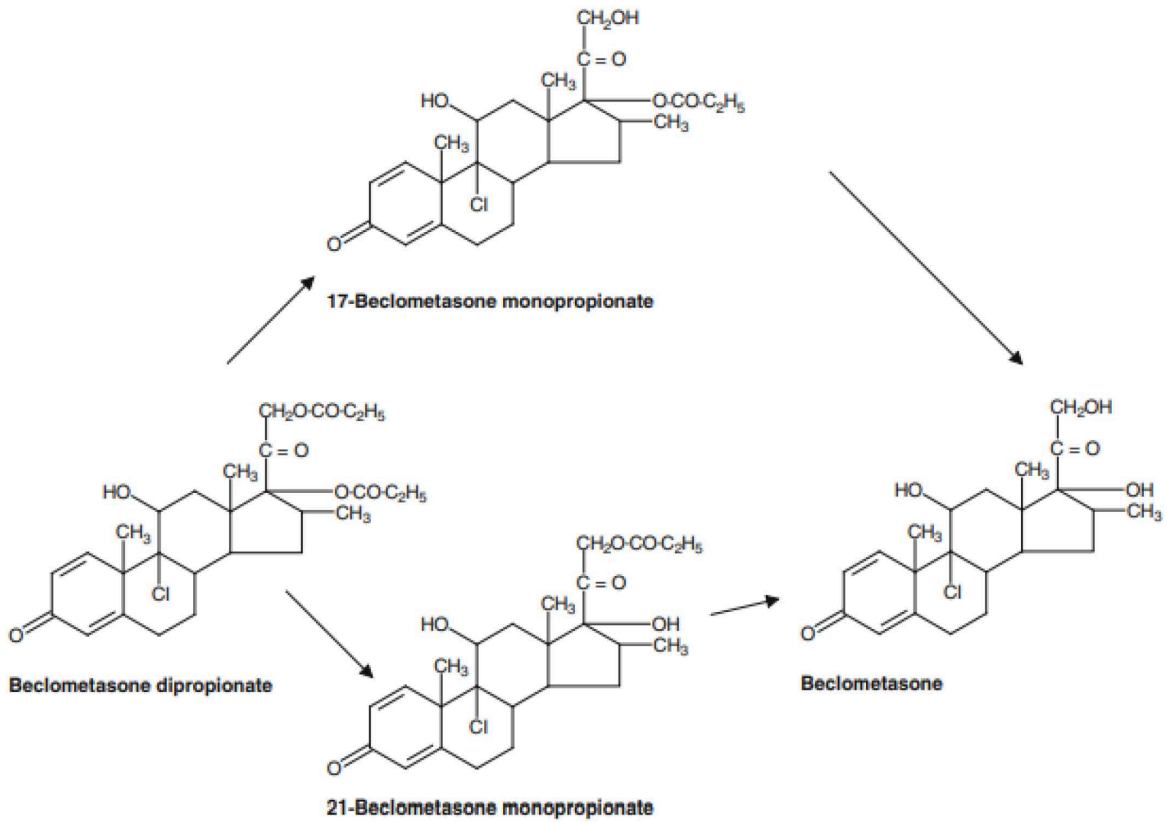
This Clinical Overview section details information on pharmacodynamics and pharmacokinetics pertaining to the use of beclometasone dipropionate and formoterol in human subjects.

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.

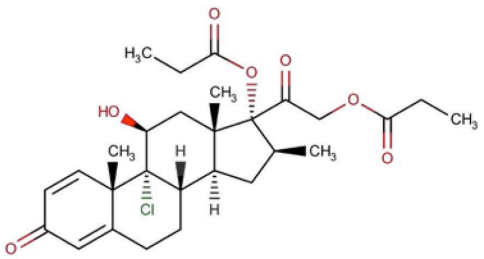
Inhaled beclometasone has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of COPD with less adverse effects than when corticosteroids are administered systemically.

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

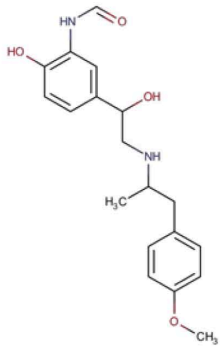


BDP is rapidly metabolized to 17-BMP. 17-BMP has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone and 25 times that of beclomethasone dipropionate. The glucocorticoid receptors dimerize and translocate into 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).