NOVARTIS

Indacaterol acetate **+**

Glycopyrronium bromide **+**

Mometasone furoate

ENERZAIR® BREEZHALER®

150 mcg/50 mcg/80 mcg Powder for Inhalation in Hard Capsule
150 mcg/50 mcg/160 mcg Powder for Inhalation in Hard Capsule

Long-acting $Beta_2$-Agonist, anticholinergic and Inhaled Corticosteroids

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Indacaterol/glycopyrronium/mometasone furoate 150/50/80 micrograms, inhalation powder, hard capsules.

Indacaterol/glycopyrronium/mometasone furoate 150/50/160 micrograms, inhalation powder, hard capsules.

Active substance(s)

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

Each capsule of 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 150/50/80 micrograms is equivalent to 114 micrograms indacaterol, 46 micrograms glycopyrronium, and 68 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.

Excipients

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

Capsule shell components: Hypromellose, Purified water, Carrageenan, Potassium chloride.

INDICATIONS

Enerzair Breezhaler is indicated as a once-daily maintenance treatment of asthma, and to reduce asthma exacerbations, in adults not adequately controlled with a maintenance combination of a long-acting beta$_2$-agonist and an inhaled corticosteroid.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Inhalation of the content of one capsule of Enerzair Breezhaler 150/50/80 micrograms or 150/50/160 micrograms once-daily is recommended in patients not adequately controlled with a combination of a long-acting beta$_2$-agonist and an inhaled corticosteroid.

Patients usually experience an improvement in lung function within 5 minutes of inhaling Enerzair Breezhaler. However, the patient should be informed that regular daily use is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic.

The maximum recommended dose is Enerzair Breezhaler 150/50/160 micrograms once daily.

Special populations

Renal impairment

No dose adjustment is required in patients with mild to moderate 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 sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for Enerzair Breezhaler in subjects with severe hepatic impairment, therefore Enerzair Breezhaler should be used in these patients only if the expected benefit outweighs the potential risk (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

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

Geriatric patients (65 years or above)

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

Method of 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 section PHARMACEUTICAL INFORMATION).

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

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

CONTRAINDICATIONS

Enerzair Breezhaler is contraindicated in patients with hypersensitivity to any of the active substances or excipients.

WARNINGS AND PRECAUTIONS

Deterioration of disease

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

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.

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.

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.

Cardiovascular effects of beta agonists

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, and/or symptoms. If such effects occur, treatment may need to be discontinued.

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

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 such as Enerzair Breezhaler should be used with caution in patients with known or suspected prolongation of the QT interval or who are treated with medicinal products affecting the QT interval.

Hypokalemia with beta agonists

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 section INTERACTIONS).

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

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.

Anticholinergic effect related to glycopyrronium

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

Patients should be advised about signs and symptoms of acute narrow-angle glaucoma, and should be instructed to stop using Enerzair Breezhaler and to contact their doctor immediately should any of these signs or symptoms develop.

Patients with severe renal impairment

For patients with severe renal impairment (estimated glomerular filtration rate below 30 mL/min/1.73 m^2) including those with end-stage renal disease requiring dialysis, Enerzair Breezhaler should be used only if the expected benefit outweighs the potential risk (see section CLINICAL PHARMACOLOGY).

Systemic effects of corticosteroids

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.

Enerzair Breezhaler should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

ADVERSE DRUG REACTIONS

Summary of the safety profile

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

The most common adverse drug reaction related to Enerzair Breezhaler was headache.

