NOVARTIS

ZIMBUS BREEZHALER
(indacaterol/glycopyrronium/mometasone furoate)

150/50/80 and 150/50160 micrograms inhalation powder, hard capsules

Professional Information

Document status: Final

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1. NAME OF THE MEDICINE

ZIMBUS BREEZHALER (indacaterol/glycopyrronium/mometasone furoate) 150/50/80 micrograms inhalation powder, hard capsules

ZIMBUS BREEZHALER (indacaterol/glycopyrronium/mometasone furoate) 150/50/160 micrograms inhalation powder, hard capsules

2. QUALITATIVE AND QUATITATIVE COMPOSITION

Each capsule of ZIMBUS BREEZHALER 150/50/80 micrograms contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol, 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms glycopyrronium and 80 micrograms mometasone furoate.

Each capsule of ZIMBUS BREEZHALER 150/50/160 micrograms contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol, 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms glycopyrronium and 160 micrograms mometasone furoate.

For the full list of excipients, see section 6.1.

Contains sugar: lactose (each capsule contains approximately 25 mg of lactose monohydrate (which may contain residual amounts of milk-related proteins)).

3. PHARMACEUTICAL FORM

ZIMBUS BREEZHALER 150/50/80 micrograms, inhalation powder, hard capsules.

ZIMBUS BREEZHALER 150/50/160 micrograms, inhalation powder, hard capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZIMBUS BREEZHALER is indicated as a once-daily maintenance treatment of asthma, and to reduce asthma exacerbations, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid.

4.2 Posology and method of administration

Posology

Inhalation of the content of one capsule of ZIMBUS BREEZHALER 150/50/80 micrograms or 150/50/160 micrograms once-daily.

Patients should be given the strength of ZIMBUS BREEZHALER containing the appropriate mometasone furoate dosage for the severity of their disease and should be regularly reassessed by a healthcare professional.

Patients usually experience an improvement in lung function within 5 minutes of inhaling ZIMBUS BREEZHALER. However, the patient should be informed that regular daily use is

necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic.

The maximum recommended dose is ZIMBUS BREEZHALER 150/50/160 micrograms once daily.

Special populations

Renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment. The safety and efficacy of ZIMBUS BREEZHALER in patients with severe renal impairment including those with end-stage renal disease requiring dialysis have not been established. (see sections 4.4 and 5)

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for ZIMBUS BREEZHALER in subjects with severe hepatic impairment. (see section 5)

Elderly population

No dose adjustment is required in elderly patients 65 years of age or older. (see section 5)

Paediatric population

The safety and efficacy of ZIMBUS BREEZHALER in paediatric patients below 18 years of age have not been established**.**

Method of administration

For inhalation use only. ZIMBUS BREEZHALER capsules must not be swallowed.

Patients should be instructed on how to administer the medicinal product correctly.

The capsules must be administered only using the ZIMBUS BREEZHALER inhaler.

The inhaler provided with each new prescription should be used.

ZIMBUS BREEZHALER should be administered at the same time of the day each day. It can be administered irrespective of the time of the day.

The capsules must always be stored in the blister to protect from moisture and light, and only removed immediately before use (see section 6).

After inhalation, patients should rinse their mouth with water without swallowing.

If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

4.3 Contraindications

ZIMBUS BREEZHALER is contraindicated in patients with hypersensitivity to any of the active substances or excipients.

4.4 Special warnings and precautions for use

Deterioration of disease

ZIMBUS BREEZHALER should not be used to treat acute asthma symptoms including acute episodes of bronchospasm, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a medical practitioner.

Patients should not stop ZIMBUS BREEZHALER treatment without medical practitioner supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with ZIMBUS BREEZHALER. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with ZIMBUS BREEZHALER.

Hypersensitivity

Immediate hypersensitivity reactions have been observed after administration of ZIMBUS BREEZHALER. 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, ZIMBUS BREEZHALER should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

Administration of ZIMBUS BREEZHALER may result in paradoxical bronchospasm which can be life-threatening. If paradoxical bronchospasm occurs, ZIMBUS BREEZHALER should be discontinued immediately and alternative therapy instituted.

