PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**ENERZAIR® BREEZHALER®**

Indacaterol (as acetate) / glycopyrronium (as bromide) / mometasone furoate inhalation powder hard capsules

150 mcg/50 mcg/160 mcg

ENERZAIR BREEZHALER capsules to be used only with the supplied ENERZAIR BREEZHALER inhalation device

Bronchodilator (Long-Acting Beta$_2$-Adrenergic Agonist (LABA)), Bronchodilator

(Long-acting muscarinic antagonist (LAMA)) and Inhaled Corticosteroid (ICS) Combination for Oral Inhalation

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RECENT MAJOR LABEL CHANGES

None at time of authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ENERZAIR BREEZHALER (indacaterol / glycopyrronium / mometasone furoate) is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta$_2$-agonist and a medium or high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous 12 months.

ENERZAIR BREEZHALER is **not** indicated for the relief of acute bronchospasm (see General).

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ENERZAIR BREEZHALER in pediatric patients below 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No dose adjustment is required in patients 65 years of age or older (see 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

- ENERZAIR BREEZHALER is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients should be made aware that ENERZAIR BREEZHALER should be used regularly, even when asymptomatic.

When treating patients with asthma, physicians should only prescribe ENERZAIR BREEZHALER for patients not adequately controlled on a long-term asthma control medication containing a LABA and a medium or high dose inhaled corticosteroid and who experienced one or more asthma exacerbations in the previous year.

As with other inhaled drugs containing beta$_2$-adrenergic agents, ENERZAIR BREEZHALER should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. When beginning treatment with ENERZAIR BREEZHALER patients who have been taking rapid onset, short duration, inhaled beta$_2$-agonists on a regular basis (e.g., q.i.d) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute respiratory symptoms while taking ENERZAIR BREEZHALER.

It is crucial to inform patients that ENERZAIR BREEZHALER should **not** be used to treat acute symptoms of asthma. Patients should be prescribed a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve acute symptoms such as shortness of breath and advised to have this available for use at all times.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of ENERZAIR BREEZHALER for patients 18 years of age and older is:

- Inhalation of the content of one capsule of ENERZAIR BREEZHALER 150/50/160 micrograms once-daily in patients not adequately controlled with a combination of a long-acting beta$_2$-agonist and a medium or high dose of an inhaled corticosteroid.

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

Dosing in special populations

Renal impairment

In patients with severe renal impairment or end-stage renal disease requiring dialysis, ENERZAIR BREEZHALER should be used only if the expected benefit outweighs the potential risk (see 7 WARNINGS AND PRECAUTIONS and 10.3 Pharmacokinetics). No dose adjustment is required in patients with mild to moderate renal impairment.

Hepatic impairment

No data are available for ENERZAIR BREEZHALER in subjects with hepatic impairment. Based on PK data available for the monocomponents, no dose adjustment is required in patients with mild or moderate hepatic impairment. However, ENERZAIR BREEZHALER should be used in patients with severe hepatic impairment only if the expected benefit outweighs the potential risk (see 10.3 Pharmacokinetics).

Geriatrics (≥65 years of age): No dose adjustment is required in patients 65 years of age or older (see 10.3 Pharmacokinetics).

Pediatrics (<18 years of age):

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

4.4 Administration

For inhalation use only. ENERZAIR BREEZHALER 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 capsule rather than inhaling it.

The capsules must be administered only using the ENERZAIR BREEZHALER inhaler. The inhaler provided with each new prescription should be used.

ENERZAIR 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 11 STORAGE, STABILITY AND DISPOSAL and 12 SPECIAL HANDLING INSTRUCTIONS).

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

4.5 Missed Dose

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.

5 OVERDOSAGE

There is limited experience with overdose in clinical studies with ENERZAIR BREEZHALER. 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 arrhythmias, metabolic acidosis, hypokalemia, hyperglycemia, 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 physician and with extreme caution since the use of $beta_2$-adrenergic blockers may provoke bronchospasm. In serious cases, patients should be hospitalized.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral inhalation	Inhalation powder hard capsules containing 150 mcg indacaterol (as acetate), 50 mcg glycopyrronium (as bromide) and 160 mcg mometasone furoate	Carrageenan, hypromellose, lactose (as monohydrate), magnesium stearate, potassium chloride, purified water

Each capsule of ENERZAIR 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

The delivered dose (the dose that leaves the mouthpiece of the inhaler) for 150/50/160 micrograms is equivalent to 114 micrograms indacaterol, 46 micrograms glycopyrronium, and 136 micrograms mometasone furoate.

The following pack types are available:

- Carton of 30 ENERZAIR BREEZHALER capsules (3 blister cards of 10 capsules) and one ENERZAIR BREEZHALER device.

7 WARNINGS AND PRECAUTIONS

General

Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death (see Salmeterol Multicenter Asthma Research Trial (SMART)). Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy.

When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonist Combination Products).

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonist Combination Products

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol with fluticasone propionate, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol with fluticasone propionate. No safety study was conducted with ENERZAIR BREEZHALER. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

The 3 adult and adolescent trials were designed to rule out a 2.0-fold increase in relative risk for ICS/LABA compared with ICS, and the pediatric trial was designed to rule out a 2.7-fold increase in this relative risk. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 2). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 2 Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older

	ICS/LABA (n=17,537)[a]	ICS (n=17,552)[a]	ICS/LABA vs. ICS Hazard Ratio (95% CI)[b]
Serious asthma-related event[c]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization	115	105	

(≥24-hour stay)			

ICS = Inhaled Corticosteroid; LABA = Long-acting Beta$_2$-adrenergic Agonist.

[a] Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

[b] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

[c] Number of subjects with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects may have had one or more events, but only the first event was counted for analysis. A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significant increase in risk of serious asthma-related events compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27). ENERZAIR BREEZHALER is not indicated in children younger than 12 years of age.

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Not for Acute Use

ENERZAIR BREEZHALER should not be used to treat acute asthma symptoms including acute episodes of bronchospasm. Patients should be prescribed a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve acute symptoms such as shortness of breath, and advised to have this available for use at all times. When beginning treatment with ENERZAIR BREEZHALER, patients who have been taking a rapid onset, short duration, inhaled bronchodilator on a regular basis (e.g., q.i.d.) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute symptoms while taking ENERZAIR BREEZHALER.

Deterioration of Disease

ENERZAIR BREEZHALER should not be initiated in patients with acutely deteriorating asthma, which may be a life-threatening condition. The use of ENERZAIR BREEZHALER in this setting is inappropriate.

