Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Glycopyrronium 12.5mcg and Formoterol Fumarate 12mcg Powder for Inhalation

2. Qualitative and quantitative composition
Glycopyrronium 12.5mcg and Formoterol Fumarate 12mcg Powder for Inhalation

Each capsule contains:

Glycopyrrolate USP equivalent to

Glycopyrronium 12.5 mcg

Formoterol Fumarate USP 12 mcg

Approved colours used in empty capsules.

3. Pharmaceutical form
Powder for Inhalation (In capsule)

4. Clinical particulars
4.1 Therapeutic indications
Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation is not indicated for the relief of an acute deterioration of COPD.

4.2 Posology and method of administration
For oral inhalation only. Do not swallow capsules, as the intended effects on the lungs will not be obtained. Capsules should only be used with the inhaler device.

The recommended dose is the inhalation of the content of one capsule twice daily using the inhaler.

Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation is recommended to be administered, at the same time of the day each day (1 capsule in the morning and 1 capsule in the evening). More frequent administration or a greater number of inhalations (more than 1 capsule twice-daily) of Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation is not recommended.

Use in Special Populations

No dosage adjustment is required for geriatric patients, patients with hepatic impairment, or patients with mild to moderate renal impairment.

Geriatric patients:

Based on available data, no adjustment of the dosage of glycopyrronium or formoterol in geriatric patients is warranted. The available data on formoterol from clinical trials performed in elderly patients do not suggest that the dosage should be different than in other adults.

Patients with renal impairment:

No dose adjustment is required for patients with mild and moderate renal impairment. Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation should be used in patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73m2), including those with end-stage renal disease requiring dialysis, if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrronium may be increased in this population.

Patients with hepatic impairment:

No dose adjustment is required for patients with hepatic impairment. The effects of hepatic impairment on the pharmacokinetics of glycopyrronium and formoterol fumarate have not been studied.

Pediatric patients:

Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation is not indicated for use in children. The safety and efficacy of Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder for Inhalation in pediatric patients have not been established.

Method of administration

For Oral inhalation use only.

The capsules must be administered only using device Instahaler-P

The capsules must only be removed from the Container immediately before use. The capsules must not be swallowed.

Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Asthma

FDC of Glycopyrronium/formoterol should not be used to treat asthma.

Paradoxical bronchospasm

In clinical studies, paradoxical bronchospasm was not observed with FDC of Glycopyrronium/formoterol at its recommended dose. If paradoxical bronchospasm does occur, treatment with the medicinal product should be stopped and other treatments considered.

Not for acute use

FDC of Glycopyrronium/formoterol is not indicated for the treatment of acute episodes of bronchospasm, i.e. as a rescue therapy.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including glycopyrronium or formoterol. Patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. FDC of Glycopyrronium/formoterol should be used with caution in patients with severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Caution should also be exercised in patients with thyrotoxicosis or known or suspected prolongation of the QTc interval.

Glycopyrronium

Deterioration of Disease and Acute Episodes

Glycopyrronium should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD. Glycopyrronium has not been studied in subjects with acutely deteriorating COPD. The initiation of glycopyrronium in this setting is not appropriate.

Glycopyrronium should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Glycopyrronium has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta2-agonist.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If glycopyrronium longer controls symptoms of bronchoconstriction; the patient's inhaled, short- acting beta2-agonist becomes less effective; or the patient needs more inhalation of a short-acting beta2-agonist than usual, these may be markers of deterioration of disease. In this setting, a re- evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of glycopyrronium beyond the recommended dose is not appropriate in this situation.

Paradoxical bronchospasm

As with other inhaled medicines, Glycopyrronium can produce paradoxical bronchospasm that may be lifethreatening. If paradoxical bronchospasm occurs following dosing with Glycopyrronium, it should be treated immediately with an inhaled, short-acting bronchodilator; Glycopyrronium should be discontinued immediately, and alternative therapy instituted.

Immediate hypersensitivity reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrronium. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips, and face), urticaria, or skin rash, glycopyrronium should be discontinued immediately and alternative therapy instituted. Glycopyrronium

should be used with caution in patients with severe hypersensitivity to milk proteins.

Worsening of Narrow-Angle Glaucoma

Glycopyrronium should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention

Glycopyrronium should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Formoterol fumarate

Concomitant conditions

Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving formoterol when the following conditions may exist:

Ischaemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, or other severe cardiovascular disorders, such as tachyarrhythmias or severe heart failure.

Formoterol may induce prolongation of the QTc-interval. Caution should be observed when treating patients with prolongation of the QTc-interval and in patients treated with drugs affecting the QTc-interval.

Caution should be used when co-administering theophylline and formoterol in patients with pre- existing cardiac conditions

Due to the hyperglycaemic effect of β2-stimulants, including formoterol, additional blood glucose controls are recommended in diabetic patients.