Cardiovascular effects of beta agonists

Long acting beta$_2$-adrenergic agonists, such as indacaterol, in ZIMBUS BREEZHALER may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. If such effects occur, treatment may need to be discontinued.

ZIMBUS BREEZHALER should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac dysrhythmias, hypertension), convulsive disorders or hyperthyroidism, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

Beta$_2$-adrenergic agonists have been reported to produce electrocardiographic (ECG) changes, such as flattening of the T wave, prolongation of QT interval, and ST segment depression. Therefore, long-acting beta2-adrenergic agonists (LABA) or LABA containing combination products such as ZIMBUS BREEZHALER should be used with caution in patients with

known or suspected prolongation of the QT interval or who are treated with medicinal products affecting the QT interval. (see section 5).

Hypokalaemia with beta agonists

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe asthma, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac dysrhythmias (see section 4.5).

Hyperglyceamia

Inhalation of high doses of beta$_2$-adrenergic agonists and corticosteroids may produce increases in plasma glucose. Upon initiation of treatment with ZIMBUS BREEZHALER, plasma glucose should be monitored more closely in diabetic patients.

Anticholinergic effect related to glycopyrronium

ZIMBUS BREEZHALER should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Patients should be advised about signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain and blurred vision), and should be instructed to stop using ZIMBUS BREEZHALER and to contact their doctor immediately should any of these signs or symptoms develop.

Patients with severe renal impairment

The safety of ZIMBUS BREEZHALER in patients with severe renal impairment (estimated glomerular filtration rate below 30 ml/min/1.73 m^2) including those with end-stage renal disease requiring dialysis have not been established (see section 5).

Systemic effects of corticosteroids

Systemic effects may occur with inhaled corticosteroids, particularly at high doses prescribed for maintenance periods.

Possible systemic effects include adrenal suppression, growth retardation in adolescents, decrease in bone mineral density, cataract and glaucoma.

ZIMBUS BREEZHALER should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Immune system

Safety and efficacy have not been established in patients with HIV.

Lactose

ZIMBUS BREEZHALER contains lactose. Patients with the rare hereditary condition of lactose or galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not use ZIMBUS BREEZHALER.

ZIMBUS BREEZHALER contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Interactions linked to ZIMBUS BREEZHALER

No specific interaction studies were conducted with ZIMBUS BREEZHALER. Information on the potential for interactions is based on the potential for each of the monotherapy components.

Clinically significant pharmacokinetic drug interactions mediated by ZIMBUS BREEZHALER at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Concomitant administration of orally inhaled indacaterol, glycopyrronium and mometasone furoate under steady-state conditions did not affect the pharmacokinetics of any of the active substances.

Medicinal products known to prolong the QTc interval

ZIMBUS BREEZHALER, contains beta$_2$-adrenergic agonists and should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants or medicinal products known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Medicinal products known to prolong the QT interval may increase the risk of ventricular dysrhythmia (see section 4.4).

Hypokalaemic treatment

Concomitant treatment with methylxanthine derivatives, steroids or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists (see section 4.4).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore, ZIMBUS BREEZHALER should not be given together with beta-adrenergic blockers unless there are compelling reasons for their use. Where required, cardio selective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Interaction with CYP3A4 and P-glycoprotein inhibitors

Inhibition of CYP3A4 and P-glycoprotein (P-gp) has no impact on safety of therapeutic doses of ZIMBUS BREEZHALER.

Inhibition of the key contributors of indacaterol clearance (CYP3A4 and P-gp) or mometasone furoate clearance (CYP3A4) raises the systemic exposure of indacaterol or mometasone furoate up to two-fold.

The magnitude of exposure increases for indacaterol due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses of 600 micrograms.

Due to the very low plasma concentration achieved after inhaled dosing, clinically significant interactions with mometasone furoate are unlikely. However, there may be a potential for

increased systemic exposure to mometasone furoate when strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, nelfinavir, ritonavir, cobicistat) are co-administered.

Cimetidine or other inhibitors of organic cation transport

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of glycopyrronium, increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport.