Adverse drug reactions from clinical trials

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

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

Adverse drug reactions	Enerzair Breezhaler		Indacaterol/mometasone furoate		Frequency category
	150/50/80 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=617	150/50/160 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=616	150/160 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=608	150/320 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=613	[based on the higher frequency between the two arms]
Infections and infestations					
Candidiasis*[1]	1.36 [10] (0.64, 2.56)	0.33 [2] (0.07, 1.14)	1.05 [9] (0.44, 2.18)	0.86 [5] (0.33, 1.91)	Common
Urinary Tract Infection*[2]	1.57 [9] (0.78, 2.86)	3.57 [22] (2.28, 5.30)	2.23 [15] (1.25, 3.69)	2.57 [17] (1.50, 4.09)	Common
Immune system disorders					
Hypersensitivity*[3]	1.34 [10] (0.64, 2.54)	1.17 [8] (0.53, 2.31)	0.17 [1] (0.02, 0.94)	0.69 [4] (0.23, 1.67)	Common
Metabolism and nutrition disorders					
Hyperglycaemia*[4]	0.50 [3] (0.14, 1.38)	0.68 [4] (0.23, 1.64)	0.35 [2] (0.07, 1.20)	0.50 [3] (0.14, 1.39)	Uncommon
Nervous system disorders					
Headache*[5]	5.20 [32] (3.59, 7.22)	4.24 [35] (2.82, 6.09)	5.95 [44] (4.21, 8.09)	4.26 [28] (2.83, 6.11)	Common
Cardiac disorders					
Tachycardia*[6]	0.50 [3] (0.14, 1.38)	1.34 [8] (0.63, 2.53)	0.52 [3] (0.15, 1.45)	1.18 [8] (0.53, 2.32)	Common
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal Pain*[7]	2.02 [12] (1.11, 3.41)	3.02 [23] (1.86, 4.62)	1.21 [10] (0.54, 2.38)	2.07 [12] (1.13, 3.48)	Common
Cough	3.24 [23] (2.02, 4.91)	4.12 [30] (2.72, 5.96)	2.43 [16] (1.39, 3.94)	1.86 [13] (0.99, 3.21)	Common
Dysphonia	2.15 [13] (1.21, 3.55)	3.99 [26] (2.63, 5.78)	1.53 [9] (0.76, 2.80)	1.66 [12] (0.85, 2.93)	Common
Gastrointestinal disorders					
Gastroenteritis*[8]	1.72 [11] (0.89, 3.05)	3.23 [22] (2.01, 4.89)	1.76 [10] (0.91, 3.11)	2.07 [13] (1.13, 3.48)	Common
Dry Mouth*[9]	1.03 [6] (0.43, 2.14)	0.67 [4] (0.23, 1.62)	0.51 [4] (0.15,1.42)	0.34 [2] (0.07,1.17)	Common
Skin and subcutaneous tissue disorders					
Rash*[10]	1.01 [7] (0.42, 2.10)	0.33 [2] (0.07, 1.14)	0 [0]	0.16 [1] (0.02, 0.89)	Common

Adverse drug reactions	Enerzair Breezhaler		Indacaterol/mometasone furoate		Frequency category
	150/50/80 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=617	150/50/160 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=616	150/160 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=608	150/320 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=613	[based on the higher frequency between the two arms]
Pruritus*[11]	0.35 [3] (0.07, 1.21)	0.68 [4] (0.23, 1.65)	0.34 [2] (0.07, 1.18)	0.34 [2] (0.07, 1.17)	Uncommon
Musculoskeletal and connective tissue disorders					
Musculoskeletal Pain*[12]	4.99 [33] (3.42, 6.98)	3.05 [19] (1.88, 4.67)	4.69 [34] (3.17, 6.63)	3.93 [26] (2.57, 5.73)	Common
Muscle Spasms	1.36 [8] (0.65, 2.58)	1.69 [11] (0.87, 2.99)	0.33 [2] (0.07, 1.13)	0.69 [5] (0.23, 1.68)	Common
Renal and Urinary disorder					
Dysuria	0.68 [4] (0.23,1.65)	0.17 [1] (0.02, 0.92)	0 [0]	0 [0]	Uncommon
General disorders and administration site conditions					
Pyrexia	2.07 [12] (1.13, 3.48)	2.90 [23] (1.76, 4.50)	1.79 [12] (0.92, 3.17)	1.86 [12] (0.99, 3.21)	Common

* Grouping of preferred terms (PTs).

[1] oral candidiasis, oropharyngeal candidiasis.

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

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

[4] blood glucose increased, hyperglycaemia.

[5] headache, tension headache.

[6] sinus tachycardia, supraventricular tachycardia, tachycardia.

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

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

[9] dry mouth, dry throat.

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

[11] eye pruritus, pruritus, pruritus genital.

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

INTERACTIONS

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 monotherapy components.

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

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

Medicinal products known to prolong the QTc interval

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 section WARNINGS AND PRECAUTIONS).