Hypokalaemia

Potentially serious hypokalaemia may result from β2-agonist therapy, including formoterol. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia and concomitant treatment. It is recommended that serum potassium levels be monitored in such situations.

Paradoxical Bronchospasm

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy substituted.

This medicine contains lactose monohydrate less than 500 micrograms per delivered dose. This amount does not normally cause problems in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Incorrect route of administration

There have been reports of patients who have mistakenly swallowed formoterol capsules instead of placing the capsules in the inhalation device. The majority of these ingestions were not associated with side effects. Healthcare providers should discuss with the patient how to correctly use formoterol. If a patient who is prescribed formoterol does not experience breathing improvement, the healthcare provider should ask how the patient is using formoterol.

4.5 Interaction with other medicinal products and other forms of interaction

Glycopyrronium

In vitro inhibition studies

In vitro inhibition studies demonstrated that glycopyrrolate has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or

CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. In vitro enzyme induction studies did not indicate a clinically relevant induction by glycopyrrolate for any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2.

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of glycopyrrolate, increased total systemic exposure (AUC) to glycopyrrolate by 22% and decreased renal clearance by 23%.

Sympathomimetics, Methylxanthines, Steroids

In clinical studies, concurrent administration of short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators (including indacaterol), methylxanthines, oral and inhaled steroids with glycopyrronium showed no increases in adverse drug reactions**.**

Anticholinergics

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid co-administration of glycopyrronium with other anticholinergic- containing drugs as this may lead to an increase in undesirable anticholinergic effects.

Formoterol fumarate

There are no clinical data to support the advice given below, but from consideration of first principles one might expect the following interactions:

Drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines, tricyclic antidepressants and erythromycin may be associated with QT-interval prolongation and an increased risk of ventricular arrhythmia.

Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of formoterol and may require titration of the dose.

Administration of formoterol to patients being treated with monoamine oxidase inhibitors, macrolides or tricyclic antidepressants should be performed with caution, since the action of ß2- adrenergic stimulants on the cardiovascular system may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of β2-agonists. Hypokalaemia may increase susceptibility to cardiac arrhythmias (for example, in patients treated with digitalis).

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs.

β-adrenergic blockers may weaken or antagonise the effect of formoterol. Therefore formoterol should not be given together with ß-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

4.6 Pregnancy and Lactation

Pregnancy

Glycopyrronium

Teratogenic Effects:

There are no adequate and well-controlled studies with glycopyrronium in pregnant women. Because animal reproduction studies are not always predictive of human response, glycopyrronium should only be used during pregnancy if the potential benefit to the patient justifies the potential risk to the fetus. Women should be advised to contact their physician if they become pregnant while taking glycopyrronium.

Glycopyrronium was not teratogenic in Wistar rats and New Zealand White rabbits at approximately 1400 and 530 times, respectively, the MRHD in adults (on an AUC basis at maternal inhaled doses up to 3.83 mg/kg/day in rats and up to 4.4 mg/kg/day in rabbits).

Non-teratogenic Effects:

Glycopyrronium had no effects on peri-natal and post-natal developments in rats at approximately 1100 times the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 1.88 mg/kg/day).

Formoterol fumarate

There were no teratogenic effects revealed in animal tests. In animal studies formoterol has caused implantation losses as well as decreased early postnatal survival and birth weight. The effects appeared at considerably higher

systemic exposures than those reached during clinical use of formoterol. However, until further experience is gained, formoterol is not recommended for use during pregnancy (particularly at the end of pregnancy or during labour) unless there is no

more established alternative. As with any medicine, use during pregnancy should only be considered if the expected benefit to the mother is greater than any risk to the foetus.

Nursing Mothers

Glycopyrronium

It is not known whether glycopyrronium is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when glycopyrronium is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of glycopyrronium by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue glycopyrronium, taking into account the importance of glycopyrronium to the mother.

It is not known whether glycopyrronium is excreted in human breast milk. Glycopyrronium (including its metabolites) have been detected in the milk of lactating rats and reached up to 10- fold higher concentrations in the milk than in the blood of the dam.

Formoterol fumarate

In reproductive studies in rats, formoterol fumarate was excreted in the milk. It is not known whether formoterol fumarate is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if formoterol fumarate is administered to nursing women. There are no well-controlled human studies of the use of formoterol fumarate in nursing mothers.

Fertility

Glycopyrronium

Impairment of fertility was observed in male and female Wistar rats at a subcutaneous dose of

1.88 mg/kg/day (approximately 1900 and 1100 times the MRHD in adults on an AUC basis) based upon findings of decreased implantation sites and live fetuses. No effects on fertility and reproductive performance in male and female rats were observed at a subcutaneous dose of 0.63 mg/kg/day (approximately 350 times the MRHD in adults on an AUC basis).