Other long acting antimuscarinics and long acting beta$_2$-adrenergic agonists

The co-administration of ZIMBUS BREEZHALER with other medicinal products containing long-acting muscarinic antagonists or long-acting beta$_2$-adrenergic agonists has not been studied and is not recommended as it may potentiate adverse reactions (see section 4.8 and 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy

Indacaterol and glycopyrronium was not teratogenic in rats or rabbits following subcutaneous administration. In animal reproduction studies with pregnant mice, rats and rabbits, mometasone furoate was teratogenic and when used, caused increased foetal malformations and decreased foetal survival and growth.

Safety in pregnancy and lactation have not been established.

Labour and Delivery

The indacaterol in ZIMBUS BREEZHALER may inhibit labour due to a relaxant effect on uterine smooth muscle.

Breast-feeding

Safety in pregnancy and lactation have not been established.

Fertility

Reproduction studies and other data in animals did not indicate a concern regarding fertility in either males or females.

4.7 Effects on ability to drive and use machines

If you experience headaches or neck pain after treatment with ZIMBUS BREEZHALER, do not drive or use machines until you have confirmed that ZIMBUS BREEZHALER does not affect your performance.

4.8 Undesirable effects

Summary of safety profile

The safety profile of ZIMBUS BREEZHALER was based on a phase 3 study with a total of 1233 adult patients with asthma treated with ZIMBUS BREEZHALER 150/50/80 micrograms or 150/50/160 micrograms once daily for up to 52 weeks.

The most common adverse drug reaction related to ZIMBUS BREEZHALER was headache.

Adverse drug reactions are listed by MedDRA system organ class. The frequency of the ADRs are based on the 52-week clinical study IRIDIUM (Table 1). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Estimated cumulative incidence (%) of adverse drug reactions in study IRIDIUM at 52 weeks

Adverse drug reactions	**ZIMBUS BREEZHALER**		**Frequency category** [based on the higher frequency between the two arms]
	150/50/80 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=617	150/50/160 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=616	
Infections and infestations			
Candidiasis*[1]	1.36 [10] (0.64, 2.56)	0.33 [2] (0.07, 1.14)	Common
Urinary Tract Infection*[2]	1.57 [9] (0.78, 2.86)	3.57 [22] (2.28, 5.30)	Common
Immune system disorders			
Hypersensitivity*[3]	1.34 [10] (0.64, 2.54)	1.17 [8] (0.53, 2.31)	Common
Metabolism and nutrition disorders			
Hyperglycaemia*[4]	0.50 [3] (0.14, 1.38)	0.68 [4] (0.23, 1.64)	Uncommon
Nervous system disorders			
Headache*[5]	5.20 [32] (3.59, 7.22)	4.24 [35] (2.82, 6.09)	Common
Cardiac disorders			
Tachycardia*[6]	0.50 [3] (0.14, 1.38)	1.34 [8] (0.63, 2.53)	Common
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain*[7]	2.02 [12] (1.11, 3.41)	3.02 [23] (1.86, 4.62)	Common
Cough	3.24 [23] (2.02, 4.91)	4.12 [30] (2.72, 5.96)	Common
Dysphonia	2.15 [13] (1.21, 3.55)	3.99 [26] (2.63, 5.78)	Common
Gastrointestinal disorders			
Gastroenteritis*[8]	1.72 [11] (0.89, 3.05)	3.23 [22] (2.01, 4.89)	Common

Adverse drug reactions	ZIMBUS BREEZHALER		Frequency category [based on the higher frequency between the two arms]
	150/50/80 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=617	150/50/160 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=616	
Dry Mouth*[9]	1.03 [6] (0.43, 2.14)	0.67 [4] (0.23, 1.62)	Common
Skin and subcutaneous tissue disorders			
Rash*[10]	1.01 [7] (0.42, 2.10)	0.33 [2] (0.07, 1.14)	Common
Pruritus*[11]	0.35 [3] (0.07, 1.21)	0.68 [4] (0.23, 1.65)	Uncommon
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain*[12]	4.99 [33] (3.42, 6.98)	3.05 [19] (1.88, 4.67)	Common
Muscle Spasms	1.36 [8] (0.65, 2.58)	1.69 [11] (0.87, 2.99)	Common
Renal and Urinary disorder			
Dysuria	0.68 [4] (0.23,1.65)	0.17 [1] (0.02, 0.92)	Uncommon
General disorders and administration site conditions			
Pyrexia	2.07 [12] (1.13, 3.48)	2.90 [23] (1.76, 4.50)	Common

* Grouping of preferred terms (PTs).