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 section WARNINGS AND PRECAUTIONS).

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 by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport.

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

The co-administration of 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 section ADVERSE DRUG REACTIONS and OVERDOSAGE).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

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 Animal data). 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.

Clinical Considerations

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

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.

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).

Animal data

The combination of indacaterol, glycopyrronium and mometasone furoate has not been studied in pregnant animals.

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 achieved following the daily inhalation of 150 micrograms in humans (based on AUC_{0-24h}). Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F1 offspring was observed in the peri- and post-natal developmental rat study.

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 were umbilical hernia in rats, cleft palate in mice and gallbladder agenesis, umbilical hernia and flexed front paws in rabbits. There were also reductions in maternal body weight gains, 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.

Lactation

Risk summary

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 breastfed child from Enerzair Breezhaler or from the underlying maternal condition.

Females and males of reproductive potential

Infertility

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

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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

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 (see section CLINICAL PHARMACOLOGY – Elimination).

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.

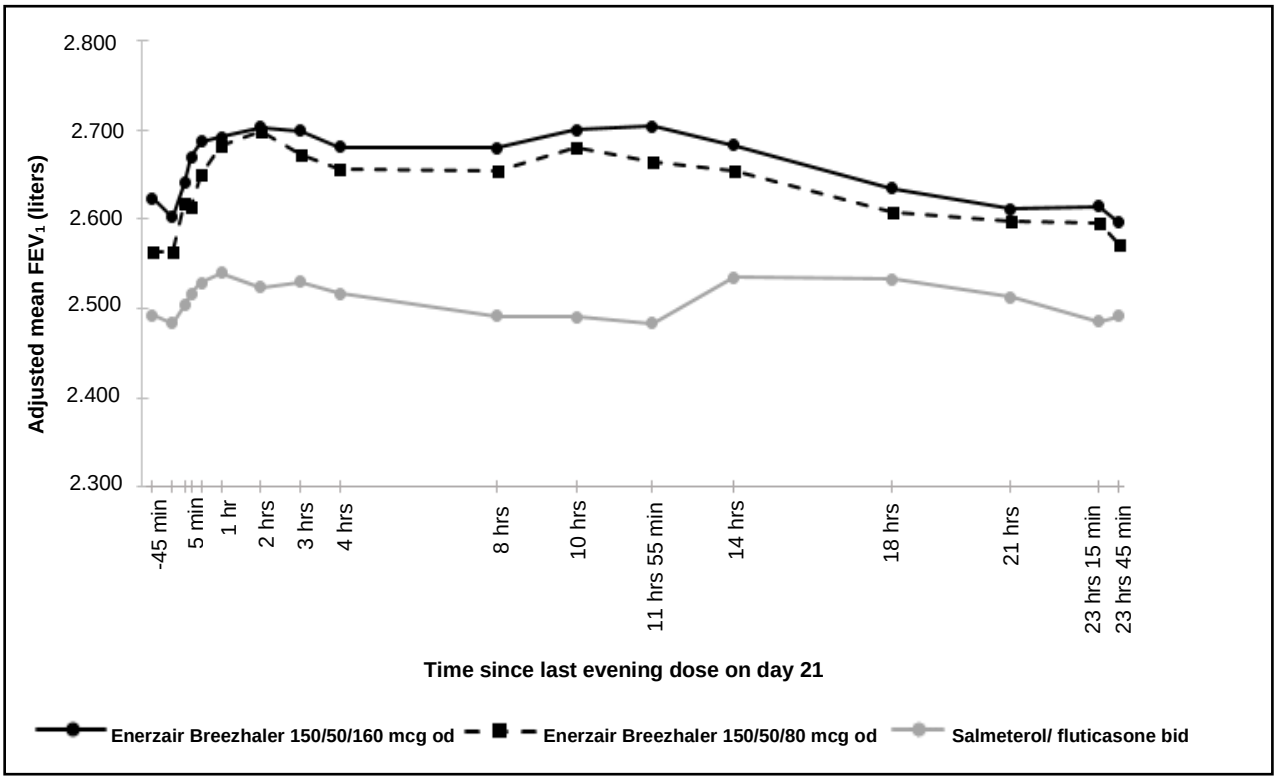
Pharmacodynamics (PD)

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

Clinical data confirmed the hypothesis that complementary bronchodilation with indacaterol and glycopyrronium coupled with the anti-inflammatory action of mometasone furoate results in improved lung function and asthma control. The indacaterol/glycopyrronium/mometasone furoate clinical program showed consistently superior lung function when Enerzair Breezhaler 150/50/80 micrograms once daily and 150/50/160 micrograms once daily were compared to salmeterol/fluticasone 50/500 micrograms twice daily, indacaterol/mometasone furoate 150/160 and 150/320 micrograms once daily, and placebo.

