1 NAME OF THE MEDICINAL PRODUCT

Enerzair Breezhaler 114 mcg/46 mcg/136 mcg

Inhalation powder hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Enerzair Breezhaler hard capsules are for oral inhalation only. They are also supplied with an Enerzair Breezhaler inhalation device to permit oral inhalation of the contents of the capsule shell.

Each capsule contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol, 63 micrograms of glycopyrronium bromide (glycopyrrolate) equivalent to 50 micrograms glycopyrronium and 160 micrograms mometasone furoate.

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

Excipients with known effect

Each capsule contains approximately 25 mg lactose (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Capsules with green transparent cap and uncoloured transparent body containing a white to practically white powder, with the product code “IGM150-50-160” printed in black above two black bars on the body and with a logo printed in black and surrounded by one black bar on the cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta$_2$-agonist and an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

Important Limitations of Use:
Enerzair Breezhaler is not indicated in patients with COPD.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Treatment must be initiated and supervised by physicians experienced in the treatment of asthma.

Adult patients

Inhalation of the content of one capsule of Enerzair Breezhaler 114/46/136 micrograms once-daily is the recommended dose.

The maximum recommended dose is Enerzair Breezhaler 114/46/136 micrograms once daily.

Treatment with Enerzair Breezhaler provides addition of a long-acting muscarinic receptor antagonist (LAMA) to an inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) combination. Treatment should be based on individual patient's benefit-risk assessment and regularly reassessed by a healthcare professional (see section 5.1).

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 5 PHARMACOLOGICAL PROPERTIES).

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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5 PHARMACOLOGICAL PROPERTIES).

Elderly patients

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

Paediatric patients

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

Method of administration

For inhalation use only. Enerzair Breezhaler capsules must not be swallowed.

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. 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.

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

The capsules must always be stored in the blister to protect from moisture and light, and only removed immediately before use (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE).

4.3 CONTRAINDICATIONS

Enerzair Breezhaler is contraindicated in patients with hypersensitivity to any of the active substances or excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 the treatment with Enerzair Breezhaler. Patients should be asked to continue the 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.

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.

Long-acting beta2 adrenergic agonists (LABA) or LABA containing combination products such as Enerzair Breezhaler should therefore be used with caution in patients with known or suspected prolongation of the QT interval or who are being 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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Enerzair Breezhaler 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.

Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a 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 5 PHARMACOLOGICAL PROPERTIES).

Use in hepatic impairment

Enerzair Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment, therefore it should be used in these patients only if the expected benefit outweighs the potential risk (see section 5.2).

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.

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.

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

Use in the elderly

See section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION.

Paediatric use

See section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 4.8 UNDESIRABLE EFFECTS and 4.9 OVERDOSE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on the effect on fertility have been conducted with indacaterol, glycopyrronium and mometasone furoate in combination. In single-agent studies, no adverse effects on fertility were observed in male and female rats given indacaterol by subcutaneous injection at doses up to 2 mg/kg/day or glycopyrronium bromide at subcutaneous doses up to 1.5 mg/kg/day, yielding systemic exposure hundreds of times higher than in patients. As with other corticosteroids, at exposure levels associated with marked signs of systemic corticosteroid toxicity, mometasone furoate had progestogenic effects on the female reproductive tract and mammary glands. However, fertility was unimpaired in a reproductive toxicity study carried out in rats.

Use in pregnancy

Risk Summary

There are insufficient data from the use of Enerzair Breezhaler or its individual components (indacaterol, glycopyrronium and mometasone furoate) in pregnant women to determine whether there is a 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 foetal malformations and decreased foetal survival and growth.

Enerzair Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Clinical Considerations

Disease-associated maternal and/or embryo/foetal 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.

Labour and Delivery

Information related to indacaterol

Like other medicinal products containing beta$_2$-adrenergic agonists, indacaterol may inhibit labour 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

Indacaterol was not teratogenic at subcutaneous doses up to 1 mg/kg/day in rats and 3 mg/kg/day in rabbits (yielding more than 180-and 1000-times, respectively, the AUC in humans at 150 µg/day). An increase in the incidence of a rib skeletal variation and retarded ossification were observed in the rabbit at 3 mg/kg/day, possibly secondary to maternal toxicity; embryo foetal development was unaffected in the species at 1 mg/kg/day (relative exposure, >400). Impaired learning and decreased fertility were observed in the pups of rats given indacaterol at a subcutaneous dose of 1 mg/kg/day during pregnancy and lactation (relative exposure, approximately 160; unaffected at 0.3 mg/kg/day, associated with a relative exposure level of 63). The potential risk for humans is unknown.