[1] oral candidiasis, oropharyngeal candidiasis.

[2] asymptomatic bacteriuria, bacteriuria, cystitis, urethritis, urinary tract infection, urinary tract infection viral.

[3] drug eruption, drug hypersensitivity, hypersensitivity, rash, rash pruritic, urticaria.

[4] blood glucose increased, hyperglycaemia.

[5] headache, tension headache.

[6] sinus tachycardia, supraventricular tachycardia, tachycardia.

[7] odynophagia, oropharyngeal discomfort, oropharyngeal pain, throat irritation.

[8] chronic gastritis, enteritis, gastritis, gastroenteritis, gastrointestinal inflammation

[9] dry mouth, dry throat.

[10] drug eruption, rash, rash papular, rash pruritic.

[11] eye pruritus, pruritus, pruritus genital.

[12] back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain.

Reporting of selected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

An overdose will likely produce signs, symptoms or adverse effects associated with the pharmacological actions of the individual components [e.g. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular dysrhythmias, metabolic acidosis,

hypokalaemia, hyperglyceamia, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), constipation, difficulties in voiding, suppression of hypothalamic pituitary adrenal axis function]. Use of cardioselective beta blockers may be considered for treating beta$_2$-adrenergic effects, but only under the supervision of a medical practitioner and with extreme caution since the use of beta$_2$-adrenergic blockers may provoke bronchospasm. In serious cases, patients should be hospitalised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine

Pharmacotherapeutic group: Long-acting inhaled therapy (beta-agonists, anticholinergics and glucocorticosteroids)

Mechanism of action

ZIMBUS BREEZHALER is a combination of indacaterol, a long-acting beta$_2$-adrenergic agonist (LABA), glycopyrronium, a long-acting muscarinic receptor antagonist (LAMA) and mometasone furoate, an inhaled synthetic corticosteroid (ICS). Following oral inhalation, indacaterol and glycopyrronium act locally on airways to produce bronchodilation by separate mechanisms and mometasone furoate reduces pulmonary inflammation.

Indacaterol

Indacaterol is a long-acting beta$_2$-adrenergic agonist for once-daily administration. The pharmacological effects of beta$_2$-adrenoceptor agonists, including indacaterol, are at least in

part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol is a weak partial agonist at $beta_1$-receptors with a potency more than 24-fold greater at $beta_2$-receptors compared to $beta_1$-receptors and is a full agonist at $beta_3$-receptors with a potency 20-fold greater at $beta_2$-receptors compared to $beta_3$-receptors.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human $beta_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action. Although $beta_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the human heart, there are also $beta_2$-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of $beta_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-adrenergic agonists may have cardiac effects.

Glycopyrronium

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic). Glycopyrronium works by blocking the broncho-constrictor action of acetylcholine on airway smooth muscle cells thereby dilating the airways. Of the five known muscarinic receptor subtypes (M1-5), only subtypes M1-3 have a defined physiological function in the human lung. Glycopyrronium is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M3 and M1 receptors over the

human M2 receptor in competition binding studies. It has a rapid onset of action, as evidenced by observed receptor association/dissociation kinetic parameters and by the onset of action after inhalation in clinical studies. The long duration of action can be partly attributed to sustained drug concentrations in the lungs as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the inhaler in contrast to the half-life after intravenous administration (see section 5.2).

Mometasone furoate

Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and local anti-inflammatory properties. Studies in asthmatic patients have demonstrated that inhaled mometasone furoate provides a favorable ratio of pulmonary to systemic activity. It is likely that much of the mechanism for the effects of mometasone furoate lies in its ability to inhibit the release of mediators of the inflammatory cascade. *In vitro*, mometasone furoate inhibits the release of leukotrienes (LT) from leukocytes of allergic patients. In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6 and TNF-alpha. It is also a potent inhibitor of LT production and an extremely potent inhibitor of the production of the Th2 cytokines, IL-4 and IL-5, from human CD4+ T-cells.

