NOVARTIS

BEMRIST BREEZHALER

(indacaterol/ mometasone furoate)

150/80, 150/160 and 150/320 micrograms inhalation powder, hard capsules

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BEMRIST BREEZHALER (indacaterol/mometasone furoate) 150/80 micrograms inhalation powder, hard capsules

BEMRIST BREEZHALER (indacaterol/mometasone furoate) 150/160 micrograms inhalation powder, hard capsules

BEMRIST BREEZHALER (indacaterol/mometasone furoate) 150/320 micrograms inhalation powder, hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of BEMRIST BREEZHALER 150/80 micrograms, contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 80 micrograms of mometasone furoate.

Each capsule of BEMRIST BREEZHALER 150/160 micrograms, contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 160 micrograms of mometasone furoate.

Each capsule of BEMRIST BREEZHALER 150/320 micrograms, contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 320 micrograms of mometasone furoate

For the full list of excipients, see section 6.1.

Contains sugar: lactose (each capsule contains approximately 25 mg of lactose monohydrate).

3. PHARMACEUTICAL FORM

BEMRIST BREEZHALER 150 micrograms/80 micrograms inhalation powder, hard capsules.

Transparent (uncoloured) capsules size 3 containing a white powder, with the product code "IM150-80" printed in blue above one blue bar on the body and with the product logo printed in blue and surrounded by two blue bars on the cap.

BEMRIST BREEZHALER 150 micrograms/160 micrograms inhalation powder, hard capsules.

Transparent (uncoloured) capsules size 3 containing a white powder, with the product code "IM150-160" printed in grey on the body and with the product logo printed in grey on the cap.

BEMRIST BREEZHALER 150 micrograms/320 micrograms inhalation powder, hard capsules.

Transparent (uncoloured) capsules size 3 containing a white powder, with the product code "IM150-320" printed in black above two black bars on the body and with the product logo printed in black and surrounded by two black bars on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BEMRIST BREEZHALER is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older, where use of a combination of a long-acting beta$_2$-agonist and an inhaled corticosteroid is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting beta$_2$-agonists, or
- patients not adequately controlled with long-acting beta$_2$-agonist and low dose of inhaled corticosteroids (for BEMRIST BREEZHALER 150/160 and 150/320 micrograms).

4.2 Posology and method of administration

Posology

Inhalation of the content of one capsule of BEMRIST BREEZHALER 150/80 micrograms once daily is recommended in patients who require a combination of a long-acting beta$_2$-agonist and a low dose of inhaled corticosteroid.

Inhalation of the content of one capsule of BEMRIST BREEZHALER 150/160 micrograms or 150/320 micrograms once-daily is recommended in patients who require a combination of a long-acting beta$_2$-agonist and a medium or high dose of inhaled corticosteroid.

Patients usually experience an improvement in lung function within 5 minutes of inhaling BEMRIST 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 BEMRIST BREEZHALER 150/320 micrograms once daily.

Special populations

Renal impairment

No dose adjustment is required in patients with renal impairment**.**

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for BEMRIST BREEZHALER in subjects with severe hepatic impairment.

Elderly population

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

Paediatric population

BEMRIST BREEZHALER may be used in patients 12 years of age and older at the same posology as in adults. The safety and efficacy of BEMRIST BREEZHALER in patients below 12 years of age have not been established.

Method of administration

For inhalation use only. BEMRIST 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 BEMRIST BREEZHALER inhaler.

The inhaler provided with each new prescription should be used.

BEMRIST 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

BEMRIST 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

BEMRIST 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 BEMRIST BREEZHALER treatment without medical practitioner supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with BEMRIST 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 BEMRIST BREEZHALER.

Hypersensitivity

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

Paradoxical bronchospasm

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

Cardiovascular effects of beta agonists

Long beta$_2$-adrenergic agonists, such as indacaterol, in BEMRIST 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.

The blood pressure should be monitored in patients treated with BEMRIST BREEZHALER.

BEMRIST 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 beta$_2$-adrenergic agonists (LABA) or LABA containing combination products such as BEMRIST 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).