Glycopyrronium

Glycopyrronium was not teratogenic in rats or rabbits following inhalational administration at doses up to 3.05 and 3.5 mg/kg/day in the respective species (yielding plasma AUC values approximately 570-times and 200-times higher than in patients at the maximum recommended human dose). 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 foetal growth (lower foetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice. In rats, subcutaneous mometasone furoate at 15 micrograms/kg prolonged gestation and difficult labor occurred with a reduction in offspring survival and body weight.

Use in lactation

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. Reduced body weight gain was observed in pups of rats treated with indacaterol or glycopyrronium, while impaired learning and decreased fertility were observed in pups of rats treated with indacaterol during pregnancy and lactation.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 UNDESIRABLE EFFECTS

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 114/46/136 micrograms once daily for up to 52 weeks.

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

Tabulated summary of 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. 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 114/46/136 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=616	Frequency category
Infections and infestations		
Candidiasis*[1]	0.33 [2] (0.07, 1.14)	Common
Urinary Tract Infection*[2]	3.57 [22] (2.28, 5.30)	Common
Immune system disorders		
Hypersensitivity*[3]	1.17 [8] (0.53, 2.31)	Common
Metabolism and nutrition disorders		
Hyperglycaemia*[4]	0.68 [4] (0.23, 1.64)	Uncommon
Nervous system disorders		
Headache*[5]	4.24 [35] (2.82, 6.09)	Common
Cardiac disorders		
Tachycardia*[6]	1.34 [8] (0.63, 2.53)	Common
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal Pain*[7]	3.02 [23] (1.86, 4.62)	Common
Cough	4.12 [30] (2.72, 5.96)	Common
Dysphonia	3.99 [26] (2.63, 5.78)	Common
Gastrointestinal disorders		
Gastroenteritis*[8]	3.23 [22] (2.01, 4.89)	Common

Adverse drug reactions	Enerzair Breezhaler 114/46/136 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=616	Frequency category
Dry Mouth*[9]	0.67 [4] (0.23, 1.62)	Uncommon
Skin and subcutaneous tissue disorders		
Rash*[10]	0.33 [2] (0.07, 1.14)	Uncommon
Pruritus*[11]	0.68 [4] (0.23, 1.65)	Uncommon
Musculoskeletal and connective tissue disorders		
Musculoskeletal Pain*[12]	3.05 [19] (1.88, 4.67)	Common
Muscle Spasms	1.69 [11] (0.87, 2.99)	Common
Renal and Urinary disorder		
Dysuria	0.17 [1] (0.02, 0.92)	Uncommon
General disorders and administration site conditions		
Pyrexia	2.90 [23] (1.76, 4.50)	Common

* Grouping of preferred terms (PTs).

[1] oral candidiasis, oropharyngeal candidiasis.

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

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

[4] blood glucose increased, hyperglycaemia.

[5] headache, tension headache.

[6] sinus tachycardia, supraventricular tachycardia, tachycardia.

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

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

[9] dry mouth, dry throat.

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

[11] eye pruritus, pruritus, pruritus genital.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 OVERDOSE

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, hypokalaemia, 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 cardio selective 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

ATC code: R03AL12

Mechanism of action

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

Indacaterol

Indacaterol is a long-acting beta$_2$-adrenergic agonist for once-daily administration. The pharmacological effects of beta$_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol is a weak partial agonist at beta$_1$ receptors with a potency more than 24-fold greater at beta$_2$-receptors compared to beta$_1$-receptors and is a full agonist at beta$_3$-receptors with a potency 20-fold greater at beta$_2$-receptors compared to beta$_3$-receptors.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human beta$_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although beta$_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the human heart, there are also beta$_2$-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of beta$_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective beta$_2$-adrenergic agonists may have cardiac effects.