Pharmacodynamic effects

The primary pharmacodynamics of ZIMBUS BREEZHALER in obstructive airway disease reflects the complementary mechanisms of action of the individual components.

Clinical data confirmed the hypothesis that complementary bronchodilation with indacaterol and glycopyrronium coupled with the anti-inflammatory action of mometasone furoate results in improved lung function and asthma control.

The pharmacodynamic response profile of ZIMBUS BREEZHALER is characterised by onset of action within 5 minutes after dosing and sustained effect over the whole 24-hour dosing interval. No tachyphylaxis to the lung function benefits of ZIMBUS BREEZHALER were observed over time.

Effects on the QTc interval

The effect of ZIMBUS BREEZHALER on the QTc interval has not been evaluated in a thorough QT (TQT) study.

For mometasone furoate, no QTc prolonging properties are known.

5.2 Pharmacokinetic properties

Absorption

Following inhalation of ZIMBUS BREEZHALER, the median time to reach peak plasma concentrations of indacaterol, glycopyrronium and mometasone furoate was approximately 15 minutes, 5 minutes and 1 hour, respectively.

Based on the *in vitro* performance data, the dose of each of the monotherapy components delivered to the lung is expected to be similar for ZIMBUS BREEZHALER and the

monotherapy products. Steady-state plasma exposure to indacaterol, glycopyrronium and mometasone furoate after ZIMBUS BREEZHALER inhalation was similar to the systemic exposure after inhalation of indacaterol maleate, glycopyrronium or mometasone furoate as monotherapy products.

Following inhalation of ZIMBUS BREEZHALER, the absolute bioavailability was estimated to be about 45% for indacaterol, 40% for glycopyrronium and less than 10% for mometasone furoate.

Indacaterol

Indacaterol concentrations increased with repeated once-daily administration. Steady state was achieved within 12 to 14 days. The mean accumulation ratio of indacaterol, i.e. AUC over the 24-hour dosing interval on Day 14 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 and 600 micrograms. Systemic exposure results from a composite of pulmonary and gastrointestinal absorption; about 75% of systemic exposure was from pulmonary absorption and about 25% from gastrointestinal absorption.

Glycopyrronium

About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption. The absolute bioavailability of orally administered glycopyrronium was estimated to be about 5%.

Mometasone furoate

Mometasone furoate concentrations increased with repeated once-daily administration via the Breezhaler device. Steady state was achieved after 12 days. The mean accumulation ratio of mometasone furoate, i.e. $AUC_{0\text{-}24hr}$ on Day 14 compared to $AUC_{0\text{-}24hr}$ on Day 1, was in the

range of 1.28 to 1.40 for once-daily inhaled doses of between 80 and 160 micrograms as part of ZIMBUS BREEZHALER.

Following oral administration of mometasone furoate, the absolute oral systemic bioavailability of mometasone furoate was estimated to be very low (<2%).

Distribution

Indacaterol

After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,361 to 2,557 litres indicating an extensive distribution. The in vitro human serum and plasma protein binding were 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Glycopyrronium

After intravenous dosing, the steady-state volume of distribution (Vss) of glycopyrronium was 83 litres and the volume of distribution in the terminal phase (Vz) was 376 litres. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7310 litres, which reflects the much slower elimination after inhalation. The in vitro human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/ml. These concentrations were at least 6-fold higher than the steady state mean peaks levels achieved in plasma for a 50 micrograms once-daily dosing regimen.

Mometasone furoate

After intravenous bolus administration, the V_d is 332 litres. The in vitro protein binding for mometasone furoate is high, 98 % to 99 % in concentration range of 5 to 500 ng/ml.

Biotransformation

Indacaterol

After oral administration of radiolabelled indacaterol in a human absorption, distribution, metabolism, excretion (ADME) study, unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 hours. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, an N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolised indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

In vitro the UGT1A1 isoform is a major contributor to the metabolic clearance of indacaterol. However, as shown in a clinical study in populations with different UGT1A1 genotypes, systemic exposure to indacaterol is not significantly affected by the UGT1A1-genotype.

Glycopyrronium

No human specific metabolites were found. Hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen.

In vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. The hydrolysis to M9 is likely to be catalysed by members of the cholinesterase family.

After inhalation, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. Since *in vitro* studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4% of parent drug C_{max} and AUC) after intravenous administration, it is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium bromide by pre-systemic hydrolysis and/or via first pass metabolism. After inhalation as well as intravenous administration, only minimal amounts of M9 were found in the urine (i.e. ≤ 0.5% of dose). Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

In vitro inhibition studies demonstrated that glycopyrronium has no relevant capacity to inhibit CYP1A2, CYP2A6, 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 glycopyrronium for any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2.

Mometasone furoate

The portion of an inhaled mometasone furoate dose that is swallowed and absorbed in the gastrointestinal tract undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. In human liver microsomes, mometasone furoate is metabolised by cytochrome P-450 3A4 (CYP3A4).

Elimination

Indacaterol

In clinical studies which included urine collection, the amount of indacaterol excreted unchanged via urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 litres/hour. When compared with the serum clearance of indacaterol of 18.8 to 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 6% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the faecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human faeces primarily as unchanged parent substance (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 52 hours which is consistent with the observed time to steady state of approximately 12 to 14 days.

Glycopyrronium

After intravenous administration of [^{3}H]-labelled glycopyrronium to humans, the mean urinary excretion of radioactivity in 48 hours amounted to 85% of the dose. A further 5% of the dose was found in the bile. Thus, mass balance was almost complete.

Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium 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 50 and 200 microgram glycopyrronium by healthy volunteers and patients with COPD, mean renal clearance of glycopyrronium was in the range of 17.4 and 24.4 litres/hour. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20% of the dose was found in urine as parent drug.

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 57 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. The elimination pattern suggests a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 h after inhalation.

Mometasone furoate

After intravenous bolus administration, mometasone furoate has a terminal elimination $T_{1/2}$ of approximately 4.5 hours. A radiolabelled, orally inhaled dose is excreted mainly in the faeces (74%) and to a lesser extent in the urine (8%)

Linearity/non-linearity

Systemic exposure of mometasone furoate (C_{max} and AUC_{0-24h}) increased in a dose proportional manner following single and multiple doses of ZIMBUS BREEZHALER 150/50/80 and 150/50/160 micrograms in healthy subjects. A less than proportional increase (1.7-fold) in steady state systemic exposure was noted in patients with asthma over the dose range of 150/50/80 and 150/50/160 micrograms. Dose proportionality assessments were not

performed for indacaterol or glycopyrronium because only one dose was used across both dose strengths of ZIMBUS BREEZHALER.

Special populations

A population PK analysis in patients with asthma after inhalation of ZIMBUS BREEZHALER indicated no significant effect of age, gender, body weight, smoking status, baseline estimated glomerular filtration rate (eGFR) and FEV_1 at baseline on the systemic exposure to indacaterol, glycopyrronium and mometasone furoate.

Paediatric patients

The safety and efficacy of ZIMBUS BREEZHALER in paediatric patients below 18 years of age have not been established.

Renal impairment

The effect of renal impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated in dedicated studies with ZIMBUS BREEZHALER. In a population pharmacokinetics analysis, estimated glomerular filtration rate (eGFR) was not a statistically significant covariate for systemic exposure of indacaterol, glycopyrronium and mometasone furoate following administration of ZIMBUS BREEZHALER in patients with asthma.

Due to the very low contribution of the urinary pathway to the total body elimination of indacaterol and mometasone furoate, the effects of renal impairment on their systemic exposure have not been investigated.

Renal impairment has an impact on the systemic exposure to glycopyrronium administered as a monotherapy. A moderate mean increase in total systemic exposure (AUC last) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease. Based on a population PK analysis of glycopyrronium in chronic obstructive pulmonary disease patients with mild and moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2), glycopyrronium can be used at the recommended dose.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated in subjects with hepatic impairment following administration of ZIMBUS BREEZHALER. However, studies have been conducted with the mono-components.

Indacaterol: Patients with mild and moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Glycopyrronium: Clinical studies in patients with hepatic impairment have not been conducted. Glycopyrronium is cleared predominantly from the systemic circulation by renal

excretion (see section 5.2). Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase in systemic exposure.

