NOVARTIS

ENERZAIR® BREEZHALER®

(indacaterol acetate, glycopyrronium bromide, and mometasone furoate fixed-dose combination)

inhalation powder hard capsules

Product Information

Based on CDS version 1.3 (11-Mar-2021)

1 Tradename(s)

ENERZAIR® BREEZHALER®

2 Description and composition

Pharmaceutical form(s)

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

Capsules with green transparent cap and uncolored transparent body containing a white powder with the product code “IGM 150-50-160” printed in black above two black bars on the body and with the product logo printed in black and surrounded by a black bar on the cap.

Active substance(s)

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. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 114 mcg of indacaterol (as acetate), 58 mcg of glycopyrronium bromide equivalent to 46 mcg of glycopyrronium and 136 mcg of mometasone furoate.

Excipients

Capsule fill: lactose monohydrate, magnesium stearate.

Capsule shell components: hypromellose, purified water, carrageenan, potassium chloride.

Each capsules contains 25 mg of lactose monohydrate.

3 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 beta2-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.

4 Dosage regimen and administration

Dosage regimen

General target population

Inhalation of the content of one capsule of Enerzair Breezhaler 150/50/160 micrograms once-daily is recommended in adult patients not adequately controlled with a maintenance combination of a long acting beta2-agonist and a medium dose or high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous 12 months.

The recommended dose is one capsule to be inhaled once daily. 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 6 Warnings and precautions and 11 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 11 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 11 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 14 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.

5 Contraindications

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

6 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.

It is recommended that treatment with this medicinal product should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment but must seek medical attention. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden and progressive deterioration in the symptoms of asthma is potentially life-threatening and the patient should undergo urgent medical assessment.

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.

Patients with unstable ischaemic heart disease, a history of myocardial infarction in last 12 months, New York Heart Association (NYHA) class III/IV left ventricular failure, arrhythmia, uncontrolled hypertension, cerebrovascular disease, history of long QT syndrome and patients being treated with medicinal products known to prolong QTc were excluded from studies in the indacaterol/glycopyrronium/mometasone furoate clinical development programme. Thus safety outcomes in these populations are considered unknown.

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 8 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.

This medicinal product has not been investigated in patients with Type I diabetes mellitus or uncontrolled Type II diabetes mellitus.

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 11 Clinical pharmacology).

Prevention of oropharyngeal infections

In order to reduce the risk of oropharyngeal candida infection, patients should be advised to rinse their mouth or gargle with water without swallowing it or brush their teeth after inhaling the prescribed dose.

Systemic effects of corticosteroids

Systemic effects of inhaled corticosteroids may occur, 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 may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataracts, glaucoma, and, more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Visual disturbance may be reported with systemic and topical (including intranasal, inhaled and intraocular) corticosteroid use. Patients presenting with symptoms such as blurred vision or other visual disturbances should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

This medicinal product should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

7 Adverse drug reactions

Summary of the safety profile

The most common adverse reactions over 52 weeks were asthma (exacerbation) (41.8%), nasopharyngitis (10.9%), upper respiratory tract infection (5.6%) and headache (4.2%).

Adverse drug reactions from clinical trials

Adverse drug reactions are listed by MedDRA system organ class (Table 7-1). The frequency of the ADRs is based on IRIDIUM study. 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 7-1 Adverse reactions

System organ class	Adverse reactions	Frequency category
Infections and infestations	Nasopharyngitis	Very common
	Upper respiratory tract infection	Common
	Candidiasis*[1]	Common
	Urinary tract infection*[2]	Common
Immune system disorders	Hypersensitivity*[3]	Common
Metabolism and nutrition disorders	Hyperglycaemia*[4]	Uncommon
Nervous system disorders	Headache*[5]	Common
Eye disorder	Cataract	Uncommon
Cardiac disorders	Tachycardia*[6]	Common
Respiratory, thoracic and mediastinal disorders	Asthma (exacerbation)	Very common
	Oropharyngeal pain*[7]	Common
	Cough	Common
	Dysphonia	Common
Gastrointestinal disorder	Gastroenteritis*[8]	Common
	Dry mouth*[9]	Uncommon
Skin and subcutaneous tissue disorders	Rash*[10]	Uncommon
	Pruritus*[11]	Uncommon
	Musculoskeletal pain*[12]	Common

Musculoskeletal and connective tissue disorders	Muscle spasms	Common
Renal and urinary disorders	Dysuria	Uncommon
General disorders and administration site conditions	Pyrexia	Common

* indicates 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.

8 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 6 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 6 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 sections 7 Adverse drug reactions and 10 Overdosage).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 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

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 $AUC_{0\text{-}24h}$). 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.

9.2 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 breast-fed child from Enerzair Breezhaler or from the underlying maternal condition.

9.3 Females and males of reproductive potential

Fertility

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

10 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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids. ATC code: R03AL12.

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 11 Clinical pharmacology – Elimination).

Mometasone furoate

Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and local anti-inflammatory properties. *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.