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting bronchodilator becomes less effective or the patient needs more inhalations of a short-acting bronchodilator than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the treatment regimen should be undertaken at once. Increasing the daily dosage of ENERZAIR BREEZHALER beyond the recommended dose is not appropriate in this situation.

Patients should not stop ENERZAIR BREEZHALER treatment without physician supervision since symptoms may recur after discontinuation.

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

Excessive Use and Use with Other LABA Products

ENERZAIR BREEZHALER should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ENERZAIR BREEZHALER should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, vilanterol, olodaterol) for any reason.

Anticholinergic Effects

Like other anticholinergic medicinal products, ENERZAIR BREEZHALER should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma

ENERZAIR BREEZHALER should be used with caution in patients with narrow-angle glaucoma. Patients should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of 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). Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Worsening of Urinary Retention

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

Cardiovascular

Like other medicinal products containing beta$_2$-adrenergic agonists, ENERZAIR BREEZHALER may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, or cardiac arrhythmias such as supraventricular tachycardia and extrasystoles. If such effects occur, treatment may need to be discontinued.

Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Cardiovascular effects such as tachycardia, arrhythmia, palpitations, myocardial ischemia, angina pectoris, hypertension or hypotension have been associated with use of beta-adrenergic agonists. Like all products containing sympathomimetic agents, ENERZAIR BREEZHALER should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension).

While 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, the clinical significance of these findings is unknown.

Therefore, long-acting beta$_2$-adrenergic agonists (LABA) or LABA containing combination products 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 10.2 Pharmacodynamics).

Ear/Nose/Throat

Localized infections of the mouth and pharynx with *Candida albicans* have been associated with the use of inhaled glucocorticosteroids.

Patients should be advised to rinse their mouth with water (without swallowing) after inhalation of ENERZAIR BREEZHALER to reduce the risk of oropharyngeal candidiasis.

Endocrine and Metabolism

Systemic effects may occur with inhaled corticosteroids, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Possible systemic effects include: Cushing's syndrome, Cushingoid features, hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation in children and adolescents, decrease in bone mineral density (BMD), cataracts, glaucoma, and central serous chorioretinopathy.

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

Hypercorticism and Adrenal Suppression

Inhaled mometasone furoate is absorbed into the circulation and can be systemically active (see ACTION & CLINICAL PHARMACOLOGY, Pharmacodynamics). Exceeding the recommended dosage or co-administration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in hypothalamic-pituitary-adrenal (HPA) dysfunction (see 9.4 Drug-Drug Interactions).

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. In light of the possibility of systemic absorption of inhaled corticosteroids, patients treated with ENERZAIR BREEZHALER should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. If such effects occur, ENERZAIR BREEZHALER should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of asthma symptoms should be considered.

Systemic Steroid Replacement by Inhaled Steroid

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards

of care.

Hyperglycemia

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

Hypokalemia

Beta$_2$-adrenergic agonists may produce significant hypokalemia 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 condition, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias (see 9 DRUG INTERACTIONS).

Clinically relevant hypokalemia has not been observed in clinical studies of ENERZAIR BREEZHALER at the recommended therapeutic dose.

Co-existing Conditions

ENERZAIR BREEZHALER, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the rapid onset, short-duration, beta$_2$-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. ENERZAIR BREEZHALER has not been investigated in patients with Type I diabetes mellitus or uncontrolled Type II diabetes mellitus.

Hematologic

Eosinophilic Conditions

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome), a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between inhaled corticosteroids and these underlying conditions has not been established.

Hepatic/Biliary/Pancreatic

No data are available for ENERZAIR BREEZHALER in subjects with hepatic impairment. Based on available PK data of the mono-components, no dose adjustment is required in patients with mild or moderate hepatic impairment: however, ENERZAIR BREEZHALER should be used in patients with severe hepatic impairment only if the expected benefit outweighs the potential risk (see 10.3 Pharmacokinetics).

Immune

Hypersensitivity

Immediate hypersensitivity reactions have been observed after administration of ENERZAIR 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, ENERZAIR BREEZHALER should be discontinued immediately and alternative therapy instituted (see 2 CONTRAINDICATIONS).

Infections

Corticosteroids may mask some signs of infection and new infections may appear. An increased susceptibility to infections has been observed during corticosteroid therapy. This may require treatment with appropriate therapy or stopping the administration of mometasone furoate until the infection is eradicated. Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such patients who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Monitoring and Laboratory Tests

Potentially serious hypokalemia has been observed with other beta-agonist therapies, which may increase susceptibility to cardiac arrhythmias. It is therefore, recommended that serum potassium levels be monitored in patients predisposed to low levels of serum potassium.

Due to the hyperglycemic effect observed with other beta-agonists, additional blood glucose monitoring is recommended in diabetic patients.

For patients at risk, monitoring of bone and ocular effects (cataract, glaucoma, and central serous chorioretinopathy) should also be considered in patients receiving maintenance therapy with ENERZAIR BREEZHALER.

Patients with severe hepatic impairment should be monitored for corticosteroid effects due to potentially increased systemic exposure of inhaled mometasone furoate.

Ophthalmologic

Glaucoma may be exacerbated by inhaled corticosteroid treatment for asthma. In patients with established glaucoma who require long-term inhaled corticosteroid treatment, it is prudent to measure intraocular pressure before commencing the inhaled corticosteroid and to monitor it subsequently. In patients without established glaucoma, but with a potential for developing intraocular hypertension (e.g. the elderly), intraocular pressure should be monitored at appropriate intervals.

In elderly patients treated with inhaled corticosteroids, the prevalence of posterior subcapsular and nuclear cataracts is probably low but increases in relation to the daily and cumulative lifetime dose. Cofactors such as smoking, ultraviolet B exposure, or diabetes may increase the risk. Children may be less susceptible.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and

intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances; this may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Renal

Patients with severe renal impairment

For patients with severe renal impairment (estimated glomerular filtration rate below 30 mL/min/1.73m2) including those with end-stage renal disease requiring dialysis, ENERZAIR BREEZHALER should be used only if the expected benefit outweighs the potential risk (see 10 CLINICAL PHARMACOLOGY). These patients should be monitored closely for potential adverse drug reactions.

Worsening of Urinary Retention (see Anticholinergic Effects).