The pharmacodynamic response profile of Enerzair Breezhaler is characterized by rapid onset of action within 5 minutes after dosing (see section Clinical studies) and sustained effect over the whole 24-hour dosing interval (see Figure 1).

Figure 1 **Adjusted mean FEV_1 (L) by time and treatment, after 21 days of treatment**



The pharmacodynamic response profile is further characterized by increased mean peak forced expiratory volume in the first second (FEV_1) of 172 mL and 159 mL following Enerzair Breezhaler 150/50/160 micrograms and 150/50/80 micrograms once daily, respectively, compared to salmeterol/fluticasone 50/500 micrograms twice daily.

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.

Pharmacokinetics (PK)

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.

Based on the *in vitro* performance data, the dose of each of the monotherapy components delivered to the lung is expected to be similar for Enerzair Breezhaler and the monotherapy products. Steady-state plasma exposure to indacaterol, glycopyrronium and mometasone furoate after Enerzair Breezhaler inhalation was similar to the systemic exposure after inhalation of indacaterol maleate, glycopyrronium or mometasone furoate as monotherapy products.

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.

Biotransformation/metabolism

Indacaterol

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

In vitro investigations indicated that UGT1A1 was the only UGT isoform that 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 consistent metabolic pathways for glycopyrronium between animals and humans. No human specific metabolites were found. Hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen.

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

The portion of an inhaled mometasone furoate dose that is swallowed and absorbed in the gastrointestinal tract undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. In human liver microsomes, mometasone furoate is 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 is excreted mainly in the feces (74%) and to a lesser extent in the urine (8%)

Linearity/non-linearity

Systemic exposure of mometasone furoate (Cmax and AUC_{0-24h}) increased in a dose proportional manner following single and multiple doses of Enerzair Breezhaler 150/50/80 and 150/50/160 micrograms in healthy subjects. A less than proportional increase (1.7-fold) in steady state systemic exposure was noted in patients with asthma over the dose range of 150/50/80 and 150/50/160 micrograms. Dose proportionality assessments were not performed for indacaterol or glycopyrronium because only one dose was used across both dose strengths of Enerzair Breezhaler.

Special populations

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.

Race/Ethnicity

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.

Pediatric patients (below 18 years)

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

Renal impairment

The effect of renal impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated in dedicated studies with 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.

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

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

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated in subjects with hepatic impairment following administration of 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 section CLINICAL PHARMACOLOGY – Elimination). Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase in systemic exposure.

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

CLINICAL STUDIES

The safety and efficacy of Enerzair Breezhaler in adult patients with asthma was evaluated in a phase III randomized, double-blind study IRIDIUM. The study was a multi-center, 52-week study evaluating Enerzair Breezhaler 150/50/80 micrograms once daily (N=620) and 150/50/160 micrograms once-daily (N=619) via Breezhaler compared to indacaterol/mometasone furoate 150/160 micrograms once daily (N=617) and 150/320 once daily (N=618), 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 and were on asthma maintenance therapy using a medium or high dose ICS and LABA combination therapy for at least 3 months prior to study entry. 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 (62.6%) and LABA and high dose of ICS (36.7%).

The primary objective of the study was to demonstrate superiority of either Enerzair Breezhaler 150/50/80 micrograms once daily over indacaterol/mometasone furoate 150/160 micrograms once daily or 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.

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.

Enerzair Breezhaler 150/50/80 and 150/50/160 micrograms once daily both demonstrated statistically significant improvements in trough FEV_1 at week 26 when compared to indacaterol/mometasone furoate at corresponding doses. Clinically meaningful improvements in morning and evening peak expiratory flow were observed when compared to indacaterol/mometasone furoate at corresponding doses. Clinically meaningful improvements in lung function (change from baseline trough FEV_1 at week 26, morning and evening peak expiratory flow) were also observed when compared to salmeterol xinafoate /fluticasone propionate 50/500 micrograms twice daily. Findings at week 52 were consistent with week 26 (See Table 2).