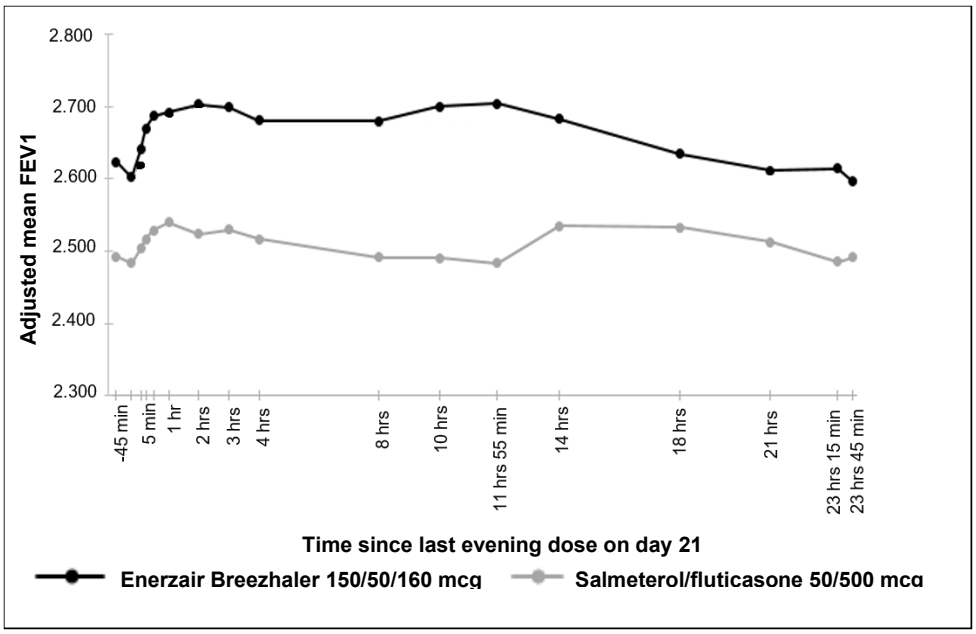
Pharmacodynamics (PD)

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 150/50/160 micrograms once daily were compared to salmeterol/fluticasone 50/500 micrograms twice daily, indacaterol/mometasone furoate 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 12 Clinical studies) and sustained effect over the whole 24-hour dosing interval (see Figure 11-1).

Figure 11-1 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 following Enerzair Breezhaler 150/50/160 micrograms once daily, 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 2,557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding were 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Glycopyrronium

After intravenous dosing, the steady-state volume of distribution (Vss) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (Vz) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7,310 L, which reflects the much slower elimination after inhalation. The *in vitro* human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/mL. These concentrations were at least 6-fold higher than the steady state mean peaks levels achieved in plasma for a 50 micrograms once-daily dosing regimen.

Mometasone furoate

After intravenous bolus administration, the V_d is 332 L. 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%)

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 pharmacokinetic analysis of glycopyrronium in asthma patients following Enerzair Breezhaler administration, $AUC_{0\text{-}24h}$ increased by 27% or decreased by 19% for patients with an absolute GFR of 58 or 143 ml/min, respectively, compared to a patient with an absolute GFR of 93 ml/min.

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 11 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.

12 Clinical studies

Comparison of Enerzair Breezhaler to fixed combinations of LABA/ICS

The safety and efficacy of Enerzair Breezhaler in adult patients with persistent asthma was evaluated in the phase III randomised, double-blind study (IRIDIUM). The IRIDIUM study was a 52-week study evaluating Enerzair Breezhaler 114 mcg/46 mcg/68 mcg once daily (N=620) and 114 mcg/46 mcg/136 mcg once daily (N=619) compared to indacaterol/mometasone furoate 125 mcg/127.5 mcg once daily (N=617) and 125 mcg/260 mcg once daily (N=618), respectively. A third active control arm included subjects treated with salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily (N=618). All subjects were required to have symptomatic asthma (ACQ-7 score ≥1.5) and were on asthma maintenance therapy using a medium or high dose inhaled synthetic corticosteroid (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 medium dose of ICS in combination with a LABA (62.6%) and high dose of ICS in combination with a LABA (36.7%).

The primary objective of the study was to demonstrate superiority of either Enerzair Breezhaler 114 mcg/46 mcg/68 mcg once daily over indacaterol/mometasone furoate 125 mcg/127.5 mcg once daily or Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily over indacaterol/mometasone furoate 125 mcg/260 mcg once daily in terms of trough FEV_1 at week 26.

Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily demonstrated statistically significant improvements in trough FEV_1 at week 26 compared to indacaterol/mometasone furoate at corresponding dose. Clinically meaningful improvements in lung function (change from baseline trough FEV_1 at week 26, morning and evening peak expiratory flow) were also observed compared to salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily. Findings at week 52 were consistent with week 26 (see Table 12-1).

All treatment groups showed clinically relevant improvements from baseline in ACQ-7 at week 26, however no statistically significant differences between groups were observed. The mean change from baseline in ACQ-7 at week 26 (key secondary endpoint) and week 52 was around -1 for all treatment groups. The ACQ-7 responder rates (defined as a change decrease in score of ≥0.5) at different time points are described in Table 12-1.

Exacerbations were a secondary endpoint (not part of confirmatory testing strategy). Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily demonstrated a reduction in the annual rate of exacerbations compared to salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily and indacaterol/mometasone furoate 125 mcg/260 mcg once daily (see Table 12-1).

Results for the most clinically relevant endpoints are described in Table 12-1.