Glycopyrronium

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic). Glycopyrronium works by blocking the broncho constrictor action of acetylcholine on airway smooth muscle cells thereby dilating the airways. Of the five known muscarinic receptor subtypes (M1-5), only subtypes M1-3 have a defined physiological function in the human lung. Glycopyrronium is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M3 and M1 receptors over the human M2 receptor in competition binding studies. It has a rapid onset of action, as evidenced by observed receptor association/dissociation kinetic parameters and by the onset of action after inhalation in clinical studies. The long duration of action can be partly attributed to sustained drug concentrations in the lungs as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the inhaler in contrast to the half-life after intravenous administration (see section 5.2 PHARMACOKINETIC PROPERTIES - Excretion).

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

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

The pharmacodynamic response profile of Enerzair Breezhaler is characterized by rapid onset of action within 5 minutes after dosing (see section 5.1 CLINICAL TRIALS) and sustained effect over the whole 24-hour dosing interval.

No tachyphylaxis to the lung function benefits of Enerzair Breezhaler were observed over time.

Effects on the QTc interval

The effect of Enerzair Breezhaler on the QTc interval has not been evaluated in a thorough QT (TQT) study. For mometasone furoate, no QTc prolonging properties are known.

Clinical trials

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 114/46/68 micrograms once daily (N=620) and 114/46/136 micrograms once-daily (N=619) via Breezhaler compared to indacaterol/mometasone furoate 215/127.5 micrograms once daily (N=617) and 125/260 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). The study was not powered for statistical comparisons between active comparator treatments.

All subjects were required to be 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%). (see section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION - Posology).

The primary objective of the study was to demonstrate superiority of either Enerzair Breezhaler 114/46/68 micrograms once daily over indacaterol/mometasone furoate 150/160 micrograms once daily or Enerzair Breezhaler 114/46/136 micrograms once daily to indacaterol/mometasone furoate 125/260 micrograms once daily in terms of trough FEV_1 at week 26.

Systemic exposures of 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 Atectura Breezhaler (indacaterol/mometasone furoate) delivered via unit dose dry powder inhaler, respectively (see Section 5.2 Pharmacokinetic Properties – Absorption).

Lung function

Enerzair Breezhaler 114/46/136 micrograms once daily demonstrated statistically significant improvements in trough FEV_1 at week 26 when compared to indacaterol/mometasone furoate at corresponding dose. The results of other lung function efficacy endpoints such as mean morning PEF and mean evening PEF are generally consistent with and support of the results of the primary endpoint. Findings at week 52 were consistent with week 26. (See Table 2).

ACQ-7

In study IRIDIUM, the mean change from baseline in ACQ-7 score at week 26 (key secondary endpoint) was around -1 for all treatment groups. The ACQ-7 responder rates (defined as a change in score of ≥0.5) were about 70% for all treatment groups at week 26. At week 52 the ACQ-7 responder rates were comparable between Enerzair Breezhaler and indacaterol/MF for both doses (See Table 2).

Exacerbations

Exacerbations were one of the "other secondary endpoints" (not part of confirmatory testing strategy). Enerzair Breezhaler 114/46/136 micrograms once daily demonstrated numerical reduction compared to indacaterol/mometasone furoate 125/260 micrograms once daily. (See Table 2).

Table 2 Results of primary and secondary endpoints in IRIDIUM study at weeks 26 and 52

Endpoint	Time Point/Duration	Enerzair Breezhaler vs IND/MF[1]
		High dose (114/46/136 od) versus high dose (125/260 od)
Lung Function		
*Trough FEV_1**		
Treatment difference P value (95% CI)	Week 26 *(Primary endpoint)*	65 mL <0.001 (31, 99)
	Week 52	86 mL <0.001 (51, 120)
Symptoms		
ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥0.5)		
Percentage	Week 26	71% vs 74%
Odds ratio (95% CI)		0.92 (0.70, 1.20)
Percentage	Week 52	79% vs 78%
Odds ratio (95% CI)		1.10 (0.83, 1.47)
Annualised rate of asthma exacerbations		
Moderate or severe exacerbations		
RR*** (95% CI)	Week 52	0.85 (0.68, 1.04)
Severe exacerbations		
RR*** (95% CI)	Week 52	0.78 (0.61,1.00)

[1] IND/MF: Indacaterol/mometasone furoate;
Mometasone furoate 136 mcg in Enerzair Breezhaler (high dose) is comparable to mometasone furoate 260 mcg in indacaterol/mometasone furoate.