Mometasone furoate: A study evaluating the administration of a single inhaled dose of 400 micrograms mometasone furoate by dry powder inhaler to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/ml). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels (assay Lower Limit of Quantification was 50pcg/ml) were few.

5.3 Preclinical safety data

No animal studies were performed with the combination of indacaterol, glycopyrronium and mometasone furoate.

For information on reproductive toxicity, (see section 4.6).

The *in vivo* studies of each monotherapy and combination products are presented below.

Indacaterol and mometasone furoate combination

The findings during the 13-week inhalation toxicity studies were predominantly attributable to the mometasone furoate and were typical pharmacological effects of glucocorticoids.

Increased heart rates associated with indacaterol were apparent in dogs after administration of indacaterol/mometasone furoate or indacaterol alone.

Indacaterol and glycopyrronium combination

Findings during the nonclinical safety studies of indatacerol/glycopyrronium were consistent with the known pharmacological effects of the indacaterol or glycopyrronium monotherapy components.

The effect on heart rate for indacatero/glycopyrronium was increased in magnitude and duration when compared with the changes observed for each monotherapy component alone.

Indacaterol

Effects on the cardiovascular system attributable to the beta$_2$-agonistic properties of indacaterol included tachycardia, dysrhythmias and myocardial lesions in dogs. Mild irritation of the nasal cavity and larynx were seen in rodents.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential.

Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent with similar findings reported for other beta$_2$-adrenergic agonists. No evidence of carcinogenicity was seen in mice.

All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Glycopyrronium

Effects attributable to the muscarinic receptor antagonist properties of glycopyrronium included mild to moderate increases in heart rate in dogs, lens opacities in rats and, reversible changes associated with reduced glandular secretions in rats and dogs. Mild irritancy or adaptive changes in the respiratory tract were seen in rats. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium. Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity.

Mometasone furoate

All observed effects are typical of the glucocorticoid class of compounds and are related to exaggerated pharmacological effects of glucocorticoids.

Mometasone furoate showed no genotoxic activity in a standard battery of *in vitro* and *in vivo* tests.

In carcinogenicity studies in mice and rats, inhaled mometasone furoate demonstrated no statistically significant increase in the incidence of tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill: Lactose (as monohydrate), Magnesium stearate.

Capsule shell components: Hypromellose, Carrageenan, Potassium chloride.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 25°C.

Protect from moisture and light.

Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Aluminium foil blisters made of silver forming foil (polyamide /aluminium/polyvinyl chloride) sealed to a white backing foil (polyethylene terephtlalate/aluminium).

Each blister strip containing 6 capsules per blister is enclosed in a cardboard carton with 1 inhaler device.

The inhaler device is a plastic device comprising white cap and white body with green translucent push buttons.

The inhaler body has a capsule chamber and two spring loaded push buttons which house the piercing needles. The piercing needles and springs are made of stainless steel.

Pack sizes: 6, 12, 30, 90, 96 or 150 capsules

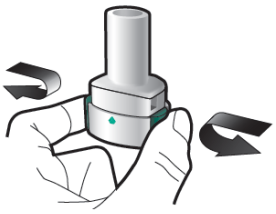
6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

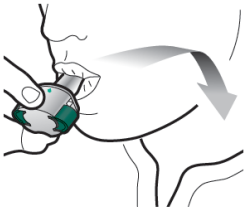
Instructions for handling and use



Insert



Pierce and release

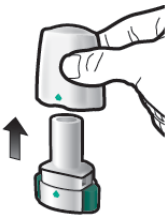


Inhale deeply

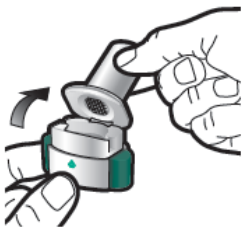


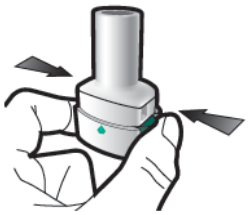
Check capsule is empty

1 **2** **3** **Check**



Step 1a:
Pull off cap





Step 2a:
Pierce capsule once
Hold the inhaler upright.
Pierce capsule by firmly pressing both side buttons at the same time.
You should hear a noise as the capsule is pierced.
Only pierce the capsule once.