Table 12-1 Results of primary and secondary endpoints in IRIDIUM study at weeks 26 and 52

Endpoint	Time point/Duration	Enerzair Breezhaler[1] vs IND/MF[2]	Enerzair Breezhaler[1] vs SAL/FP[3]
Lung function			
Trough FEV1[4]			
Treatment difference P value (95% CI)	Week 26 (Primary endpoint)	65 ml <0.001 (31, 99)	119 ml <0.001 (85, 154)
	Week 52	86 ml <0.001 (51, 120)	145 ml <0.001 (111, 180)
Mean morning peak expiratory flow (PEF)			
Treatment difference (95% CI)	Week 52*	18.7 l/min (13.4, 24.1)	34.8 l/min (29.5, 40.1)
Mean evening peak expiratory flow (PEF)			
Treatment difference (95% CI)	Week 52*	17.5 l/min (12.3, 22.8)	29.5 l/min (24.2, 34.7)
Symptoms			
ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥0.5)			
Percentage	Week 4	66% vs 63%	66% vs 53%
Odds ratio (95% CI)		1.21 (0.94, 1.54)	1.72 (1.35, 2.20)
Percentage	Week 12	68% vs 67%	68% vs 61%
Odds ratio (95% CI)		1.11 (0.86, 1.42)	1.35 (1.05, 1.73)
Percentage	Week 26	71% vs 74%	71% vs 67%
Odds ratio (95% CI)		0.92 (0.70, 1.20)	1.21 (0.93, 1.57)
Percentage	Week 52	79% vs 78%	79% vs 73%
Odds ratio (95% CI)		1.10 (0.83, 1.47)	1.41 (1.06, 1.86)
Annualised rate of asthma exacerbations			
Moderate or severe exacerbations			
AR	Week 52	0.46 vs 0.54	0.46 vs 0.72
RR** (95% CI)	Week 52	0.85 (0.68, 1.04)	0.64 (0.52, 0.78)
Severe exacerbations			
AR	Week 52	0.26 vs 0.33	0.26 vs 0.45
RR** (95% CI)	Week 52	0.78 (0.61, 1.00)	0.58 (0.45, 0.73)

* Mean value for the treatment duration.
** RR <1.00 favours indacaterol/glycopyrronium/mometasone furoate.
1 Enerzair Breezhaler 114 mcg/46 mcg/136 mcg od.
2 IND/MF: indacaterol/mometasone furoate high dose: 125 mcg/260 mcg od.
Mometasone furoate 136 mcg in Enerzair Breezhaler is comparable to mometasone furoate 260 mcg in indacaterol/mometasone furoate.
3 SAL/FP: salmeterol/fluticasone propionate high dose: 50 mcg/500 mcg bid (content dose).
4 Trough FEV_1: the mean of the two FEV_1 values measured at 23 hours 15 min and 23 hours 45 min after the evening dose.
Primary endpoint (trough FEV_1 at week 26) and key secondary endpoint (ACQ-7 score at week 26) were part of confirmatory testing strategy and thus controlled for multiplicity. All other endpoints were not part of confirmatory testing strategy.

RR = rate ratio, AR = annualised rate
od = once daily, bid = twice daily

Comparison of Enerzair Breezhaler to the concurrent open-label administration of salmeterol/fluticasone + tiotropium

A randomised, partially-blinded, active-treatment-controlled, non-inferiority study (ARGON) comparing Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily (N=476) and 114 mcg/46 mcg/68 mcg once daily (N=474) to the concurrent administration of salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily + tiotropium 5 mcg once daily (N=475) over 24 weeks of treatment was conducted.

Enerzair Breezhaler demonstrated non-inferiority to salmeterol/fluticasone + tiotropium for the primary endpoint (change from baseline for Asthma Quality of Life Questionnaire [AQLQ-S]), in previously symptomatic patients on ICS and LABA therapy with a difference of 0.073 (one-sided lower 97.5% confidence limit [CL]: -0.027).

13 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 9 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.

Shortening of electrocardiograph intervals and decreased systolic and diastolic blood pressure were also apparent. Indacaterol administered to dogs alone or in the indacaterol/glycopyrronium combination was associated with a similar incidence of myocardial lesions.

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.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C.

Shelf life: the expiry date is indicated on the packaging.

Protect from light and moisture.

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

Instructions for use and handling

For correct administration/use of the product, please refer to Method of administration in section 4 Dosage regimen and administration and to the Instruction for use (IFU) contained in the Patient Information Leaflet (*Informasi Produk untuk Pasien*).

Pack size

Enerzair Breezhaler 150/50/160 mcg Reg. No.
Box, 3 blisters @ 10 capsules + 1 inhaler

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by Siegfried Barbera S.L., Barberà del Vallès, Spain for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Product Information based on CDS version 1.3 (11-Mar-2021) and DP site transfer to Siegfried Barbera S.L., Spain.

NOVARTIS

ENERZAIR® BREEZHALER®

(kombinasi dosis tetap *indacaterol acetate*, *glycopyrronium bromide* dan *mometasone furoate*)

serbuk inhalasi dalam kapsul

Informasi Produk untuk Pasien

Berdasarkan BPL versi 1.3 (11-Mar-2021)

Bacalah seluruh brosur ini dengan saksama sebelum menggunakan obat ini.

Simpanlah brosur ini. Anda mungkin perlu membacanya kembali.

Obat ini hanya diresepkan untuk Anda. Jangan menggunakan obat ini untuk penyakit lain. Jangan memberikannya pada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakitnya sama dengan Anda.

Jika Anda mengalami efek samping, termasuk yang tidak tercantum pada brosur ini, hubungi dokter, apoteker, atau tenaga kesehatan Anda.

Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker, atau tenaga kesehatan Anda.

Isi Brosur:

1 Apa itu Enerzair® Breezhaler® dan apa kegunaannya

Apa itu Enerzair Breezhaler dan bagaimana cara kerjanya

Enerzair Breezhaler mengandung tiga zat aktif yang disebut *indacaterol, glycopyrronium,* dan *mometasone furoate*.

Indacaterol dan *glycopyrronium* termasuk ke dalam golongan obat-obatan yang disebut bronkodilator. Obat-obat ini merelaksasi otot-otot yang terdapat pada saluran-saluran udara kecil yang ada di paru-paru Anda. Hal ini membantu saluran udara tersebut terbuka dan membuat udara lebih mudah masuk dan keluar dari paru-paru. Ketika digunakan secara teratur, obat-obat ini membantu menjaga saluran udara tersebut tetap terbuka.

Mometasone furoate termasuk ke dalam golongan obat-obatan yang disebut kortikosteroid, atau sering disebut steroid. Kortikosteroid mengurangi pembengkakan dan iritasi/peradangan pada saluran-saluran udara kecil yang ada di paru-paru sehingga secara bertahap meringankan masalah pernapasan Anda. Kortikosteroid juga membantu mencegah serangan asma.

Pada kemasan obat ini, Anda akan menemukan sebuah alat inhalasi (*inhaler*) dan kapsul dalam blister yang berisi obat dalam bentuk serbuk inhalasi. Alat inhalasi ini digunakan untuk menghirup serbuk obat yang terdapat di dalam kapsul. Gunakan hanya alat inhalasi yang terdapat dalam kemasan obat ini.

Apa kegunaan Enerzair Breezhaler

Dokter Anda meresepkan obat ini untuk mengobati asma pada pasien dewasa.

Asma merupakan penyakit paru-paru yang serius dan bersifat jangka panjang, di mana otot-otot yang ada di sekitar saluran udara paru-paru menjadi tegang (bronkokonstriksi), bengkak dan mengalami iritasi (peradangan). Gejala-gejala penyakit dapat datang dan pergi, termasuk kesulitan bernapas, mengi (bernapas menimbulkan bunyi), sesak dada, dan batuk.

Anda harus menggunakan Enerzair Breezhaler setiap hari seperti yang disarankan oleh dokter Anda, tidak hanya pada saat Anda mengalami kesulitan bernapas atau gejala asma. Hal ini untuk memastikan obat ini bekerja sebagaimana mestinya dalam mengontrol penyakit asma Anda. Obat ini tidak boleh digunakan dengan tujuan untuk menangani atau melegakan serangan asma (seperti kesulitan bernapas atau mengi) yang terjadi secara tiba-tiba.

Jika Anda memiliki pertanyaan mengenai bagaimana cara kerja Enerzair Breezhaler atau mengapa obat ini diresepkan untuk Anda, tanyakan kepada dokter Anda.

2 Apa yang harus Anda ketahui sebelum dan ketika Anda menggunakan Enerzair Breezhaler

Ikuti seluruh petunjuk dokter secara hati-hati.

Jangan gunakan Enerzair Breezhaler

- Jika Anda alergi terhadap *indacaterol*, *glycopyrronium*, *mometasone furoate*, atau komponen lain yang terdapat dalam obat ini (tercantum pada bagian 6 Isi kemasan dan informasi lainnya).
- Jika Anda berpikir bahwa Anda mungkin alergi, tanyakan pada dokter Anda.

Peringatan dan perhatian

Sebelum menggunakan Enerzair Breezhaler, beri tahu dokter, apoteker, atau tenaga kesehatan Anda jika Anda memiliki salah satu atau lebih kondisi berikut:

- jika Anda memiliki masalah jantung, termasuk detak jantung yang cepat atau tidak teratur, hipertensi tidak terkontrol dan penyakit pembuluh darah di otak.
- jika Anda memiliki masalah kelenjar tiroid.
- jika Anda memiliki atau pernah diberi tahu memiliki diabetes atau kadar gula darah yang tinggi.
- jika Anda menderita kejang atau gejala serupa.
- jika Anda memiliki kadar kalium yang rendah dalam darah.
- jika Anda memiliki masalah organ hati yang berat.
- jika Anda memiliki masalah ginjal yang berat.
- jika Anda memiliki penyakit mata yang disebut glaukoma sudut sempit.
- jika Anda memiliki kesulitan urinasi (buang air kecil).
- jika Anda menderita tuberkulosis, atau infeksi lain yang berlangsung lama atau tidak diobati.

Untuk mengurangi resiko infeksi kandida pada orofaring (mulut dan tenggorokan), Anda disarankan agar mencuci mulut atau berkumur dengan air atau menyikat gigi setelah menggunakan obat.

Selama menggunakan Enerzair Breezhaler:

- **hentikan penggunaan Enerzair Breezhaler dan segera cari pertolongan medis** jika Anda mengalami salah satu atau lebih kondisi berikut:
  - sesak dada, batuk, mengi (bernapas mengeluarkan bunyi), atau kesulitan bernapas segera setelah Anda menghirup Enerzair Breezhaler (tanda-tanda bronkospasme paradoksikal).
  - kesulitan bernapas atau menelan, pembengkakan pada lidah, bibir, atau wajah, ruam kulit, gatal-gatal, kemerahan atau benjolan pada kulit (tanda-tanda reaksi alergi).
  - nyeri atau rasa tidak nyaman pada mata, penghilatan kabur untuk sementara waktu, melihat bundaran/lingkaran putih atau gambar berwarna yang disertai dengan mata merah (tanda-tanda serangan akut glaukoma sudut sempit).