Formoterol fumarate

There is no available data on the effect of formoterol on human fertility. No impairment of fertility was observed in studies performed in male and female rats.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients experiencing dizziness or other similar side effects should be advised to refrain from driving or using machines.

4.8 Undesirable effects

Glycopyrronium/formoterol fumarate dihydrate DPI (12.5/12 mcg)

A phase 3, randomized, double-blind, active-controlled, comparative, prospective multicentre, parallel study was conducted to evaluate the efficacy and safety of the FDC of glycopyrronium/formoterol fumarate dihydrate DPI (12.5/12 mcg) administered as a single inhalation twice-daily in comparison with once-daily single administration of Glenmark AirzTM in subjects with chronic obstructive pulmonary disease (COPD). A total of 330 randomized subjects were included in the safety population. Overall, the incidence of AEs in the safety population was low (39.7%; 131/330) and comparable across the 2 treatment groups (37.8% [62/164] in glycopyrronium/formoterol fumarate dihydrate group versus 41.6% [69/166] in Glenmark AirzTM group). Most of the AEs were mild or moderate in intensity.

The incidence of TEAEs was low (36.1%; 119/330) and comparable across the 2 treatment groups (34.1% in glycopyrronium/formoterol fumarate dehydrate group versus 38.0% in Glenmark AirzTM group). Most of the TEAEs were mild or moderate in intensity and not related to the study drug.

Among subjects receiving glycopyrronium/formoterol fumarate dihydrate, the most commonly reported TEAEs (occurring in at least five subjects) by PT in the decreasing order of incidence were urinary retention (9 [5.5%]), pyrexia (8 [4.3%]), chronic obstructive pulmonary disease (7 [4.3%]), upper respiratory tract infection and hyperglycaemia (6 [3.7%] each), and diarrhoea and vomiting (5 [3.0%] each). In the Glenmark AirzTM group, the most commonly reported AEs (occurring in at least five subjects) by PT in the decreasing order of incidence were urinary retention (12 [7.2%]), chronic obstructive pulmonary disease (10 [6.0%]), pyrexia (8 [4.8%]), pain, upper respiratory tract infection, and hyperglycaemia (6 [3.6%] each), and constipation (5 [3.0%]).

The incidence of study drug related TEAEs was comparable between the 2 treatment groups (6.7% in glycopyrronium/formoterol fumarate dihydrate group versus 9.0% in Glenmark AirzTM group). In the glycopyrronium/formoterol fumarate dihydrate group, the study drug related TEAEs were hyperglycemia (5 [3.0%]), abdominal pain, and diarrhoea (3 [1.8%] each), vomiting, urinary retention (2 [1.2%] each), and insomnia (1 [0.6%]). In the Glenmark AirzTM group, the study drug related TEAEs were hyperglycemia (5 [3.0%]), urinary retention (3 [1.8%]), abdominal pain and pyrexia (2 [1.2%] each), pain, tremor, insomnia, proteinuria and urethral stenosis (1 [0.6%] each).

Glycopyrronium

The following adverse reactions are described in greater detail, in other sections

- Paradoxical bronchospasm.

- Immediate hypersensitivity reactions.
- Worsening of narrow-angle glaucoma.
- Worsening of urinary retention.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

The glycopyrronium (glycopyrrolate) safety database included 3415 subjects with COPD in four 12-week lung function trials and one 52-week long-term safety study. A total of 1202 subjects received treatment with glycopyrrolate 15.6 mcg (equivalent to 12.5 mcg of glycopyrronium) twice-daily (BID). The safety data described below are based on the four 12-week trials and the one 52-week trial.

12-Week Trials

The incidence of adverse reactions associated with glycopyrronium in Table below is based on four 12-week, placebo controlled trials in 2908 subjects with COPD. In the total population, 61.2% of patients had moderate COPD and 37.8% had severe COPD. In these trials, 951 subjects received glycopyrrolate 15.6 mcg BID (glycopyrronium 12 mcg), 511 subjects received indacaterol 27.5 mcg BID, 508 subjects received a fixed-dose combination of indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg BID, and 938 subjects received placebo. Overall, 62% were males, 90% were Caucasian, and the mean age was 63 years (ranging from 41 to 89 years). In this population, 53% were identified as current smokers with an average smoking history of 48 pack-years.

The most common adverse reactions (incidence greater than or equal to 2% and higher than placebo) were upper respiratory tract infection and nasopharyngitis. The proportion of subjects who discontinued treatment due to adverse reactions was 2.4% for the glycopyrronium treated patients and 3.8% for placebo-treated patients.