Respiratory

Paradoxical bronchospasm

As with other inhalation therapy, administration of ENERZAIR BREEZHALER may result in paradoxical bronchospasm which can be life-threatening. If paradoxical bronchospasm occurs, ENERZAIR BREEZHALER should be discontinued immediately and alternative therapy instituted.

7.1 Special Populations

7.1.1 Pregnant Women

There are insufficient data on the use of ENERZAIR BREEZHALER or its individual components (indacaterol, glycopyrronium and mometasone furoate) in pregnant women to inform a drug-associated risk.

Indacaterol and glycopyrronium were not teratogenic in rats and rabbits following subcutaneous or inhalation administration respectively (see 16 NON-CLINICAL TOXICOLOGY). In animal reproduction studies with pregnant mice, rats and rabbits, mometasone furoate caused increased fetal malformations and decreased fetal survival and growth.

ENERZAIR BREEZHALER should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Disease-associated maternal and/or embryo/fetal risk

In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of ENERZAIR BREEZHALER during labour and delivery.

Information related to indacaterol: Like other medicinal products containing beta$_2$-adrenergic agonists, indacaterol may inhibit labor due to a relaxant effect on uterine smooth muscle. Therefore, ENERZAIR BREEZHALER should be used during labour only if the potential benefit justifies the potential risk.

Information related to glycopyrronium: In pregnant women undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide, the concentration of glycopyrronium in the umbilical venous (0.28 (0.25) ng/ml) and in the umbilical arterial (0.18 (0.11) ng/ml) plasma were low (clinically insignificant).

7.1.2 Breast-feeding

There is no information available on the presence of indacaterol, glycopyrronium or mometasone in human milk, on the effects on a breastfed child, or on the effects on milk production. Other inhaled corticosteroids, similar to mometasone furoate, are transferred into human milk. Indacaterol, glycopyrronium and mometasone furoate have been detected in the milk of lactating rats. Glycopyrronium reached up to 10-fold higher concentrations in the milk of lactating rats than in the blood of the dam after intravenous administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENERZAIR BREEZHALER and any potential adverse effects on the breast-fed child from ENERZAIR BREEZHALER or from the underlying maternal condition.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Based on the available data, no dose adjustment is required in patients 65 years of age or older (see 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Use of LABA monotherapy (without ICS treatment) increases the risk of serious asthma-related events (death, hospitalizations, and intubations) (see General).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of ENERZAIR BREEZHALER was evaluated in a phase 3 study (B2302) with a total of 616 adult patients with asthma treated with ENERZAIR BREEZHALER 150/50/160 micrograms once-daily for up to 52 weeks.

Adverse drug reactions from the 52-week study (B2302) are listed by MedDRA system organ class (Table 3). The most common adverse drug reactions related to ENERZAIR BREEZHALER were headache, cough and dysphonia.

Table 3 - Adverse drug reactions with ≥ 1% estimated cumulative incidence (%) in study B2302 at 52 weeks

Adverse drug reactions	ENERZAIR BREEZHALER	Indacaterol/mometasone furoate	
	150/50/160 micrograms once-daily Rate (N=616)	150/160 micrograms once-daily Medium dose Rate (N=608)	150/320 micrograms once-daily High dose Rate (N=613)
Infections and infestations			
Urinary Tract Infection*[1]	3.57	2.23	2.57
Immune system disorders			
Hypersensitivity*[2]	1.17	0.17	0.69
Nervous system disorders			
Headache*[3]	4.24	5.95	4.26
Cardiac disorders			
Tachycardia*[4]	1.34	0.52	1.18
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain*[5]	3.02	1.21	2.07
Cough	4.12	2.43	1.86
Dysphonia	3.99	1.53	1.66
Gastrointestinal disorders			
Gastroenteritis*[6]	3.23	1.76	2.07
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain*[7]	3.05	4.69	3.93
Muscle Spasms	1.69	0.33	0.69
General disorders and administration site conditions			
Pyrexia	2.90	1.79	1.86

* Grouping of preferred terms (PTs).

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

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

[3] headache, tension headache.

[4] sinus tachycardia, supraventricular tachycardia, tachycardia.

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

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

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

8.3 Less Common Clinical Trial Adverse Reactions

Adverse drug reactions with <1% estimated cumulative incidence (%) in study B2302 at 52 weeks:
candidiasis, dry mouth, dysuria, hyperglycaemia, pruritus, rash

8.5 Post-Market Adverse Reactions

No post marketing Adverse Drug Reactions have been identified to date for ENERZAIR BREEZHALER.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions linked to ENERZAIR BREEZHALER

No specific interaction studies were conducted with ENERZAIR BREEZHALER. Information on the potential for interactions is based on the potential for each of the mono components as well as interactions studies for the dual combinations of indacaterol maleate and glycopyorronium and indacaterol acetate and mometasone furoate.

Medicinal products known to prolong the QTc interval

ENERZAIR BREEZHALER, like other medicinal products containing beta$_2$-adrenergic agonists, 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 arrhythmia (see Cardiovascular).

Hypokalemic treatment

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

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonize the effect of beta$_2$-adrenergic agonists. Therefore, ENERZAIR BREEZHALER should not be given together with beta-adrenergic blockers unless there are compelling reasons for their use. Where required, cardioselective 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 the safety of therapeutic doses of ENERZAIR 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 drug 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 (administered as monotherapy) 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.

In vitro, glycopyrronium was a substrate for the multidrug and toxin extrusion protein MATE1 found on renal tubule cells. Therefore the plasma levels of glycopyrronium may be increased by inhibitors of MATE1, and the plasma levels of MATE1 substrates may be increased by glycopyrronium. No clinical drug interaction studies were performed. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see 10 CLINICAL PHARMACOLOGY). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

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

The co-administration of ENERZAIR 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 8 ADVERSE REACTIONS and 5 OVERDOSAGE).