Anak-anak dan remaja (di bawah 18 tahun)

Anda tidak boleh menggunakan Enerzair Breezhaler jika Anda berumur di bawah 18 tahun.

Pasien usia lanjut (65 tahun ke atas)

Jika Anda berumur 65 tahun ke atas, Anda dapat menggunakan Enerzair Breezhaler dengan dosis yang sama dengan orang dewasa.

Penggunaan obat lain (interaksi dengan obat-obatan lain termasuk vaksin)

Beri tahu dokter, apoteker, atau tenaga kesehatan Anda jika Anda sedang menggunakan, atau belum lama menggunakan obat-obat lain, termasuk obat-obat tanpa resep. Hal ini termasuk namun tidak terbatas pada obat-obat berikut:

- obat yang digunakan untuk mengobati depresi (misalnya antidepresan trisiklik, monoamine oxidase inhibitor).
- obat lain yang mungkin serupa dengan Enerzair Breezhaler (mengandung zat aktif yang sama atau serupa); penggunaan obat-obat ini dapat meningkatkan risiko efek samping.
- obat yang menurunkan kadar kalium dalam darah Anda. Hal ini termasuk diuretik (terkadang disebut “pil air”, dan digunakan juga untuk mengobati tekanan darah tinggi, misalnya hidroklorotiazid atau HCT), obat-obat bronkodilator lain seperti metilxantin yang digunakan untuk masalah pernapasan (misalnya teofilin), atau steroid (misalnya prednisolon).
- obat yang digunakan untuk mengobati tekanan darah tinggi atau penyakit jantung (misalnya propranolol) atau untuk mengobati glaukoma (misalnya timolol).
- obat yang digunakan untuk mengobati infeksi fungi/jamur (misalnya ketokonazol atau itrakonazol).
- obat yang digunakan untuk mengobati infeksi HIV (misalnya ritonavir, nelfinavir, atau *cobicistat*).

Kehamilan dan menyusui

Jika Anda hamil, berpikir bahwa Anda mungkin hamil, atau berencana untuk hamil, beri tahu dokter Anda. Dokter Anda akan berdiskusi dengan Anda terkait potensi risiko yang mungkin terjadi dan apakah Anda dapat menggunakan Enerzair Breezhaler selama kehamilan.

Jika Anda sedang menyusui, beri tahu dokter Anda. Dokter Anda akan berdiskusi dengan Anda terkait potensi risiko yang mungkin terjadi dan apakah Anda dapat menggunakan Enerzair Breezhaler selama menyusui.

Mengemudi dan menggunakan mesin

Kecil kemungkinan obat ini akan memengaruhi kemampuan Anda mengemudi dan menggunakan mesin.

Zat tambahan/eksipien tertentu

Obat ini mengandung laktosa. Jika Anda pernah diberi tahu dokter bahwa Anda intoleran terhadap gula tertentu, konsultasikan dengan dokter Anda sebelum menggunakan Atectura Breezhaler.

3 Cara penggunaan Enerzair Breezhaler

Gunakan selalu obat ini sama seperti yang disarankan oleh dokter atau apoteker Anda. Tanyakan pada dokter atau apoteker Anda jika Anda tidak yakin.

Berapa banyak Enerzair Breezhaler yang harus dihirup

Dosis umum adalah satu kapsul sehari. Anda hanya perlu menghirup obat ini sekali sehari karena efeknya bertahan selama 24 jam. Jangan menggunakan obat ini lebih dari yang disarankan oleh dokter Anda.

Gunakan satu kapsul Enerzair Breezhaler setiap hari dengan cara inhalasi/dihirup (menggunakan alat inhalasi) dan terus gunakan obat ini walaupun Anda tidak mengalami gejala-gejala asma.

Kapan menggunakan Enerzair Breezhaler

Gunakan Enerzair Breezhaler pada waktu yang sama setiap hari. Hal ini membantu mengurangi timbulnya gejala-gejala pada waktu siang atau malam. Hal ini juga membantu Anda untuk mengingat kapan Anda harus menggunakan obat ini.

Bagaimana cara menggunakan Enerzair Breezhaler

Enerzair Breezhaler digunakan dengan cara inhalasi/dihirup serbuknya menggunakan alat inhalasi yang terdapat pada kemasan obat ini. Jangan menggunakan Enerzair Breezhaler dengan cara menelan kapsulnya. Setelah menggunakan obat ini, berkumurlah dengan air tanpa menelannya.

Untuk informasi lebih lanjut mengenai cara penggunaan, lihat Instruksi Penggunaan Enerzair Breezhaler yang terdapat pada bagian akhir brosur ini.

Berapa lama penggunaan Enerzair Breezhaler

Terus gunakan Enerzair Breezhaler selama dokter Anda menyarankannya. Jangan berhenti kecuali jika disarankan oleh dokter Anda, walaupun Anda merasa lebih baik, karena gejala-gejala Anda dapat memburuk.

Jika Anda memiliki pertanyaan tentang berapa lama Anda harus menjalani pengobatan dengan Enerzair Breezhaler, tanyakan pada dokter atau apoteker Anda.