Adverse reactions with glycopyrronium (greater than or equal to 1% incidence and higher than placebo) in COPD patients

Nasopharyngitis	**20 (2.1)**	**18 (1.9)**
Urinary tract infection	13 (1.4)	12 (1.3)
Sinusitis	13 (1.4)	7 (0.7)
Oropharyngeal pain	17 (1.8)	11 (1.2)

Other adverse reactions occurring more frequently with glycopyrronium than with placebo, but with an incidence of less than 1% include rash, pruritus, gastroenteritis, hypersensitivity, atrial fibrillation, insomnia, pain in extremity, dysuria, vomiting, productive cough, and diabetes mellitus/hyperglycemia.

52-Week Trial

In a long-term safety trial, 507 subjects were treated for up to 52 weeks with glycopyrrolate 15.6 mcg twice-daily or indacaterol 75 mcg once-daily. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the placebo-controlled trials of 12 weeks. Additional adverse reactions that occurred with a frequency greater than or equal to 2% in the group receiving glycopyrrolate 15.6 mcg twice-daily that exceeded the frequency of indacaterol 75 mcg once-daily in this trial were: diarrhea, nausea, upper abdominal pain, fatigue, bronchitis, pneumonia, rhinitis, back pain, arthralgia, dyspnea, and wheezing.

Postmarketing Experience

The following additional adverse reactions have been identified during worldwide post-approval use of glycopyrrolate, at higher than the recommended dose. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: angioedema, paradoxical bronchospasm and dysphonia.

Formoterol fumarate

Adverse reactions (Table below) are ranked in descending order of frequency, as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000,

<1/1,000); very rare (< 1/10,000); unknown (frequency cannot be estimated from available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Immune system disorders	
Very rare:	Hypersensitivity (including hypotension, angioneurotic oedema)
Rare	Hypersensitivity reactions e.g. bronchospasm, exanthema, urticaria, pruritus
Metabolism and nutrition disorders	
Rare	Hypokalaemia,

Very Rare	**Hyperglycaemia**
Psychiatric disorders	
Uncommon:	Agitation, anxiety, nervousness, restlessness, insomnia
Central Nervous system disorders	
Common:	Headache, tremor
Uncommon:	Dizziness
Very rare:	Dysgeusia
Cardiac disorders	
Common:	Palpitations
Uncommon:	Tachycardia
Rare:	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
Very rare:	Peripheral oedema. Angina pectoris, prolongation of QTc-interval

Very Rare	Hyperglycaemia
Respiratory, thoracic and mediastinal disorders	
Uncommon: Unknown:	Bronchospasm, throat irritation, including paradoxical bronchospasm, acute asthma exacerbation* Cough**
Skin and subcutaneous tissue disorders	
Unknown:	Rash**
Gastrointestinal disorders	
Uncommon Rare:	Dry mouth Nausea
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle cramps, myalgia
Investigations	
Unknown	Increased blood pressure (including hypertension)**
Vascular Disorders	
Very rare	Variations in blood pressure

*The percent of patients with serious asthma exacerbations in clinical studies was higher for formoterol than for placebo, and the biggest numerical imbalance was observed in children 5-12 years old.

** These adverse events were reported in patients treated with formoterol during the post- marketing experience.

As with all inhalation therapy, paradoxical bronchospasm may occur in very rare cases. Treatment with β2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies. The excipient lactose contains small amounts of milk proteins. These may cause allergic reactions.

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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4.9 Overdose

There are no data available from clinical trials on overdose with Fixed Dose Combination of Glycopyrronium and Formoterol Fumarate Powder; however, data on overdose with both single drugs are given below:

Glycopyrronium

An overdose of glycopyrrolate may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding.

In COPD patients, repeated orally inhaled administration of glycopyrrolate at total doses of

124.8 and 249.6 mcg once-daily for 28 days were well tolerated.

Accidental ingestion: Acute intoxication by inadvertent oral ingestion of glycopyrrolate capsules is unlikely due to the low oral bioavailability (about 5%).

Peak plasma levels and total systemic exposure following intravenous administration of 150 mcg glycopyrrolate (equivalent to 120 mcg active moiety) in healthy volunteers were respectively about 270-fold and 13-fold higher than the peak and total systemic exposure at steady-state achieved with the recommended daily dose of 31.2 mcg of glycopyrrolate (i.e., 15.6 mcg glycopyrrolate twice-daily) and were well-tolerated.

Formoterol fumarate

Symptoms

There is no clinical experience to date on the management of overdose, however, an overdosage of formoterol would be likely to lead to effects that are typical of β2-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, prolonged QTc-interval, hypertension.

Treatment

Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-blockers may be considered, but only subject to extreme caution since the

use of β-adrenergic blocker medication may provoke bronchospasm.Serum potassium should be monitored.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics, formoterol fumarate and glycopyrronium bromide.