9.4 Drug-Drug Interactions

Table 4 - Established or Potential Drug-Drug Interactions

Drug	Source of Evidence	Effect	Clinical comment
Beta-adrenergic blockers (including ophthalmic agents)	T	Potential pharmacodynamic interaction (antagonism of pulmonary effects resulting in severe bronchospasm	If concomitant therapy is required, cardioselective beta-blockers could be considered, although they should be administered with caution.
Methylxanthine derivatives, Corticosteroids, Non-potassium sparing diuretics	T	Potential pharmacodynamic interaction (increased risk of hypokalemia)	Caution is recommended during concomitant use

Drugs that prolong the QTc interval, including Monoamine Oxidase inhibitors and Tricyclic Antidepressants	T	Potential pharmacodynamic interaction (prolongation of the QTc interval and increased risk of ventricular arrhythmias)	Caution is recommended during concomitant use
Other long-acting beta$_2$-adrenergic agonists	T	Potential pharmacodynamic interaction (additive pharmacologic and adverse effects)	Co-administration is not recommended
Other long-acting muscarinic antagonist	T	Potential pharmacodynamic interaction (additive pharmacologic and adverse effects)	Co-administration is not recommended
Inhibitors of CYP3A4 and P-gp efflux transporter	CT, T	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 potential magnitude of exposure increase for indacaterol does not raise any safety concerns. Clinically significant drug interactions with inhaled mometasone furoate are unlikely. There may be a potential for increased systemic exposure to mometasone furoate when strong CYP3A4 inhibitors are co-administered.
Cimetidine or other inhibitors of organic cation transport	CT	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 co-administered with cimetidine or other inhibitors of the organic cation transport.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established. No clinically relevant effect of food would be expected.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ENERZAIR 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 catalyzes 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.

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.

10.2 Pharmacodynamics

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

The pharmacodynamic response profile of ENERZAIR BREEZHALER is characterized by rapid 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 ENERZAIR BREEZHALER were observed over time.

Effects on the QTc interval

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

For mometasone furoate, no QTc prolonging properties are known. The effects of indacaterol/glycopyrronium on QTc-interval were investigated in healthy volunteers after inhalation of indacaterol/glycopyrronium 440/200 micrograms in four dose steps separated by one hour. No clinically relevant prolongation of the QT interval was observed.

10.3 Pharmacokinetics

The systemic pharmacokinetics of the components of ENERZAIR BREEZHALER were assessed in 36 healthy subjects following oral inhalation of ENERZAIR BREEZHALER 150/50/160 micrograms once-daily for 14 days (see Table 5).

Table 5 Summary of steady state systemic pharmacokinetic parameters of indacaterol, glycopyrronium and mometasone furoate in healthy subjects[a]

Enerzair Breezhaler 150/50/160 mcg	Cmax,ss [pg/mL]	AUC0-24h,ss [pg.h/mL]	Tmax,ss (h)
Indacaterol	311 (72.9)	1910 (377)	0.25 [0.25;0.50]
Glycopyrronium	220 (95.5)	597 (148)	0.0833 [0.0833-0.117]
Mometasone furoate	215 (37.0)	1910 (287)	1.00 [0.25;3.00]

[a]Pharmacokinetic parameters derived using non-compartmental analysis. Data in healthy subjects (N=36) at steady state on Day 14 following once-daily inhalation of ENERZAIR BREEZHALER 150/50/160 mcg for 14 days. Data represent arithmetic mean (SD), except for Tmax which is presented as median (range).

Population PK analyses for ENERZAIR BREEZHALER were conducted for phase III studies in asthma patients. Steady state C_{max} and AUC values of indacaterol, glycopyrronium and mometasone furoate following administration of ENERZAIR BREEZHALER 150/50/160 micrograms are presented in Table 6.

Table 6 Summary of steady state systemic pharmacokinetic parameters of indacaterol, glycopyrronium and mometasone furoate in asthma patients[a]

Enerzair Breezhaler 150/50/160 mcg	Cmax,ss [pg/mL]	AUC0-24h,ss [pg.h/mL]
Indacaterol	293 (108)	3014 (1395)
Glycopyrronium	131 (65.4)	617 (255)
Mometasone furoate	184 (63.0)	1593 (822)

[a]Pharmacokinetic parameters derived using population pharmacokinetic analysis. Data represent arithmetic mean (SD) simulated steady state systemic exposure parameters for an individual with a body weight of 75 kg following once-daily inhalation of ENERZAIR BREEZHALER 150/50/160 mcg.

Absorption:

Following inhalation of ENERZAIR 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.

Following inhalation of ENERZAIR 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 ENERZAIR 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 2,557L 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 83L and the volume of distribution in the terminal phase (Vz) was 376L. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7310L, 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 332L. The *in vitro* protein binding for mometasone furoate is high, 98 % to 99 % in concentration range of 5 to 500 ng/ml

Metabolism:

Indacaterol

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) 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 metabolized 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

In vitro metabolism studies showed glycopyrronium undergoes 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 catalyzed 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

Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver to multiple metabolites. In human liver microsomes, mometasone furoate is metabolized 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 L/h. When compared with the serum clearance of indacaterol of 18.8 to 23.3 L/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 fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces 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 L/h. 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 was excreted mainly in the feces (74%) and to a lesser extent in the urine (8%)

Special Populations and Conditions

A population pharmacokinetics analysis in patients with asthma after inhalation of ENERZAIR 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 or mometasone furoate.

- ***Pediatrics:*** The safety and efficacy of ENERZAIR BREEZHALER in pediatric patients below 18 years of age have not been established.
- ***Genetic Polymorphism:*** The pharmacokinetics of indacaterol was investigated in two different UGT1A1 genotypes – the fully functional [$(TA)_6$, $(TA)_6$] genotype and the low activity [$(TA)_7$, $(TA)_7$] genotype (Gilbert's syndrome genotype). The study demonstrated that steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [$(TA)_7$, $(TA)_7$] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.
- ***Ethnic origin:*** A PK study showed that the geometric mean ratios (GMRs) (Japanese/Caucasian) of steady-state PK parameters (C_{max} and $AUC_{0\text{-}24h}$) on Day 14 were 1.31 and 1.17, respectively for indacaterol, 1.38 and 1.05 for glycopyrronium, and 1.07 and 1.15 for mometasone furoate. This study showed that there were no major differences in total systemic exposure (AUC) for indacaterol, glycopyrronium or mometasone furoate between Japanese and Caucasian subjects. Insufficient pharmacokinetic data are available for other ethnicities or races.
- ***Hepatic Insufficiency:*** The effect of hepatic impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated following administration of ENERZAIR 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 10.3 Pharmacokinetics). 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.

- ***Renal Insufficiency:*** The effect of renal impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated in dedicated studies with ENERZAIR 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 ENERZAIR BREEZHALER in patients with asthma.

  The contribution of the urinary pathway to total body elimination of indacaterol, and mometasone furoate is low; the effects of renal impairment on their systemic exposure have not been investigated. Similarly, systemic exposure of indacaterol and mometasone furoate delivered via BREEZHALER has not been characterized in subjects with renal impairment.

  Glycopyrronium: 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature, 15°C to 30°C. Protect from moisture and light.