Enerzair Breezhaler 150/50/160 micrograms once daily demonstrated a clinically meaningful reduction in the annual rate of exacerbations (36% for moderate or severe, 42% for severe, 40% for all exacerbations) compared to salmeterol xinafoate /fluticasone propionate 50/500 micrograms twice daily and numerical reduction compared to indacaterol/mometasone furoate 150/320 micrograms once daily. Enerzair Breezhaler 150/50/80 micrograms once daily also demonstrated reduction in the annual rate of exacerbations compared to indacaterol/mometasone furoate 150/160 micrograms once daily and to salmeterol xinafoate /fluticasone propionate 50/500 micrograms twice daily. (See Table 5).

Lung function

Table 2 Results of primary and secondary endpoints

Endpoint	**Time Point/Duration**	**Enerzair Breezhaler vs IND/MF***		**Enerzair Breezhaler vs SAL/FP***	
		Medium dose (150/50/80 od) versus medium dose (150/160 od)	High dose (150/50/160 od) versus high dose (150/320 od)	Medium dose (150/50/80 od) versus high dose (50/500 bid)	High dose (150/50/160 od) versus high dose (50/500 bid)
Lung Function					
Trough FEV_1 **					
Treatment difference P value (95% CI)	Week 26 *(Primary endpoint)*	76 mL <0.001 (41, 111)	65 mL <0.001 (31, 99)	99 mL <0.001 (64, 133)	119 mL <0.001 (85, 154)
	Week 52	62 mL <0.001	86 mL <0.001	87 mL <0.001	145 mL <0.001

		(27, 96)	(51, 120)	(52, 122)	(111, 180)
Mean Morning Peak Expiratory Flow (PEF)					
Treatment difference P value (95% CI)	Week 1-52***	15.6 L/min <0.001 (10.2, 20.9)	18.7 L/min <0.001 (13.4, 24.1)	28.5 L/min <0.001 (23.2, 33.8)	34.8 L/min <0.001 (29.5, 40.1)
Mean Evening Peak Expiratory Flow (PEF)					
Treatment difference P value (95% CI)	Week 1-52***	15.0 L/min <0.001 (9.7, 20.2)	17.5 L/min <0.001 (12.3, 22.8)	25.8 L/min <0.001 (20.5, 31.0)	29.5 L/min <0.001 (24.2, 34.7)

* IND/MF: Indacaterol/mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate

** 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.

*** Mean value for the treatment duration.

Onset of action

In study IRIDIUM, Enerzair Breezhaler demonstrated a rapid onset of bronchodilator effect within 5 minutes after administration (see Table 3).

Table 3 Onset of action on Day 1 based on treatment difference in FEV_1 by time points

	Treatment difference Day 1
Enerzair Breezhaler (medium dose) vs IND/MF* (medium dose)	
5 min	55 mL**
15 min	68 mL**
30 min	87 mL**
Enerzair Breezhaler (high dose) vs IND/MF* (high dose)	
5 min	50 mL**
15 min	68 mL**
30 min	81 mL**
Enerzair Breezhaler (medium dose) vs SAL/FP* (high dose)	
5 min	117 mL**
15 min	123 mL**
30 min	130 mL**
Enerzair Breezhaler (high dose) vs SAL/FP* (high dose)	
5 min	114 mL**
15 min	123 mL**
30 min	129 mL**

*IND/MF: Indacaterol/mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate

** p-value <0.001

ACQ-7

In study IRIDIUM, the mean change from baseline in ACQ-7 score at week 26 (key secondary endpoint) and week 52 was around -1 for all treatment groups. The ACQ-7

responder rates (defined as a decrease in score of ≥0.5) at different time points are described in Table 4).