ATC-code: R03AL07

Mechanisms of action and pharmacodynamic effects Glycopyrronium

Mechanisms of action

Glycopyrrolate is a long-acting muscarinic antagonist which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, glycopyrrolate exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrronium is predominantly a site-specific effect.

Pharmacodynamic effects

Cardiac Electrophysiology

The effect of glycopyrrolate (glycopyrronium 12.5mcg) on the QTc interval was evaluated in a randomized placebo and positive controlled double-blind, single-dose, crossover thorough QTc study in 73 healthy subjects. At the dose 16-fold the therapeutic daily dose, glycopyrrolate (glycopyrronium 12.5mcg) did not prolong QTc to any clinically relevant extent.

Clinical studies

The safety and efficacy of glycopyrrolate (Glycopyrronium) were evaluated in a clinical development program that included 2 dose ranging trials, 4 efficacy and safety trials of 12 weeks duration (placebo-controlled), and a 52-week long-term safety trial. Two of these efficacy and safety trials were conducted in support of the indacaterol/glycopyrrolate combination clinical development program, included glycopyrrolate 15.6 mcg twice daily (BID) treatment arms, and are included in the overall safety database. Therefore, the efficacy of Glycopyrronium is based

primarily on the dose-ranging trials in 471 subjects with COPD and the 2 placebo-controlled confirmatory trials in 867 subjects with COPD.

Dose Ranging Trial

Dose selection for glycopyrrolate in COPD was supported by a 28-day, randomized, double- blind, placebo-controlled, 2- period, crossover study evaluating 7 doses of glycopyrrolate (15.6 mcg, 31.2 mcg, 62.4 mcg, and 124.8 mcg once-daily (QD) and 15.6 mcg, 31.2 mcg, and 62.4 mcg twice-daily) or placebo in 388 subjects with COPD. The differences in trough FEV1 from baseline after 28 days compared to placebo for the 15.6 mcg, 31.2 mcg, 62.4 mcg, and 124.8 mcg once daily and for 15.6 mcg, 31.2 mcg, and 62.4 mcg twice-daily doses were 0.083 L (95% CI: 0.030, 0.136), 0.098 L (0.048, 0.148), 0.090 L (0.038, 0.142), 0.176 L (0.132, 0.220) 0.139 L

(0.089, 0.189), 0.167 L (0.115, 0.219), and 0.177 L (0.132, 0.222), respectively. The dose-

ranging results supported the evaluation of glycopyrrolate 15.6 mcg twice-daily in the confirmatory COPD trials.

Adjusted mean change from baseline in FEV1 (L) over 24 hours on Days 1 and 28

Confirmatory Trials

The clinical development program for glycopyrrolate (glycopyrronium) included two (Trial 1 and Trial 2) similar 12-week, randomized, double-blinded, placebo-controlled, parallel-group trials in subjects with COPD designed to evaluate the efficacy of glycopyrrolate (glycopyrronium) on lung function.

The 12-week trials treated 867 subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a post-bronchodilator FEV1 greater than or equal to 30% and less than 80% of predicted normal values, had a ratio of FEV1/FVC of less than 0.7, and were symptomatic as determined by a Modified Medical Research Council (mMRC) score greater than or equal to 2. Of the 867 subjects included

in the efficacy analysis, 58% were male and 89% were Caucasian. They had a mean age of 63 years and an average smoking history of 53 packyears, with 57% identified as current smokers, and 29% using inhaled corticosteroids. At screening, the mean postbronchodilator percent predicted FEV1 was 55% (range: 30% to 83%), the mean post-bronchodilator percent FEV1/FVC was 51% (range: 24% to 69%), and the mean percent reversibility was 20% (0% to 169%).

Trial 1 and Trial 2 evaluated glycopyrrolate 15.6 mcg twice-daily and placebo twice-daily. The primary endpoint was the change from baseline in FEV1 AUC0-12h following the morning dose at Day 85 (defined as the mean FEV1 change from baseline over 0 to 12 hours divided by 12 hours) compared with placebo. In both trials, glycopyrrolate twice-daily demonstrated a larger increase in mean change from baseline in FEV1 AUC0-12h compared to placebo.

Least Squares (LS) mean change from baseline in FEV1 (L) AUC(0-12h) at Day 85 in Trials 1 and 2 (Intent to- Treat Population)

powder for Inhalation			**powder for Inhalation - Placebo**		
Placebo	213	- 0.008 L (0.0153)			

In Trial 1 and Trial 2, serial spirometric evaluations throughout the 12-hour dosing interval were performed in all subjects at Days 1 and 85. The spirometric curves from Trial 1 at Days 1 and 85 are displayed in Figure below. In Trial 2, the results for glycopyrronium powder for inhalation in FEV1 AUC0-12h were similar to those observed in Trial 1.