ENERZAIR BREEZHALER must be kept out of the reach and sight of children.

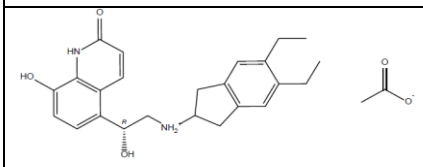
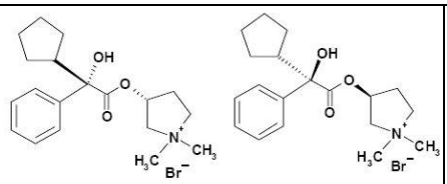
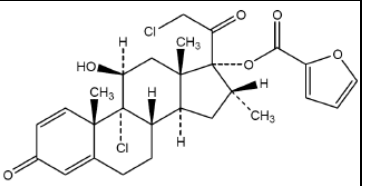
12 SPECIAL HANDLING INSTRUCTIONS

- ENERZAIR BREEZHALER capsules should be used with the ENERZAIR BREEZHALER inhalation device only. The ENERZAIR BREEZHALER inhalation device should not be used with any other capsules.
- Capsules should always be stored in the blister and only removed from the blister immediately before use.
- Always use the new ENERZAIR BREEZHALER inhalation device provided with each new prescription and discard the old device.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name		
indacaterol acetate	glycopyrronium bromide	mometasone furoate
Chemical name:		
5,6-Diethyl-N-[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]- 2,3-dihydro-1H-inden-2-aminium acetate	3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidinium bromide	9,21-Dichloro-1 1 ß, 1 7-dihydroxy-1 6α-methylpregna-1 ,4-diene-3,20-dione 17- (2- furoate)
Molecular formula and molecular mass		
$(C_{24}H_{29}N_2O_3)(C_2H_3O_2)$ - 452.55	$C_{19}H_{28}NO_3$ Br Salt form on anhydrous basis - 398.33	$C_{27}H_{30}Cl_2O_6$ - 521.44
Structural formula		
	 [2S, 3R]-stereoisomer [2R, 3S]-stereoisomer	
Physicochemical properties		
Indacaterol acetate is a single isomer with R-configuration. Indacaterol maleate consists of a single polymorphic form, form A. The pH of a 0.1 % (m/V) suspension of Indacaterol acetate in water at room temperature is found to be 4.8. The melting point of Indacaterol acetate is 160°C. Indacaterol acetate is a white to yellow or beige powder.	Glycopyrronium bromide presents 2 asymmetric carbon atoms and is an optically inactive racemic mixture of 2 stereoisomers (2S, 3R and 2R, 3S), hereafter referred to as the stereoisomers (S,R) and (R,S). The pH of glycopyrronium bromide in 1.0% m/V (g/100 mL) solution in water at room temperature is 6.0. Melting range: 193 – 198 °C (but the range between beginning and end of melting does not exceed 2 °C).	White powder; at 23 °C, practically insoluble in water; slightly soluble in ethyl acetate, methanol, ethanol and isopropanol; soluble in acetone.

Indacaterol acetate is practically insoluble in 0.1N Hydrochloric acid and pH 6.8 buffer		

ENERZAIR BREEZHALER INHALATION DEVICE

The ENERZAIR BREEZHALER is a plastic inhalation device used for inhaling the content of ENERZAIR BREEZHALER (indacaterol, glycopyrronium and mometasone furoate) capsules. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time.

Peak inspiratory flow rates (PIFR) achievable through the BREEZHALER inhalation device were evaluated in 26 adult patients with COPD of varying severity. Mean PIFR was 95 L/min (range 52-133 L/min) for adult patients.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Asthma

The safety and efficacy of ENERZAIR BREEZHALER 150/50/160 micrograms in adult patients with asthma was evaluated in a phase III randomized, double-blind study (B2302). The study was a multi-center, 52-week study evaluating indacaterol/glycopyrronium/mometasone furoate 150/50/80 micrograms once-daily (N=620) and 150/50/160 micrograms once-daily (N=619) via BREEZHALER (inhaler) compared to indacaterol/mometasone furoate 150/160 micrograms once-daily (N=617) and 150/320 once-daily (N=618) via BREEZHALER, respectively. A third active control arm included subjects treated with salmeterol xinafoate/fluticasone propionate (SAL/FP) 50/500 micrograms twice daily (N=618). All subjects were required to be asthma symptomatic on asthma maintenance therapy of a medium or high dose ICS and LABA combination therapy for at least 3 months prior to study entry. Patients were also to have had one or more asthma exacerbations in the previous year. The mean age was 52.2 years. At screening, 99.9% of patients reported a history of exacerbation in the past year. At study entry, the most common asthma medications reported were LABA and medium dose of ICS (63%) and LABA and high dose of ICS (37%). During the study two week run-in period, patients received open-label medium dose ICS/LABA.

Mometasone furoate (MF) 80 (medium dose) and 160 (high dose) micrograms in ENERZAIR BREEZHALER once-daily are comparable to MF 160 (medium dose) and 320 (high dose) micrograms in indacaterol/mometasone furoate delivered via unit dose dry powder inhaler, respectively.

The primary objective of the study was to demonstrate superiority of ENERZAIR BREEZHALER 150/50/160 micrograms once-daily to indacaterol/mometasone furoate 150/320 micrograms once-daily in terms of trough FEV_1 at week 26.

The key secondary endpoint was to demonstrate superiority of ENERZAIR BREEZHALER to indacaterol/mometasone furoate in terms of asthma control as assessed by the Asthma Control Questionnaire (ACQ-7).

Table 7 - Summary of patient demographics for the clinical trial in Asthma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
B2302	52-week Phase III randomized, double-blind study in adult patients with asthma to evaluate efficacy and safety of ENERZAIR BREEZHALER with medium and high mometasone furoate doses compared to indacaterol/mometasone furoate with medium and high mometasone furoate doses		Total: 3092	52.2 (18 – 75)	Male: 38.0% Female: 62.0%
		indacaterol/ glycopyrronium/mometasone furoate 150/50/80 mcg od	619		
		ENERZAIR BREEZHALER 150/50/160 mcg od	620		
		indacaterol/mometasone furoate 150/160 mcg od	617		
		indacaterol/mometasone furoate 150/320 mcg od	618		
		salmeterol xinafoate /fluticasone propionate 50/500 mcg bid	618		

Lung function

ENERZAIR BREEZHALER 150/50/160 micrograms once-daily demonstrated a statistically significant improvement in trough FEV_1 at week 26 when compared to indacaterol/mometasone furoate 150/320 micrograms once-daily (Table 8). Clinically meaningful improvements in morning and evening peak expiratory flow were observed when compared to indacaterol/mometasone furoate. ENERZAIR BREEZHALER 150/50/160 micrograms once-daily demonstrated an improvement in trough FEV_1 at week 52 of 86 mL when compared to indacaterol/mometasone furoate 150/320 micrograms once-daily. Findings at week 52 were consistent with week 26.