Step 3a:
Breathe out fully
Do not blow into the inhaler.



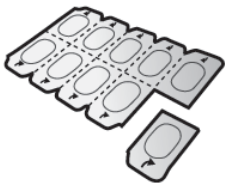


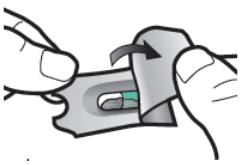
Check capsule is empty
Open the inhaler to see if any powder is left in the capsule.

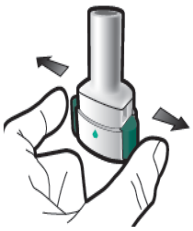
If there is powder left in the capsule:

- Close the inhaler.
- Repeat steps 3a to 3d.

Step 1b:
Open inhaler







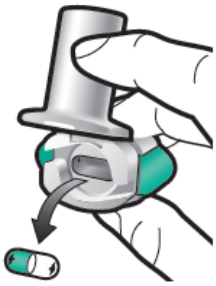
Step 2b:
Release side buttons

Step 3b:
Inhale medicine deeply
Hold the inhaler as shown in the picture.
Place the mouthpiece in your mouth and close your lips firmly around it.
Do not press the side buttons.

Breathe in quickly and as deeply as you can.
During inhalation you will hear a whirring noise.
You may taste the medicine as you inhale.



Powder
Empty
remaining



Step 1c:

Remove capsule

Separate one of the blisters from the blister card.

Peel open the blister and remove the capsule.

Do not push the capsule through the foil.

Do not swallow the capsule.



Step 3c:

Hold breath

Hold your breath for up to 5 seconds.

Step 3d :

Rinse mouth

Rinse your mouth with water after each dose and spit it out.

Remove empty capsule

Put the empty capsule in your household waste.

Close the inhaler and replace the cap.



Step 1d:

Insert capsule

Never place a capsule directly into the mouthpiece.

Important Information

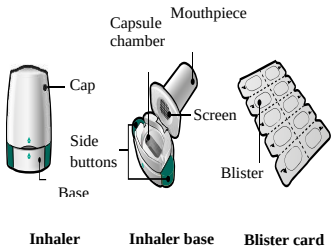
- ZIMBUS BREEZHALER capsules must always be stored in the blister card and only removed immediately before use.



Step 1e:
Close inhaler

- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the ZIMBUS BREEZHALER capsules with any other inhaler.
- Do not use the ZIMBUS BREEZHALER inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Do not blow into the mouthpiece.
- Do not press the side buttons while inhaling through the mouthpiece.
- Do not handle capsules with wet hands.
- Never wash your inhaler with water.

Your ZIMBUS BREEZHALER Inhaler pack contains: • One ZIMBUS BREEZHALER inhaler • One or more blister cards, each containing either 6 or	**Frequently Asked Questions** **Why didn't the inhaler make a noise when I inhaled?** The capsule may be stuck in the capsule	**Cleaning the inhaler** Wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry. Never wash your inhaler with water.

10 ZIMBUS BREEZHALER capsules to be used in the inhaler  **Inhaler** **Inhaler base** **Blister card**	chamber. If this happens, carefully loosen the capsule by tapping the base of the inhaler. Inhale the medicine again by repeating steps 3a to 3d. **What should I do if there is powder left inside the capsule?** You have not received enough of your medicine. Close the inhaler and repeat steps 3a to 3d.	

	I coughed after inhaling – does this matter? This may happen. As long as the capsule is empty you have received enough of your medicine. **I felt small pieces of the capsule on my tongue – does this matter?** This can happen. It is not harmful. The chances of the capsule breaking into small pieces will be increased if the capsule is pierced more than once.	**Disposing of the inhaler after use** Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

8. REGISTRATION NUMBER(S)

ZIMBUS BREEZHALER 150/50/80: 54/10.2.1/0875.873

ZIMBUS BREEZHALER 150/50/160: 54/10.2.1/0876.874

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

17 May 2021

10. DATE OF REVISION OF THE TEXT

04 August 2023