Table 4 ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥ 0.5)

Time point		Enerzair Breezhaler vs IND/MF*		Enerzair Breezhaler vs SAL/FP*	
		Medium dose (150/50/80 od) versus medium dose (150/160 od)	High dose (150/50/160 od) versus high dose (150/320 od)	Medium dose (150/50/80 od) versus high dose (50/500 bid)	High dose (150/50/160 od) versus high dose (50/500 bid)
Week 4	Percentage	60% vs 58%	66% vs 63%	60% vs 53%	66% vs 53%
	Odds ratio P value (95% CI)	1.14 0.277 (0.90, 1.46)	1.21 0.140 (0.94, 1.54)	1.28 0.045 (1.01, 1.63)	1.72 <0.001 (1.35, 2.20)
Week 12	Percentage	66% vs 67%	68% vs 67%	66% vs 61%	68% vs 61%
	Odds ratio P value (95% CI)	1.03 0.836 (0.80, 1.32)	1.11 0.435 (0.86, 1.42)	1.19 0.173 (0.93, 1.52)	1.35 0.019 (1.05, 1.73)
Week 26	Percentage	72% vs 71%	71% vs 74%	72% vs 67%	71% vs 67%
	Odds ratio P value (95% CI)	1.13 0.380 (0.86, 1.48)	0.92 0.535 (0.70, 1.20)	1.20 0.172 (0.92, 1.57)	1.21 0.151 (0.93, 1.57)
Week 52	Percentage	73% vs 73%	79% vs 78%	73% vs 73%	79% vs 73%
	Odds ratio P value (95% CI)	1.05 0.744 (0.79, 1.38)	1.10 0.510 (0.83, 1.47)	0.99 0.922 (0.75, 1.29)	1.41 0.017 (1.06, 1.86)

* IND/MF: Indacaterol/mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate.

Exacerbations

Table 5 Analysis of Exacerbation endpoints**

Endpoint	Enerzair Breezhaler vs IND/MF*		Enerzair Breezhaler vs SAL/FP*	
	Medium dose (150/50/80 od) versus medium dose (150/160 od)	High dose (150/50/160 od) versus high dose (150/320 od)	Medium dose (150/50/80 od) versus high dose (50/500 bid)	High dose (150/50/160 od) versus high dose (50/500 bid)
Annualized rate of asthma exacerbations				
Moderate or severe exacerbations				
Annualized rate	0.58 vs 0.67	0.46 vs 0.54	0.58 vs 0.72	0.46 vs 0.72
Rate Ratio	0.87	0.85	0.81	0.64

Endpoint	Enerzair Breezhaler vs IND/MF*		Enerzair Breezhaler vs SAL/FP*	
	Medium dose (150/50/80 od) versus medium dose (150/160 od)	High dose (150/50/160 od) versus high dose (150/320 od)	Medium dose (150/50/80 od) versus high dose (50/500 bid)	High dose (150/50/160 od) versus high dose (50/500 bid)
(RR) p-value (95% CI)	0.170 (0.71, 1.06)	0.120 (0.68, 1.04)	0.041 (0.66, 0.99)	<0.001 (0.52, 0.78)
Severe exacerbations				
Annualized rate	0.38 vs 0.41	0.26 vs 0.33	0.38 vs 0.45	0.26 vs 0.45
Rate Ratio (RR) p-value (95% CI)	0.93 0.531 (0.74,1.17)	0.78 0.050 (0.61,1.00)	0.84 0.117 (0.67,1.05)	0.58 <0.001 (0.45,0.73)
All exacerbations (mild, moderate or severe)				
Annualized rate	0.86 vs 0.98	0.74 vs 0.93	0.86 vs 1.23	0.74 vs 1.23
Rate Ratio (RR) p-value (95% CI)	0.87 0.161 (0.72,1.06)	0.79 0.016 (0.66,0.96)	0.70 <0.001 (0.58,0.84)	0.60 <0.001 (0.50,0.72)

* IND/MF: Indacaterol/mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate.

NON-CLINICAL SAFETY DATA

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

For information on reproductive toxicity, see section Pregnancy, lactation, females and males of reproductive potential.

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

Indacaterol and mometasone furoate combination

The findings during the 13-week inhalation toxicity studies were predominantly attributable to the mometasone furoate and were typical pharmacological effects of glucocorticoids. Increased heart rates associated with indacaterol were apparent in dogs after administration of indacaterol/mometasone furoate or indacaterol alone.