Table 8 - Results of primary and key secondary endpoints

Endpoint	ENERZAIR BREEZHALER 150/50/160 od vs IND/MF* 150/320 od
Lung Function	
*Trough FEV_1 (Primary endpoint)***	
Treatment difference P value (95% CI)	65 mL <0.001 (31, 99)
ACQ-7 (Key secondary endpoint)	
Treatment difference P value (95% CI)	0.014 0.729 (-0.066, 0.094)

* IND/MF: Indacaterol/mometasone furoate

** Trough FEV_1: the mean of the two FEV_1, values measured at 23 hour 15 min and 23 hour 45 min after the evening dose.

The results of other lung function efficacy endpoints such as mean morning PEF and mean evening PEF are generally consistent with and support of the results the primary endpoint.

ACQ-7

The mean change from baseline in ACQ-7 score at week 26 (key secondary endpoint) and week 52 were around -1 for all treatment groups. Therefore, there was no meaningful difference (defined as a decrease in score of ≥0.5) between the treatment groups for ACQ-7 score (Table 8). The ACQ-7 responder rate (defined as a change in score of ≥0.5) was 71% for ENERZAIR BREEZHALER 150/50/160 mcg and 74% for indacaterol/mometasone furoate 150/320 mcg at week 26. The findings at week 52 were consistent with week 26.

Exacerbations

ENERZAIR BREEZHALER once-daily demonstrated a numerical reduction in the annual rate of moderate or severe asthma exacerbations by 15% and in the annual rate of severe exacerbations by 22% compared to indacaterol/mometasone furoate 150/320 micrograms once-daily.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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

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

General Toxicity:

Indacaterol and mometasone furoate combination

The findings during the 13-week inhalation toxicity studies in rats and dogs 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 indacaterol/glycopyrronium were consistent with the known pharmacological effects of the indacaterol or glycopyrronium monotherapy components. The effect on heart rate for indacaterol/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, arrhythmias and myocardial lesions in dogs. Mild irritation of the nasal cavity and larynx were seen in rodents.

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 salivary and ocular gland 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.

Mometasone furoate

All observed effects are typical of the glucocorticoid class of compounds and are related to exaggerated pharmacologic effects of glucocorticoids. In studies with rats and dogs, effects included lymphoid depletion, adrenal atrophy, and an increase in bone adipose tissue.

Carcinogenicity:

Indacaterol

Carcinogenicity was assessed in a two-year inhalation rat study and a six-month oral-administration 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.

Glycopyrronium

Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity.

Mometasone furoate

In carcinogenicity studies in mice and rats, inhaled mometasone furoate demonstrated no statistically significant increase in the incidence of tumours that would be relevant to human therapeutic use.

Genotoxicity:

Indacaterol

Genotoxicity studies did not reveal any mutagenic or clastogenic potential.

Glycopyrronium

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium.

Mometasone furoate

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

Reproductive and Developmental Toxicity:

The combination of indacaterol, glycopyrronium and mometasone furoate has not been studied in pregnant animals. The effects of each when administered alone in animal studies were as follows:

Indacaterol

Following subcutaneous administration in a rabbit study, adverse effects of indacaterol with respect to pregnancy and embryonal/fetal development could only be demonstrated at doses more than 500-fold than that achieved following the daily inhalation of 150 micrograms in humans (based on AUC0-24h).

Although indacaterol did not affect general reproductive performance in a rat fertility study, F1 offspring exposed to indacaterol did show an effect on fertility in the peri- and post-natal developmental rat study. Following subcutaneous administration of 1 mg/kg/day indacaterol from post-natal day 4 to day 20, there was a decrease in the number of pregnant F1 offspring observed following mating.

Glycopyrronium

Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Glycopyrronium and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Published data for glycopyrronium in animals do not indicate any reproductive toxicity issues. Fertility and pre- and post-natal development were not affected in rats.

Mometasone furoate

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Effects noted with oral, topical, or subcutaneous administration were umbilical hernia in rats; cleft palate in mice; and gall bladder agenesis, umbilical hernia and flexed front paws in rabbits. There were also reductions in maternal body weight gains and effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice; and reduced offspring survival in mice.

In studies of reproductive function, subcutaneous mometasone furoate at 15 micrograms/kg prolonged gestation and difficult labor occurred with a reduction in offspring survival and body weight. Reproduction studies and other data in animals did not indicate a concern regarding fertility in either males or females.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ONBREZ® BREEZHALER® 75 mcg indacaterol (as maleate) inhalation powder hard capsules, submission control 178064, Product Monograph, Novartis Pharmaceuticals Canada Inc. (Jan 02, 2015)
2. SEEBRI® BREEZHALER® 50 mcg glycopyrronium (as bromide) inhalation powder hard capsules submission control 196095, Product Monograph, Novartis Pharmaceuticals Canada Inc. (Sep 29, 2016)
3. ASMANEX* Twisthaler* 100 mcg, 200 mcg and 400 mcg mometasone furoate per metered inhalation, submission control 210617, Product Monograph, Merck Canada Inc. (Jan 24, 2018)
4. ATECTURA® BREEZHALER® 150 mcg/80 mcg, 150 mcg/160 mcg and 150 mcg/320 mcg indacaterol (as acetate)/mometasone furoate inhalation powder hard capsules submission control 227987, Product Monograph, Novartis Pharmaceuticals Canada Inc. (May 5, 2020)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrENERZAIR® BREEZHALER®

Indacaterol (as acetate) / glycopyrronium (as bromide) / mometasone furoate inhalation powder hard capsules

Read this carefully before you start taking **ENERZAIR® BREEZHALER®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ENERZAIR BREEZHALER**.

What is ENERZAIR BREEZHALER used for?