Jika Anda menggunakan Enerzair Breezhaler lebih dari yang seharusnya

Jika Anda menghirup Enerzair Breezhaler lebih banyak dari yang disarankan oleh dokter Anda, beri tahu segera dokter atau rumah sakit untuk mendapatkan saran lebih lanjut. Anda mungkin membutuhkan perhatian atau tindakan medis. Bawalah kemasan Enerzair Breezhaler bersama Anda.

Jika Anda lupa menggunakan Enerzair Breezhaler

Jika Anda lupa menggunakan satu dosis obat namun masih pada hari yang sama, segera hirup dosis yang terlewat itu sesegera mungkin. Kemudian gunakan dosis hari berikutnya pada waktu biasanya. Jangan menghirup dosis ganda pada hari yang sama.

Jika Anda berhenti menggunakan Enerzair Breezhaler

Jika Anda berhenti menggunakan obat ini, gejala-gejala asma Anda dapat muncul kembali. Jika penyakit asma Anda tidak mengalami perbaikan atau mengalami perburukan walaupun Anda telah menggunakan Enerzair Breezhaler, diskusikan hal tersebut dengan dokter Anda. Anda tidak disarankan melakukan penghentian Enerzair Breezhaler secara mendadak. Jika Anda memiliki pertanyaan lebih lanjut terkait penggunaan obat ini, tanyakan pada dokter atau apoteker Anda.

4 Efek samping yang mungkin terjadi

Seperti pada penggunaan semua obat, pasien yang menggunakan Enerzair Breezhaler dapat mengalami efek samping, walaupun tidak semua orang mengalaminya.

Beberapa efek samping yang mungkin serius

Hentikan penggunaan Enerzair Breezhaler dan segera cari pertolongan medis apabila Anda mengalami salah satu atau lebih hal-hal berikut:

- kesulitan bernapas atau menelan, pembengkakan pada lidah, bibir, atau wajah, ruam kulit, gatal-gatal, kemerahan atau benjolan pada kulit (tanda-tanda reaksi alergi atau angioedema).

Jika Anda mengalami efek samping apapun yang serius, hentikan penggunaan obat ini dan segera beri tahu dokter atau tenaga kesehatan Anda.

Efek samping lain yang mungkin terjadi

Efek samping lain termasuk apa yang dicantumkan di bawah. Jika efek samping ini menjadi berat, beri tahu dokter atau tenaga kesehatan Anda.

Sangat umum: dapat terjadi pada > 1 dari 10 orang

- sakit tenggorokan
- pilek
- kesulitan bernapas secara tiba-tiba dan merasa sesak di dada ketika bersin atau batuk

Umum: dapat terjadi hingga pada 1 dari tiap 10 orang

- sariawan pada mulut (tanda-tanda kandidiasis). Setelah Anda selesai menggunakan dosis Anda, bilas mulut Anda dengan air atau cairan obat kumur kemudian keluarkan. Hal ini akan membantu dalam pencegahan terjadinya sariawan.
- keinginan urinasi (buang air kecil) yang seperti tidak bisa di tahan dan rasa nyeri atau terbakar ketika urinasi (tanda-tanda infeksi saluran kemih)
- sakit kepala
- detak jantung yang cepat
- batuk
- perubahan suara (serak/parau)
- diare, kram pada bagian abdomen (perut), mual, dan muntah (gastroenteritis)
- nyeri pada otot, tulang, atau sendi (nyeri muskuloskeletal)
- spasme/kejang otot
- demam

Tidak umum: dapat terjadi hingga pada 1 dari tiap 100 orang

- mulut kering
- ruam
- kadar gula darah tinggi dalam arah
- gatal-gatal pada kulit
- kesulitan dan nyeri ketika urinasi/buang air kecil (tanda-tanda disuria)
- kabut pada lensa mata Anda (tanda-tanda katarak)

5 Cara penyimpanan Enerzair Breezhaler

- Simpan pada suhu tidak lebih dari 30°C.
- Simpan obat pada kemasannya dan di tempat yang kering untuk melindunginya dari kelembapan dan cahaya. Jangan mengeluarkan kapsul dari blisternya sampai ketika akan segera digunakan.
- Jauhkan obat ini dari penglihatan dan jangkauan anak-anak.
- Jangan gunakan obat setelah tanggal kedaluwarsa yang tercantum pada kemasan obat.

- Tanyakan pada apoteker Anda terkait bagaimana cara membuang obat yang tidak lagi Anda gunakan.

6 Isi kemasan dan informasi lainnya

Apa kandungan Enerzair Breezhaler

Zat aktif obat ini adalah *indacaterol acetate*, *glycopyrronium bromide*, dan *mometasone furoate*.

- Tiap kapsul Enerzair Breezhaler 150/50/160 mikrogram mengandung 173 mikrogram *indacaterol acetate* yang setara dengan 150 mikrogram *indacaterol*, 63 mikrogram *glycopyrronium bromide* yang setara dengan 50 mikrogram *glycopyrronium*, dan 160 mikrogram *mometasone furoate*.

Kandungan/komposisi lain (atau disebut "**eksipien**") dari Enerzair Breezhaler adalah:

- Isi kapsul: laktosa monohidrat, magnesium stearat.
- Cangkang kapsul: hipromelosa, karagenan, kalium klorida, air murni (terpurifikasi).