Indacaterol and glycopyrronium combination

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

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

Indacaterol

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

Genotoxicity studies did not reveal any mutagenic or clastogenic potential.

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

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

Glycopyrronium

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

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

Mometasone furoate

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

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

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

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Do not store above 30°C.

Protect from moisture and light.

Do not use after the expiry date shown on the box.

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

INSTRUCTIONS FOR USE AND HANDLING

For correct administration/use of the product, please refer to Section METHOD OF ADMINISTRATION and the INSTRUCTION FOR USE (IFU).

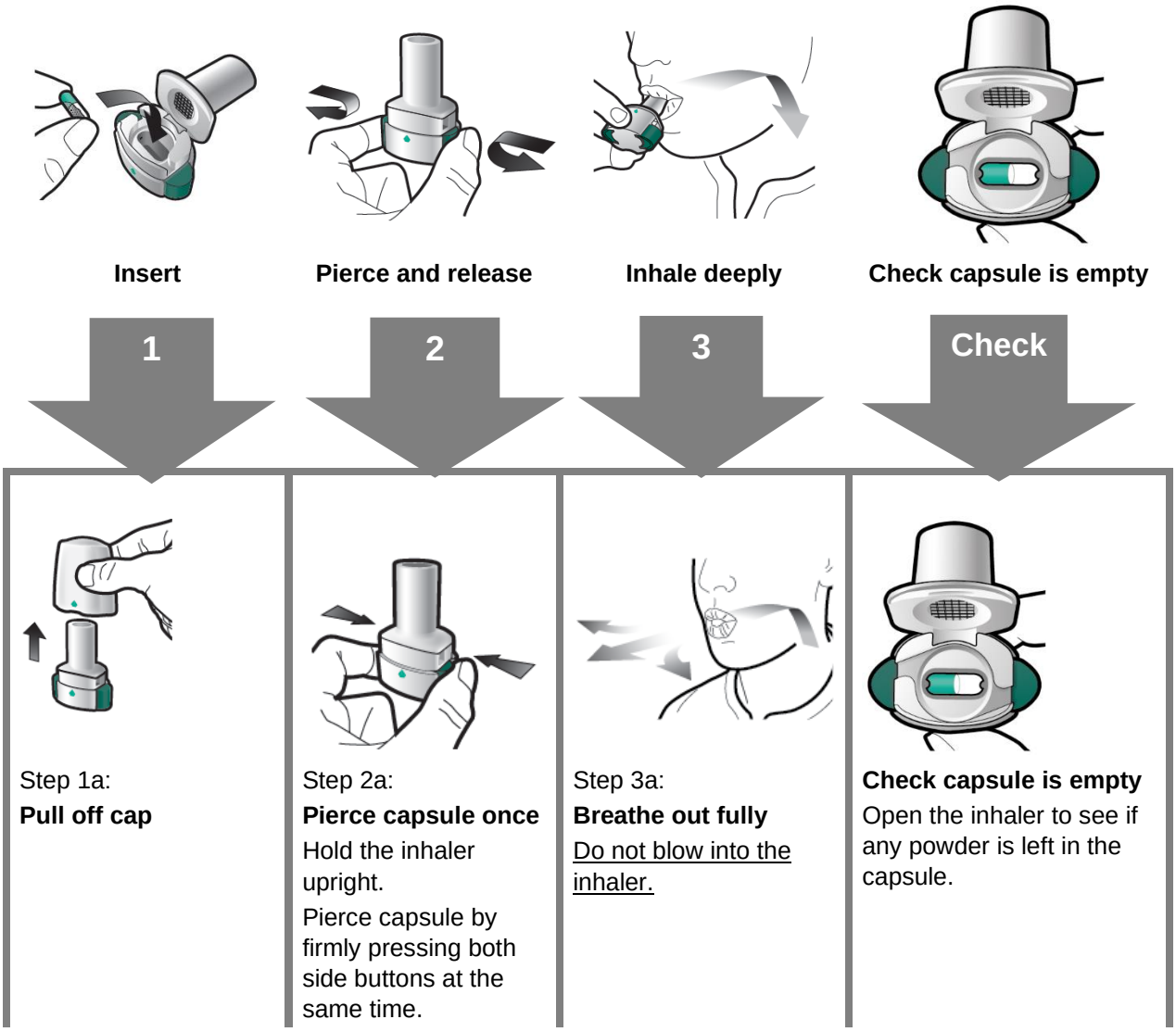
INFORMATION FOR PATIENTS

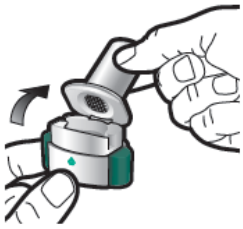
Instructions for use Enerzair Breezhaler

This part explains how to use and care for your Enerzair Breezhaler inhaler. Please read carefully and follow these instructions.