Hyperglycaemia

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

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. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained. It is recommended that the height of adolescents receiving prolonged treatment with an inhaled corticosteroid is regularly monitored.

Patients on corticosteroid therapy may have adrenocortical suppression. Treatment with BEMRIST BREEZHALER should not be stopped abruptly as adrenal insufficiency may be precipitated in this way.

Patients in a medical or surgical emergency, who require high doses of inhaled steroids and/or intermittent treatment with oral steroids, are at risk of impaired adrenal reserve. The possibility of residual impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.

BEMRIST BREEZHALER should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections. Regular monitoring for activation of these infections is required and BEMRIST BREEZHALER must be stopped if the infections progress.

Immune system

The safety and efficacy have not been established in patients with HIV

Lactose

BEMRIST 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 BEMRIST BREEZHALER.

BEMRIST 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 BEMRIST BREEZHALER

No specific interaction studies were conducted with BEMRIST 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 BEMRIST BREEZHALER at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

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

Medicinal products known to prolong the QTc interval

BEMRIST 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 dysrhythmias (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, BEMRIST 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 BEMRIST 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.

Other long acting beta$_2$-adrenergic agonists

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

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation have not been established.

Pregnancy

Indacaterol 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.

Breast-feeding

Both indacaterol and mometasone furoate are excreted in rat's milk.

Mothers who are breastfeeding their infants should not use BEMRIST BREEZHALER.

Labour and Delivery

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

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 BEMRIST BREEZHALER, do not drive or use machines until you have confirmed that BEMRIST BREEZHALER does not affect your performance.

4.8 Undesirable effects

Summary of safety profile

The safety profile of BEMRIST BREEZHALER was based on safety data from three phase 3 studies with a total of 2497 adult or adolescent patients with asthma treated with BEMRIST BREEZHALER 150/80, 150/160 or 150/320 micrograms once daily for up to 52 weeks.

The most common adverse drug reaction related to BEMRIST 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 PALLADIUM (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 PALLADIUM at 52 weeks

Adverse drug reactions	BEMRIST BREEZHALER		Frequency category [based on the higher frequency between the two arms]
	150/160 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=437	150/320 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=443	
Infections and infestations			
Candidiasis*[1]	0.48 [2]	0.25 [1]	Uncommon

	(0.10, 1.63)	(0.02, 1.34)	
Immune system disorders			
Hypersensitivity*[2]	1.20 [6] (0.46, 2.64)	1.88 [8] (0.89, 3.53)	Common
Angioedema*[3]	0.47 [2] (0.10, 1.58)	0 [0]	Uncommon
Metabolism and nutrition disorders			
Hyperglycaemia*[4]	0.98 [4] (0.33, 2.36)	0.97 [5] (0.33, 2.33)	Uncommon
Nervous system disorders			
Headache*[5]	5.29 [25] (3.42, 7.73)	6.22 [39] (4.18, 8.82)	Common
Cardiac disorders			
Tachycardia*[6]	0.23 [1] (0.02, 1.25)	0.73 [3] (0.21, 2.00)	Uncommon
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain*[7]	1.92 [9] (0.91, 3.60)	3.11 [14] (1.74, 5.10)	Common
Dysphonia	1.64 [7] (0.73, 3.22)	1.86 [9] (0.88, 3.49)	Common
Skin and subcutaneous tissue disorders			
Rash*[8]	0 [0]	0.93 [4] (0.31, 2.23)	Uncommon
Pruritus*[9]	0.25 [1] (0.02, 1.32)	0.48 [2] (0.10, 1.62)	Uncommon
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain*[10]	4.53 [24] (2.83, 6.83)	2.65 [11] (1.41, 4.54)	Common
Muscle Spasms	0.47 [2] (0.10, 1.58)	0.47 [2] (0.10, 1.57)	Uncommon

* Indicates grouping of preferred terms (PTs) observed in the three Phase 3 studies.

[1] oral candidiasis, oropharyngeal candidiasis.

[2] drug eruption, drug hypersensitivity, hypersensitivity, rash, rash erythematous, rash pruritic, urticaria.