Adjusted mean change from baseline in FEV1 (L) over 12 hours on Days 1 and 85 in Trial 1 (All Patient Population)

The peak FEV1 was defined as the maximum FEV1 recorded within 4 hours after the morning dose on Days 1 and 85. The mean peak FEV1 improvement from baseline for glycopyrronium

powder for inhalation compared with placebo at Day 1 and at Day 85 was 0.142L and 0.163L (Trial 1), and 0.137L and 0.148L (Trial 2), respectively.

In Trials 1 and 2, patients treated with glycopyrronium powder for inhalation used less daily rescue albuterol during the trial compared to patients treated with placebo.

The St. George's Respiratory Questionnaire (SGRQ) was assessed in Trials 1 and 2. In Trial 1, the SGRQ responder rate (defined as an improvement in score of 4 or more as threshold) for the glycopyrronium powder for inhalation treatment arm was 49% compared to 41% for placebo [Odds Ratio: 1.43, 95% CI: 0.95, 2.15]. In Trial 2, the SGRQ responder rate for the glycopyrronium powder for inhalation treatment arm was 55% compared to 42% for placebo [Odds Ratio: 1.78; 95% CI: 1.17, 2.71].

Pediatric Use

Glycopyrronium powder for inhalation is not indicated for use in children. The safety and efficacy of glycopyrronium powder for inhalation in pediatric patients have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of Glycopyrronium powder for inhalation in geriatric patients is warranted. Glycopyrronium powder for inhalation can be used at the recommended dose in elderly patients 75 years of age and older.

Of the total number of subjects in clinical studies of Glycopyrronium powder for inhalation, 45% were aged 65 and older, while 10% were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Formoterol fumarate

Mechanisms of action/ Pharmacodynamics

Formoterol is a potent selective β2-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction. The effect sets in rapidly (within 1-3 minutes) and is still significant 12 hours after inhalation.

In man, formoterol has been shown to be effective in preventing bronchospasm induced by exercise and methacholine.

Formoterol has been studied in the treatment of conditions associated with COPD, and has been shown to improve symptoms and pulmonary function and quality of life. Formoterol acts on the reversible component of the disease.

Combination Clinical study

Glenmark conducted a 12-week, randomized, double blind, active comparator, parallel group clinical trial to evaluate the efficacy and safety of fixed dose combination dry powder inhaler of Glycopyrronium and Formoterol Fumarate in comparison with Glenmark AirzTM (dry powder inhaler of Glycopyrronium). 331 subjects with moderate-to-severe COPD were randomized in the ratio of 1:1 to receive fixed dose combination dry powder inhaler of Glycopyrronium and Formoterol Fumarate (12.5mcg/12mcg) twice daily or Glenmark AirzTM (dry powder inhaler of Glycopyrronium 50mcg) once daily for a treatment period of 12 weeks. The subjects were between 40 years and 65 years of age, had a history of smoking of at least 10 pack years, had post-salbutamol ratio of FEV1/FVC of less than 0.70 and FEV1 less than 80% and more than or equal to 30% of predicted normal values.

The primary endpoint was change from baseline in peak FEV1 at week 12. Peak FEV1 was defined as the maximum FEV1 recorded within 2 hours after the administration of trial medication. The mean peak FEV1 improvement from baseline in the group receiving fixed dose combination dry powder inhaler of Glycopyrronium and Formoterol Fumarate was 318 mL (95% CI: 269, 367). The mean peak FEV1 improvement from baseline in the group receiving

Glenmark AirzTM was 203 mL (95% CI: 157, 249). Fixed dose combination dry powder inhaler of Glycopyrronium and Formoterol Fumarate provided 115 mL (95% CI: 61, 170) more improvement in peak FEV1 compared with Glenmark AirzTM. The improvement in trough FEV1 at week 12 was also more with fixed dose combination dry powder inhaler of Glycopyrronium and Formoterol Fumarate (mean improvement 194 mL, 95% CI: 139, 249) compared with

Glenmark AirzTM (mean improvement 116 mL, 95% CI: 63, 169) (mean difference = 78 mL, 95% CI: 15, 141). Subjects receiving fixed dose combination dry powder inhaler of Glycopyrronium and Formoterol Fumarate used lesser rescue medication and had larger reduction in symptom scores compared to the group receiving Glenmark AirzTM.

5.2 Pharmacokinetic properties

Absorption

Glycopyrronium

Linear pharmacokinetics of glycopyrrolate was observed following inhalation of daily doses of

31.2mcg to 249.6mcg.

Following oral inhalation, glycopyrrolate was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

The absolute bioavailability of glycopyrrolate was estimated to be about 40%. About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption.