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

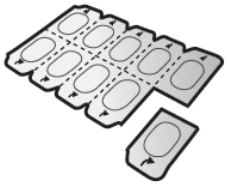
Please read the full **Instructions for use and handling** before using the Enerzair Breezhaler.

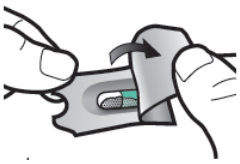




Step 1b:

Open inhaler





Step 1c:

Remove capsule

Separate one of the blisters from the blister card.

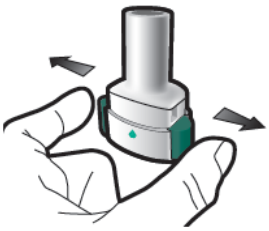
Peel open the blister and remove the capsule.

Do not push the capsule through the foil.

Do not swallow the capsule.

You should hear a noise as the capsule is pierced.

Only pierce the capsule once.



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.

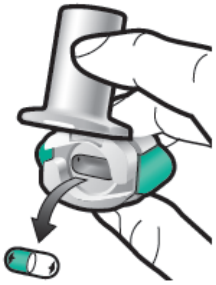
Step 3d :

Rinse mouth

If there is powder left in the capsule:

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

Powder remaining **Empty**



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

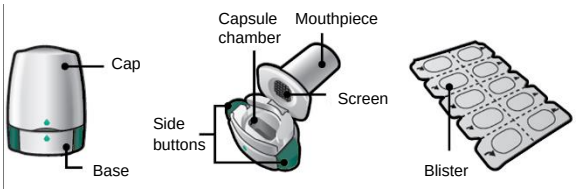
Rinse your mouth with water after each dose and spit it out.

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.

Your Enerzair Breezhaler Inhaler pack contains:

- One Enerzair Breezhaler inhaler
- One or more blister cards, each containing either 10 Enerzair Breezhaler capsules to be used in the inhaler



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

Frequently Asked Questions

Why didn't the inhaler make a noise when I inhaled?
The capsule may be stuck in the capsule chamber. If this happens, carefully loosen the capsule by tapping the base of the inhaler. Inhale the medicine again by repeating steps 3a to 3d.

What should I do if there is powder left inside the capsule?
You have not received enough of your medicine. Close the inhaler and repeat steps 3a to 3d.

I coughed after inhaling – does this matter?
This may happen. As long as the capsule is empty you have received enough of your medicine.

I felt small pieces of the capsule on my tongue – does this matter?
This can happen. It is not harmful. The chances of the capsule breaking into small pieces will be increased if the capsule is pierced more than once.

Cleaning the inhaler
Wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry. Never wash your inhaler with water.

Disposing of the inhaler after use
Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Registration No.:
150 mcg/50 mcg/80 mcg Powder for Inhalation in Hard Capsule: DR-XY48407
150 mcg/50 mcg/160 mcg Powder for Inhalation in Hard Capsule: DR-XY48483

Date of First Authorization:
150 mcg/50 mcg/80 mcg Powder for Inhalation in Hard Capsule: 07 October 2022
150 mcg/50 mcg/160 mcg Powder for Inhalation in Hard Capsule: 22 November 2022

Manufactured by:
Siegfried Barbera S.L.
Ronda de Santa Maria, 158, Barberà del Vallès,
Barcelona, 08210, Spain

Imported by:
Novartis Healthcare Philippines, Inc.
5th and 6th Floors Ayala North Exchange Building, Tower 1 Ayala
Avenue corner Salcedo & Amorsolo Sts, Brgy. San Lorenzo
Makati, Metro Manila

Information issued: Mar 2020

® = registered trademark

Novartis Pharma AG, Basel, Switzerland