[3] allergic oedema, angioedema, periorbital swelling, swelling of eyelid.

[4] blood glucose increased, hyperglycaemia.

[5] headache, tension headache.

[6] heart rate increased, tachycardia, sinus tachycardia, supraventricular tachycardia.

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

[8] drug eruption, rash, rash erythematous, rash pruritic

[9] anal pruritus, eye pruritus, nasal pruritus, pruritus, pruritus genital.

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

Reporting of suspected 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, hyperglycaemia, suppression of hypothalamic pituitary adrenal axis function).

Use of cardio selective 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-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 and glucocorticosteroids)

Mechanism of action

BEMRIST BREEZHALER is a combination of indacaterol, a long-acting beta$_2$-adrenergic agonist (LABA), and mometasone furoate, an inhaled synthetic corticosteroid (ICS). Following oral inhalation, indacaterol acts locally on airways to produce bronchodilation 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.

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 favourable 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 BEMRIST BREEZHALER in obstructive airway disease reflects the complementary mechanisms of action of the individual components of BEMRIST BREEZHALER.

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

The pharmacodynamic response profile of BEMRIST BREEZHALER is characterised by rapid onset of action within 5 minutes after dosing-and sustained effect over the 24 h dosing interval as evidenced by improvements in trough forced expiratory volume in the first second (FEV_1) versus comparators, 24 hours after dosing.

No tachyphylaxis to the lung function benefits of BEMRIST BREEZHALER were observed over time.

Effects on the QTc interval

The effect of BEMRIST 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 BEMRIST BREEZHALER, the median time to reach peak plasma concentrations of indacaterol and mometasone furoate was approximately 15 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 BEMRIST BREEZHALER and the monotherapy products. Steady-state plasma exposure to indacaterol and mometasone furoate after BEMRIST BREEZHALER inhalation was similar to the systemic exposure after inhalation of indacaterol maleate or mometasone furoate as monotherapy products.

Following inhalation of BEMRIST BREEZHALER, the absolute bioavailability was estimated to be about 45% for indacaterol 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.

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 Day 1, was in the range of 1.61 to 1.71 for once-daily inhaled doses of between 80 and 320 micrograms as part of BEMRIST 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.

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.

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 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/h. When compared with the serum clearance of indacaterol of 18.8 to 23.3 litres/h, 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.

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 increased in a dose proportional manner following single and multiple doses of BEMRIST BREEZHALER 150/80 and 150/320 micrograms in healthy subjects. A less than proportional increase in steady state systemic exposure was noted in patients with asthma over the dose range of 150/80 to 150/320 micrograms. Dose proportionality assessments were not performed for indacaterol as only one dose was used across all dose strengths of BEMRIST BREEZHALER.

Special populations

A population PK analysis in patients with asthma after inhalation of BEMRIST 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 and mometasone furoate.

Paediatric patients

BEMRIST BREEZHALER may be used in patients 12 years of age and older at the same posology as in adults. The safety and efficacy of BEMRIST BREEZHALER in patients below 12 years of age have not been established.

No data are available.

Renal impairment

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

Hepatic impairment

The effect of indacaterol/mometasone furoate has not been evaluated in subjects with hepatic impairment. However, studies have been conducted with the mono-components.

Indacaterol**:** Patients with mild or 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. No data are available for subjects with severe hepatic impairment.

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

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

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.

Mometasone furoate

All observed effects are typical of the glucocorticoid class of compounds and are related to exaggerated pharmacologic 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).

Capsule shell components: Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 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.

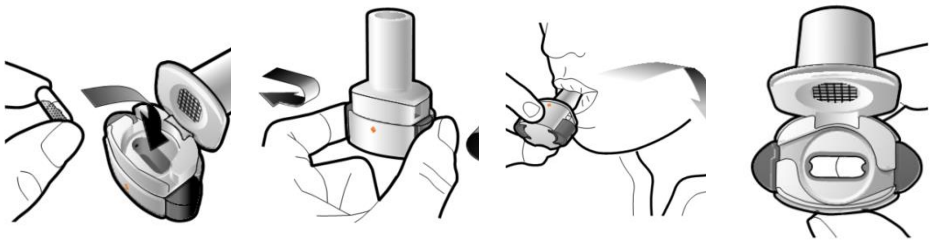
The inhaler device is a plastic device comprising white cap and white body with yellow translucent push buttons.