Following repeated once-daily inhalation in patients with COPD, PK steady-state of glycopyrrolate was reached within 1 week of treatment. There was no indication that the glycopyrrolate pharmacokinetics changes over time.

Formoterol fumarate

Formoterol has a therapeutic dose range of 12 to 24 micrograms b.i.d. Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses. Urinary excretion of unchanged formoterol, used as an indirect measure of systemic exposure, correlates with plasma drug disposition data. The elimination half-lives calculated for urine and plasma are similar.

Following inhalation of a single 120 microgram dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of

266 pmol/l within 5 minutes of inhalation. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 micrograms b.i.d. the plasma concentrations of formoterol ranged between 11.5 and 25.7 pmol/L and 23.3 and 50.3 pmol/L respectively at 10 minutes, 2 hours and 6 hours post inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (R,R) and (S,S)- enantiomers, after inhalation of dry powder (12-96

micrograms) or aerosol formulations (12-96 micrograms), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 micrograms or 24 micrograms formoterol powder b.i.d., the urinary excretion of unchanged formoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children, suggesting a modest and self- limiting accumulation of formoterol in plasma after repeated dosing.

As reported for other inhaled drugs, it is likely that about 90% of formoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. This means that the pharmacokinetic characteristics of the oral formulation largely apply also to the inhalation powder. When 80 micrograms of 3H-labelled formoterol fumarate was orally administered to two healthy volunteers, at least 65% of the drug was absorbed.

Distribution

Glycopyrronium

After intravenous administration, the steady-state volume of distribution of glycopyrrolate was 83L and the volume of distribution in the terminal phase was 376L. The in vitro human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/ml.

Formoterol

The plasma protein binding of formoterol is 61-64% (34% primarily to albumin).

There is no saturation of binding sites in the concentration range reached with therapeutic doses. Metabolism

Glycopyrronium

In vitro metabolism studies show glycopyrrolate hydroxylation resulting in a variety of mono- and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9). Further in vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrrolate and the hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family pre-systemically and/or via first pass metabolism from the swallowed dose fraction of orally inhaled glycopyrrolate. Glucuronide and/or sulfate conjugates of glycopyrrolate were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

Formoterol

Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9,

and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol are similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination

Glycopyrronium

Renal elimination of parent drug accounts for about 60% to 70% of total clearance of systemically available glycopyrrolate whereas non-renal clearance processes account for about 30% to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non- renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 62.4 mcg and 249.6 mcg glycopyrrolate by healthy volunteers and patients with COPD, mean renal clearance of glycopyrrolate was in the range of 17.4 L/h and 24.4 L/h indicating active tubular secretion contributes to the renal elimination of glycopyrrolate.

Glycopyrrolate plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 53 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration.

Formoterol fumarate

In asthmatic and COPD patients treated for 12 weeks with 12 or 24 micrograms formoterol fumarate b.i.d., approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. In asthmatic children, approximately 6% of the dose was recovered in the urine as unchanged formoterol after multiple dosing of 12 and 24 micrograms. The (R,R) and (S,S)-enantiomers accounted, respectively, for 40% and 60% of urinary recovery of unchanged formoterol, after single doses (12 to 120 micrograms) in healthy volunteers and after single and repeated doses in asthma patients.

After a single oral dose of 3H-formoterol, 59-62% of the dose was recovered in the urine and 32- 34% in the faeces. Renal clearance of formoterol is 150 mL/min.

After inhalation, plasma formoterol kinetics and urinary excretion rate data in healthy volunteers indicate a biphasic elimination, with the terminal elimination half-lives of the (R,R)- and (S,S)- enantiomers being 13.9 and 12.3 hours, respectively.

Approximately 6.4-8% of the dose was recovered in the urine as unchanged formoterol, with the (R,R) and (S,S)-enantiomers contributing 40% and 60% respectively.

Linearity/non-linearity

Glycopyrronium

Linear pharmacokinetics of glycopyrronium was observed following inhalation of daily doses of

31.2 mcg to 249.6 mcg. In COPD patients both systemic exposure and total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about dose-proportionally over the dose range of 44 to 176 mcg.

Special populations Gender, Age, Race ***Glycopyrronium***

Population pharmacokinetic analysis showed no evidence of a clinically relevant effect of age (40 to 85 years) or body weight (45 to 120 kg) on systemic exposure to glycopyrrolate. In addition, there was no evidence of a clinically significant ethnic/race effect (across Caucasian, Chinese, Hispanic/Latino, Japanese subjects). Gender, smoking status, and baseline FEV1 have no apparent effect on maximal or average glycopyrrolate systemic exposure.

Formoterol fumarate

Elderly Patients (older than 65 years)

The pharmacokinetics of formoterol has not been studied in the elderly population. The available data from clinical trials performed in elderly patients do not suggest that the dosage should be different than in other adults.