ENERZAIR BREEZHALER is a combination of a long-acting beta$_2$-adrenergic agonist (LABA), a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS). It is used as a maintenance treatment for asthma in adults:

- whose asthma is not being adequately controlled with a maintenance long-acting beta$_2$-agonist (LABA) and a medium or high dose of an inhaled corticosteroid (ICS)
- who have experienced one or more asthma attacks in the previous year

You should not take this medication:

- for the relief of the sudden (acute) symptoms of asthma (i.e. as rescue therapy for the treatment of sudden episodes of bronchospasm)

How does ENERZAIR BREEZHALER work?

ENERZAIR BREEZHALER contains 3 medicinal ingredients:

- indacaterol – a long-acting beta$_2$ agonist (LABA)
- glycopyrronium – a long-acting muscarinic antagonist (LAMA)
- mometasone furoate – an inhaled corticosteroid (ICS)

Indacaterol and glycopyrronium belong to a group of medicines called bronchodilators. They relax the muscles of the small airways in the lungs. This helps to open the airways and makes it easier for air to get in and out of the lungs. When it is taken regularly, it helps the small airways to remain open.

Mometasone furoate belongs to a group of medicines called corticosteroids, often simply called steroids. Corticosteroids reduce inflammation. They reduce the swelling and irritation in the small airways in the lungs and gradually ease breathing problems. Corticosteroids also help to prevent attacks of asthma.

What are the ingredients in ENERZAIR BREEZHALER?

Medicinal ingredients: indacaterol (as acetate), glycopyrronium (as bromide) and mometasone furoate

Non-medicinal ingredients: carrageenan, hypromellose, lactose (as monohydrate), magnesium stearate, potassium chloride, purified water

ENERZAIR BREEZHALER comes in the following dosage forms:

Capsules for oral inhalation: 150 mcg / 50 mcg / 160 mcg

indacaterol (as acetate), glycopyrronium (as bromide) and mometasone furoate

Do not use ENERZAIR BREEZHALER if:

you are allergic to or have had an allergic reaction to:

- indacaterol
- glycopyrronium
- mometasone furoate
- any other ingredients in ENERZAIR BREEZHALER
- lactose or milk proteins

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENERZAIR BREEZHALER. Talk about any health conditions or problems you may have, including if you:

- have heart problems such as:
  - an irregular or fast heartbeat (arrhythmia)
  - sensations that your heart has skipped a beat or added an extra beat (palpitations)
  - your heart muscle does not get enough blood (myocardial ischemia)
  - chest pain (angina)
  - an abnormal electrical signal called “prolongation of the QT interval”
- are taking similar medicines for your lung disease
- have low or high blood pressure
- if you have problems with your thyroid or adrenal glands
- if you have ever been told you have diabetes or high blood sugar
- have been taking other corticosteroids by mouth or inhalation
- have a fungal infection (thrush) in your mouth or throat
- have or have ever had pulmonary tuberculosis
- have chronic or untreated infections:
  - bacterial infection
  - viral infection
  - fungal infection
  - parasitic infection
  - herpes simplex infection of the eye
- if you suffer from seizures or fits
- if you have low potassium in your blood
- if you have severe liver problems
- if you have severe kidney problems
- if you have an eye problem called narrow-angle glaucoma
- if you have difficulty / pain passing urine. Talk to your doctor **right away** if you develop these signs or symptoms
- have a severe allergy to lactose or milk proteins

Other warnings you should know about:

General: When LABA medicines are used alone without an ICS, they increase the risk of hospitalization and death from asthma problems. ENERZAIR BREEZHALER contains both a LABA and ICS. Studies showed that when a LABA and ICS are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.

ENERZAIR BREEZHALER does not relieve the sudden (acute) symptoms of asthma. You should always have a short-acting bronchodilator medicine ("rescue" inhaler) (such as salbutamol) with you to treat your sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. Use the medication as directed by your doctor.

Stop taking ENERZAIR BREEZHALER and get medical help right away if you have any of the following:

- tightness of the chest, coughing, wheezing or feeling breathlessness immediately after inhaling ENERZAIR BREEZHALER (signs of paradoxical bronchospasm)
- trouble breathing or swallowing, swelling of the tongue, lips or face, skin rash, itching and hives (signs of allergic reaction)

Do not stop taking ENERZAIR BREEZHALER without talking to your doctor. You should talk to your doctor **right away** if:

- there is a change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness
- you are using increasing amounts of your fast acting 'reliever' medicine

These could be warning signs that your condition may be getting worse.

Pregnancy: Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. Your doctor will discuss the potential risks of taking this medicine and whether you can use ENERZAIR BREEZHALER.

Breast-feeding: It is not known whether the ingredients of ENERZAIR BREEZHALER can pass into breast milk. If you are breast-feeding, check with your doctor before you use ENERZAIR BREEZHALER

Narrow-angle glaucoma: You should avoid getting the powder in the capsules into your eyes. If you do, it may cause:

- eye pain and/or discomfort,
- temporary blurring of vision, and/or
- coloured images in association with red eyes

If you have narrow-angle glaucoma, getting the powder in your eyes may cause it to get worse. It can also cause acute narrow-angle glaucoma. If you develop any of these symptoms, talk to your doctor **right away**.

Risk of Bone Fractures: When using medicines like ENERZAIR BREEZHALER for long-term treatment, you may be at risk of:

- breaking a bone
- osteoporosis (brittle bones)

Eye disorders: Medicines like ENERZAIR BREEZHALER can cause eye disorders:

- Cataracts: clouding of the lens in the eye, blurry vision, eye pain
- Glaucoma: an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss
- Central serous chorioretinopathy (CSCR): blurry vision or other changes in vision.

Contact your healthcare professional if you experience blurry vision or other vision problems.
You should also have regular eye exams.

Chicken pox and measles: You should avoid exposure to chicken pox and measles, and notify your doctor if are exposed. This is important if you are taking any corticosteroid and your immune system is not functioning well (if you have difficulty in fighting an infection).