Bagaimana tampilan Enerzair Breezhaler dan isi kemasannya

Pada setiap kemasan (dus obat), Anda akan menemukan blister yang berisikan kapsul obat beserta alat inhalasi (*inhaler*). Lihat bagian Kemasan untuk informasi lebih lanjut.

Kapsul Enerzair Breezhaler terdiri dari cangkang kapsul keras berwarna hijau transparan pada salah satu bagian (kepala/tutup kapsul) dan transparan tanpa warna pada bagian yang lain (badan kapsul) dengan isi kapsul berupa serbuk putih. Pada kapsul Enerzair Breezhaler 150/50/160 mikrogram terdapat tulisan "IGM150-50-160" berwarna hitam.

Kemasan

Enerzair Breezhaler 150/50/160 mikrogram No. Reg.
Dus, 3 blister @ 10 kapsul + 1 inhaler

HARUS DENGAN RESEP DOKTER

Pemegang Izin Edar

PT Novartis Indonesia

Informasi Produsen

Diproduksi oleh Siegfried Barbera S.L., Barberà del Vallès, Spanyol untuk Novartis Pharma AG, Basel, Swiss.
Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Informasi Produk untuk Pasien berdasarkan BPL versi 1.3 (11-Mar-2021) dan DP site transfer ke Siegfried Barbera S.L., Spanyol.

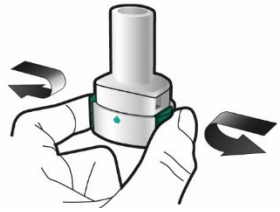
Instruksi Penggunaan Enerzair Breezhaler

Bagian ini menjelaskan bagaimana menggunakan Enerzair Breezhaler dengan alat inhalasi (*inhaler*) yang terdapat pada kemasan obat serta bagaimana memperlakukan *inhaler* tersebut. Bacalah instruksi ini dengan saksama dan ikuti setiap langkahnya.

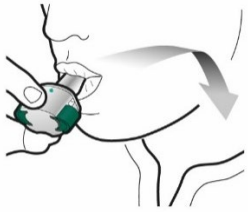
Jika Anda memiliki pertanyaan, tanyakan pada dokter atau apoteker Anda.

Bacalah **seluruh Instruksi Penggunaan** sebelum Anda menggunakan Enerzair Breezhaler.

Masukkan kapsul



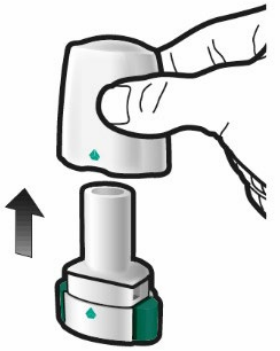
Tekan dan lepas



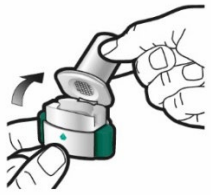
Bernapas dengan dalam

Periksa apakah kapsul sudah kosong

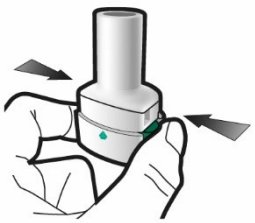
1 → 2 → 3 → Periksa



Langkah 1a:
Buka penutup *inhaler*



Langkah 1b:
Buka *inhaler*-nya

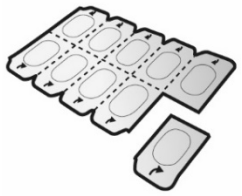


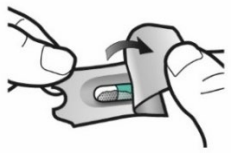
Langkah 2a:
Lubangi kapsul sekali dengan alat
Pegang *inhaler* menghadap ke atas.
Lubangi kapsul dengan cara menekan kuat kedua tombol yang ada di sisi samping *inhaler* pada waktu yang bersamaan.
Anda akan mendengar bunyi saat kapsul dilubangi.
Lubangi kapsul hanya sekali.

Langkah 3a:
Hembuskan napas secara penuh
Jangan menghembuskan napas ke dalam *inhaler*.

Langkah 3b:
Hirup obat secara dalam

Periksa apakah kapsul sudah kosong
Buka *inhaler* untuk melihat apakah masih ada serbuk obat yang tertinggal dalam kapsul.
Jika masih ada serbuk yang tersisa dalam kapsul:
- Tutup kembali *inhaler*.
- Ulangi Langkah 3a hingga 3d.





Langkah 1c:

Keluarkan kapsul dari blister

Pisahkan satu bagian blister yang berisi satu kapsul.

Buka (sobek) bagian belakang (foil) dan keluarkan kapsulnya.

Jangan mengeluarkan kapsul dari dalam foil dengan cara mendorong kapsul sehingga menembus foil.

Jangan menelan kapsul (lihat instruksi selanjutnya).

Langkah 1d:

Masukkan kapsul ke dalam *inhaler*

Jangan memasukkan kapsul langsung pada corong mulut *inhaler*.

Langkah 1e:

Tutup *inhaler*

Langkah 2b:

Lepaskan kedua tombol samping

Pegang *inhaler* tanpa menekan tombol sampingnya, seperti yang ditunjukkan pada gambar.

Masukkan corong *inhaler* ke dalam mulut Anda dan tutup rapat dengan menggunakan bibir Anda.