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

6.6 Special precautions for disposal

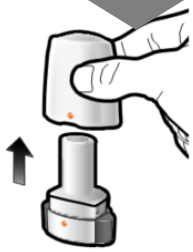
Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for handling and use



Insert **Pierce and release** **Inhale deeply** **Check capsule is empty**

1

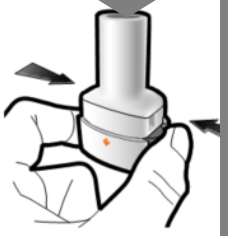


Step 1a:
Pull off cap



Step 1b:
Open inhaler

2



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.

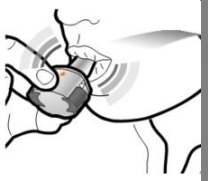


Step 2b:
Release side buttons

3

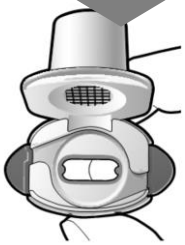


Step 3a:
Breathe out fully
Do not blow into the inhaler.



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.

Check

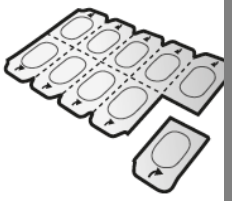


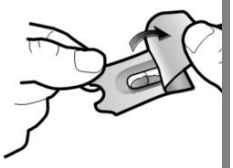
Check capsule is empty
Open the inhaler to see if any powder is left in the capsule.

If there is powder left in the capsule:
- Close the inhaler.
- Repeat steps 3a to 3d.



Powder remaining **Empty**





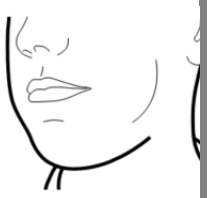
Step 1c:
Remove capsule
Separate one of the blisters from the blister card.

Peel open the blister and remove the capsule. Do not push the capsule through the foil.
Do not swallow the capsule.



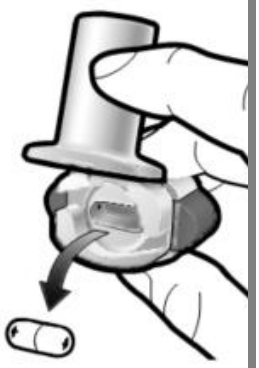
Step 1d:
Insert capsule
Never place a capsule directly into the mouthpiece.

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.



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.

Important Information
- BEMRIST BREEZHALER capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the



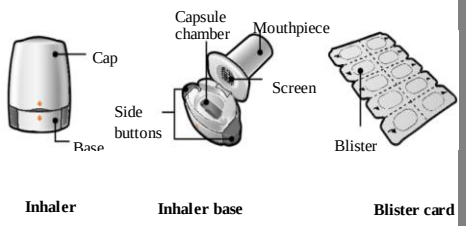
Step 1e:
Close inhaler

capsule through the foil to remove it from the blister.

- Do not swallow the capsule.
- Do not use the BEMRIST BREEZHALER capsules with any other inhaler.
- Do not use the BEMRIST 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 BEMRIST BREEZHALER Inhaler pack contains:

- One BEMRIST BREEZHALER inhaler
- One or more blister cards each containing either 6 or 10 BEMRIST BREEZHALER capsules to be used in the inhaler



Inhaler **Inhaler base** **Blister card**

Frequently Asked Questions

Why didn't the inhaler make a noise when I inhaled?
The capsule may be stuck in the capsule 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.

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.

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)

BEMRIST BREEZHALER 150/80: 54/10.2.1/0870.867

BEMRIST BREEZHALER 150/160: 54/10.2.1/0871.868

BEMRIST BREEZHALER 150/320: 54/10.2.1/0872.869

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

12 October 2021

10. DATE OF REVISION OF THE TEXT

N/A