Patients with hepatic impairment

Glycopyrronium

The effects of hepatic impairment on the pharmacokinetics of glycopyrrolate have not been studied.

Glycopyrrolate is cleared predominantly from systemic circulation by renal excretion.

Formoterol fumarate

There is no theoretical reason to suggest that formoterol dosage requires adjustment in patients with hepatic impairment, however no clinical data have been generated to support its use in these groups.

Patients with renal impairment

Glycopyrronium

Renal impairment has an impact on the systemic exposure to glycopyrrolate. A moderate mean increase in total systemic exposure (AUClast) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment [estimated GFR greater than or equal to 30 mL/min/1.73m2] and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease [estimated GFR less than 30 mL/min/1.73m2]

Formoterol fumarate

There is no theoretical reason to suggest that formoterol dosage requires adjustment in patients with renal impairment, however no clinical data have been generated to support its use in these groups.

5.3 Preclinical safety data

Glycopyrronium Carcinogenesis, Mutagenesis

Glycopyrrolate produced no treatment-related increases in the incidence of tumors in a 2-year inhalation study in Wistar rats at inhaled doses up to 0.56 mg/kg/day (approximately 170 times the MRHD in adults on an AUC basis, respectively).

A 26-week oral (gavage) study in male and female TgrasH2 mice that received glycopyrrolate at doses up to 93.8 and 125.1 mg/kg/day, respectively, did not show any evidence of tumorigenicity.

Glycopyrrolate tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro human lymphocyte chromosomal aberration assay, and in vivo rat bone marrow micronucleus assay.

Animal Toxicology

Eye findings were observed in Wistar rats at inhaled doses of 0.67 mg/kg/day and higher (approximately 280 times the MRHD in adults on an AUC basis) based upon findings of anterior capsule opacity, prominent anterior suture line, and anterior cataract. No eye findings in Wistar rats were observed at an inhaled dose of 0.09 mg/kg/day (approximately 60 times the MRHD in adults on an AUC basis). Eye findings were observed in beagle dogs at an inhaled dose of 0.33mg/kg/day (approximately 150 times the MRHD in adults on an AUC basis) based upon findings of conjunctival hyperemia and corneal opacity. No eye findings in beagle dogs were observed at an inhaled dose of 0.12 mg/kg/day (approximately 100 times the MRHD in adults on an AUC basis).

Formoterol fumarate

Mutagenicity

Mutagenicity tests covering a broad range of experimental endpoints have been conducted. No genotoxic effects were found in any of the in vitro or in vivo tests performed.

Carcinogenicity

Two-year studies in rats and mice did not show any carcinogenic potential.

Male mice treated at very high dose levels showed a slightly higher incidence of benign adrenal subcapsular cell tumours, which are considered to reflect alterations in the physiological ageing process.

Two studies in rats, covering different dose ranges, showed an increase in mesovarial leiomyomas. These benign neoplasms are typically associated with long-term treatment of rats at high doses of β2-adrenergic drugs. Increased incidences of ovarian cysts and benign granulosa/theca cell tumours were also seen; β-agonists are known to have effects on the ovary

in rats in which are very likely specific to rodents. A few other tumour types noted in the first study using the higher doses were within the incidences of the historical control population, and were not seen in the lower-dose experiment.

None of the tumour incidences were increased to a statistically significant extent at the lowest dose of the second study, a dose leading to a systemic

exposure 10 times higher than that expected from the maximum recommended dose of formoterol.

On the basis of these findings and the absence of a mutagenic potential, it is concluded that use of formoterol at therapeutic doses does not present a carcinogenic risk.

Reproductive toxicity

Animal tests have shown no teratogenic effects. Formoterol was evaluated for its effect on fertility and general reproductive performance in sexually mature male and female rats. Reproduction studies in rats revealed no impairment of fertility or effect on early embryonic development at oral doses up to 3 mg/kg (approximately 1200 times the maximum recommended daily inhalation powder dose in human on a mg/m2 basis).

After oral administration, formoterol was excreted in the milk of lactating rats.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose Monohydrate & hydroxypropyl methylcellulose capsules

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store below 30°C. Store the capsules in original package & do not remove until immediately before use. Close the container tightly after each use.

6.5 Nature and Content of container

Available as a labeled HDPE bottle fitted with cap containing a 1g silica gel canister and 30 Capsules. Such one HDPE bottle is packed in a carton along with a device and pack insert.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing Authorization Holder

Glenmark Pharmaceuticals Limited, B/2,

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Manufacturing Site Address

Glenmark Pharmaceuticals Limited,

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8. Marketing Authorization Number

H2026/CTD11592/25262

9. Date of first authorization/renewal of the authorization

2026 June 12

10. Date of revision of the text

2026 June 12