Jangan menekan tombol samping pada saat memegang *inhaler*.

Bernapaslah dengan cepat dan dalam semampu Anda.

Selama inhalasi, Anda akan mendengar bunyi mendesing.

Anda juga mungkin merasakan obat ini selama Anda menghirupnya.

Langkah 3c:

Tahan napas Anda

Tahan napas Anda selama 5 detik.

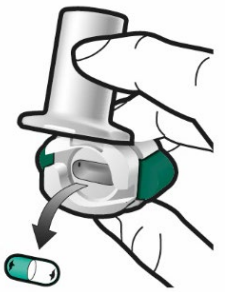
Langkah 3d:

Bilas mulut Anda

Bilas mulut Anda setiap kali selesai menghirup obat dengan cara berkumur dengan air dan mengeluarkannya.

Serbuk masih tertinggal

Kosong



Keluarkan kapsul yang telah kosong

Buang kapsul yang telah kosong pada tempat limbah rumah tangga Anda.

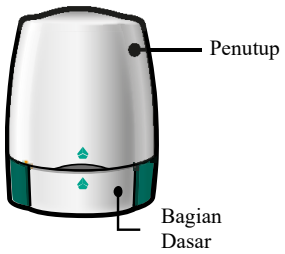
Tutup *inhaler* dan pasang kembali penutup alat.

Membersihkan *inhaler*
Gosok corong mulut bagian dalam dan luar dengan sebuah kain yang bersih, kering, bebas serat untuk menghilangkan serbuk-serbuk yang mungkin masih tertinggal. Jaga *inhaler* tetap kering. Jangan mencuci *inhaler* dengan air.

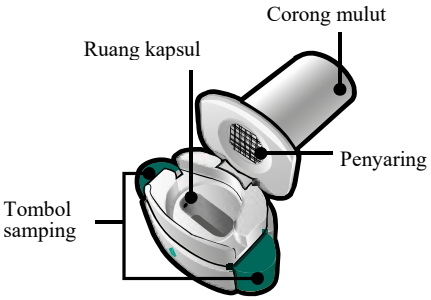
Membuang *inhaler*
Buang *inhaler* ketika seluruh kapsul yang terdapat dalam kemasan obat telah habis digunakan. Tanyakan pada dokter atau apoteker Anda atau pihak setempat yang berwenang terkait bagaimana cara membuang obat dan alat inhalasi (*inhaler*) yang tidak lagi Anda gunakan.

Informasi Penting
- Kapsul Enerzair Breezhaler harus selalu disimpan pada blister dan hanya dikeluarkan ketika akan segera digunakan.
- Jangan mendorong kapsul menembus foil untuk mengeluarkannya dari blister.
- Jangan menelan kapsul.
- Jangan menghirup kapsul Enerzair Breezhaler menggunakan alat inhalasi lain.
- Jangan menggunakan alat inhalasi Enerzair Breezhaler untuk menghirup obat lain.
- Jangan meletakkan kapsul pada mulut Anda atau pada corong mulut *inhaler*.
- Jangan menekan tombol samping *inhaler* lebih dari sekali.
- Jangan meniup atau menghembuskan napas ke dalam corong mulut *inhaler*.
- Jangan menekan tombol samping *inhaler* ketika sedang bernapas/menghirup obat menggunakan *inhaler*.
- Jangan memegang kapsul dengan tangan basah.
- Jangan mencuci alat/*inhaler* Anda dengan air.

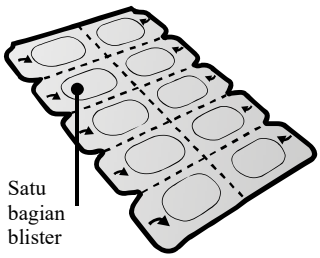
Kemasan (satu dus obat) Enerzair Breezhaler berisi:
- Satu alat inhalasi (*inhaler*) Enerzair Breezhaler
- Tiga kartu blister (atau secara singkat disebut “blister”) dimana masing-masing kartu blister berisi 10 kapsul Enerzair Breezhaler.



Inhaler



Bagian dasar inhaler



Blister

Pertanyaan yang Sering Diajukan

Mengapa *inhaler* tidak mengeluarkan bunyi ketika saya sedang menghirup obat?
Kemungkinan kapsul macet/tertahan di dalam ruang kapsul. Jika hal ini terjadi, cobalah bebaskan kapsul dengan cara mengetuk bagian dasar *inhaler* secara hati-hati. Hirup kembali obat dengan mengulangi Langkah 3a hingga 3d.

Apa yang saya harus lakukan jika masih terdapat serbuk yang tertinggal di dalam kapsul?
Jika hal tersebut terjadi, Anda mungkin belum mendapatkan dosis obat yang cukup. Tutuplah kembali *inhaler* dan ulangi Langkah 3a hingga 3d.

Saya batuk setelah menghirup obat – apakah hal ini berpengaruh?
Hal ini mungkin terjadi. Namun, selama kapsul sudah kosong, Anda telah mendapatkan dosis obat yang cukup.

Saya merasakan beberapa partikel kecil kapsul di dalam mulut saya – apakah hal ini bermasalah?
Hal ini mungkin terjadi, namun tidak membahayakan. Kemungkinan kapsul pecah menjadi partikel-partikel kecil dapat meningkat apabila Anda melubangi kapsulnya (menekan tombol samping *inhaler*) lebih dari sekali.