Monitoring and Laboratory Tests: your doctor may monitor you and perform the tests to check your:

- potassium levels in your blood. Low levels of potassium have been seen in people taking beta-agonist therapies, which may increase your risk of heart arrhythmia.
- blood sugar levels. High blood glucose levels have been seen in people taking beta-agonist medicines. This is important if you are diabetic.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ENERZAIR BREEZHALER:

- medicines that prolong QT interval (your hearts electrical signal) including medicines used in the treatment of depression (e.g. tricyclic antidepressants, monoamine oxidase inhibitors)
- any medicines that may be similar to ENERZAIR BREEZHALER (contain similar ingredients) used to treat your lung disease. Using these together with ENERZAIR BREEZHALER may increase the risk of experiencing possible side effects
- atropine or other medications that contain a short-acting, or a long-acting muscarinic antagonist (LAMA) (such as ipratropium, tiotropium, aclidinium, umeclidinium)
- medicines that decrease the level of potassium in your blood. These include:
    - diuretics (also known as “water pills”) and are used to treat high blood pressure, e.g. hydrochlorothiazide)
    - other bronchodilators such as methylxanthines used for breathing problems (e.g. theophylline) or steroids (e.g. prednisolone)
- beta blockers used to treat high blood pressure or other heart problems (e.g. propranolol) or to treat glaucoma (e.g. timolol)
- medicine used to treat fungal infections (e.g., ketoconazole or itraconazole)
- medicine used to treat HIV infection (e.g., ritonavir, nelfinavir or cobicistat)

How to take ENERZAIR BREEZHALER:

Important:

- **The capsules are for oral inhalation only. DO NOT SWALLOW.**
- ENERZAIR BREEZHALER does not relieve sudden symptoms of asthma. Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your doctor to have one prescribed for you.
- Always use this medicine exactly as your doctor has told you. Do not stop using it unless your doctor tells you to.
- It is important that you continue to take ENERZAIR BREEZHALER regularly even if

you feel fine and do not have any symptoms
- If your asthma is not getting better or it gets worse after you have started using ENERZAIR BREEZHALER, talk to your doctor

Usual dose:

Adults: Inhale the contents of 1 capsule once a day at about the same time each day. Rinse your mouth with water after each inhalation. **Do not** swallow the water.

Instructions for use

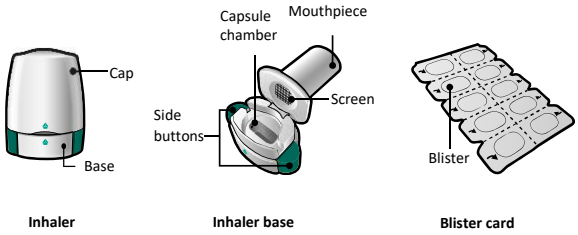
This part of the leaflet explains how to use and care for your ENERZAIR BREEZHALER inhaler. Please read carefully and follow these instructions.

Please read the full **Instructions for Use** before using the ENERZAIR BREEZHALER.

If you have any questions, ask your doctor or pharmacist.

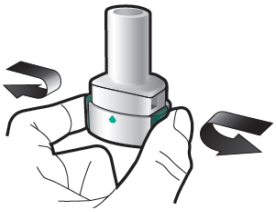
Your ENERZAIR BREEZHALER Inhaler pack contains:

- 1 inhaler device
- Blister cards containing the ENERZAIR BREEZHALER capsules to be used in the inhaler

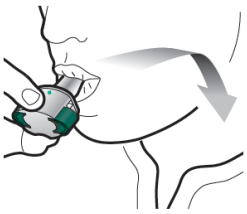


Steps:

Insert



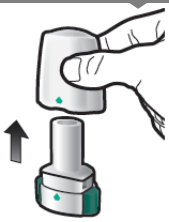
Pierce and release



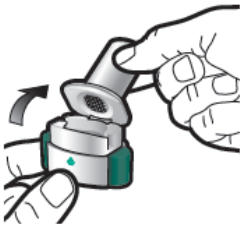
Inhale deeply

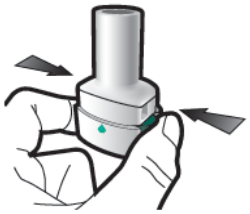
Check capsule is empty

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.

Powder remaining

Empty

Step 1b:

Open inhaler

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 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.

Step 3c:

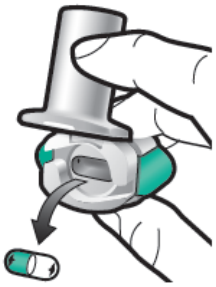
Hold breath

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

<u>Never place a capsule directly into the mouthpiece.</u>

Step 1e:

Close inhaler

Important Information

- ENERZAIR BREEZHALER capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the ENERZAIR BREEZHALER capsules with any other inhaler.
- Do not use the ENERZAIR 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.

Frequently Asked Questions	Cleaning the inhaler
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.	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.

Overdose:

If you think you, or a person you are caring for, have taken too much ENERZAIR BREEZHALER , contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Symptoms of an overdose include:

- fast heart rate
- feeling shaky
- sensations that your heart has skipped a beat or added an extra beat
- an irregular or fast heartbeat
- headache
- nausea
- vomiting
- feeling drowsy

Missed Dose:

If you forget to inhale a dose, inhale the dose as soon as possible. Then inhale the next dose at the usual time. **Do not** inhale 2 doses (i.e. 2 capsules) on the same day.

What are possible side effects from using ENERZAIR BREEZHALER?

These are not all the possible side effects you may have when taking ENERZAIR BREEZHALER. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- a frequent urge to urinate and pain or burning when urinating (signs of urinary tract infection)
- headache
- sore throat or pain and irritation in the back of the mouth and throat
- cough
- hoarseness and changes to your voice
- diarrhea, abdominal cramps, nausea, and vomiting (gastroenteritis)
- dry mouth
- rash
- muscle spasm
- pain in muscles, bones or joints
- fever
- itchy skin

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON **Allergic Reaction:** difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			X
Thrush (yeast infection): white patches in the mouth and tongue, sore throat		X	
Fast heart beat		X	
UNCOMMON **Hyperglycemia** (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		X	
Dysuria: difficulty and pain when passing urine		X	
UNKNOWN **Paradoxical Bronchospasm** (worsening of symptoms related to breathing): Tightness of the chest associated with coughing, sudden worsening of shortness of breath and wheezing right			X

after inhaling ENERZAIR BREEZHALER			
Glaucoma: increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, and changes in vision, hazy or blurred vision, sudden sight loss		X	
Cataract: clouding of the lens in the eye, blurry vision, dim vision and/or eye pain		X	
Central Serous Chorioretinopathy (CSCR): distorted vision/blurred vision		X	
Irregular heartbeat		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep this medicine out of the sight and reach of children.
- At room temperature (15-30°C) in the original package to protect from moisture and light. Remove capsules from the package only when ready to use.
- Do not use after the expiry date shown on the box.

If you want more information about ENERZAIR BREEZHALER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-

product-database.html); the manufacturer's website www.novartis.ca, the distributor's website www.valeopharma.com or by calling 1-855-694-0151.

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