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

** Mean value for the treatment duration.

***RR <1.00 favours indacaterol/glycopyrronium/mometasone furoate
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, od = once daily, bid = twice daily

5.2 PHARMACOKINETIC PROPERTIES

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%).

Systemic exposures of 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 Atectura Breezhaler (indacaterol/mometasone furoate) delivered via unit dose dry powder inhaler, respectively. This is due to an increase in fine particle mass of MF in Enerzair Breezhaler related to a physicochemical interaction through the presence of glycopyrronium bromide in the powder blend.

Distribution

Indacaterol

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

Glycopyrronium

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

Mometasone furoate

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

Metabolism

Indacaterol

After oral administration of radiolabelled indacaterol in a human 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).

Excretion

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

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

Glycopyrronium

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

Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium whereas non-renal clearance processes account for about 30 to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 50 and 200 microgram glycopyrronium by healthy volunteers and patients with COPD, mean renal clearance of glycopyrronium was in the range of 17.4 and 24.4 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%).

Specific 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.

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 5.2 PHARMACOKINETIC PROPERTIES - Excretion). 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.

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Indacaterol

Indacaterol was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including bacterial reverse mutation, chromosomal aberrations in Chinese hamster V79 cells and the rat bone marrow micronucleus test.

Glycopyrronium

Glycopyrronium bromide was not genotoxic in assays for bacterial mutagenicity, chromosomal aberrations in vitro (human lymphocytes) or in vivo clastogenicity (rat bone marrow micronucleus test).

Mometasone furoate

Mometasone furoate is not considered to be genotoxic. There was no evidence of mutagenicity in in vitro tests which included tests for reverse mutation in Salmonella typhimurium and Escherichia coli and forward gene mutation in a mouse lymphoma cell line. Limited evidence of clastogenicity was obtained in Chinese Hamster ovary cells, although this finding was not confirmed in a second assay in Chinese Hamster lung cells in vitro, nor in vivo assays including a chromosomal aberration assay in mouse spermatogonia, a mouse micronucleus assay or in a rat bone marrow clastogenicity assay. Mometasone furoate did not cause DNA damage in rat liver cells.

Carcinogenicity

No carcinogenicity studies have been conducted with indacaterol, glycopyrronium and mometasone furoate in combination.

Indacaterol

The carcinogenic potential of indacaterol has been evaluated in a 26-week oral gavage study in transgenic mice (CB6F1/TgrasH2) and a 2-year inhalation study in rats. No carcinogenicity was observed in mice at doses up to 600 mg/kg/day (approximately 200-times in males and 450-times in females the AUC in humans at the maximum recommended clinical dose of 150 μg/day). Lifetime treatment of rats at 2.1 mg/kg/day (relative exposure, 61) resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females. Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other β2-adrenergic agonist drugs. Their development is consistent with proliferation in response to prolonged relaxation of the smooth muscle (pharmacologically mediated), and the finding is not considered to indicate a carcinogenic hazard to patients. Squamous metaplasia was observed in the upper respiratory tract tissues of mice, rats and dogs following inhalation administration of indacaterol. This finding is consistent with an adaptive response to irritation and occurred at large multiples of the human dose. It is not considered to indicate a carcinogenic hazard to humans with the therapeutic use of indacaterol. No data are available to determine whether exposure to tobacco smoke enhances the respiratory tract toxicity of indacaterol.

Glycopyrronium

Carcinogenicity studies of six months duration in transgenic mice (rasH2) using oral administration and 2 years duration in rats using inhalation administration revealed no evidence of carcinogenicity with glycopyrronium bromide. The highest dose levels employed (75 and 100 mg/kg/day in male and female mice and 0.45 mg/kg/day in rats) were associated with systemic exposures (AUC) of approximately 55-fold higher in mice and 61-fold higher in rats than in humans at the maximum recommended dose of 50 µg once-daily. The lung deposited dose in rats (per unit alveolar surface area) was up to almost 200-fold higher than the level anticipated in patients.

Mometasone furoate

Mometasone furoate demonstrated no statistically significant increase in the incidence of tumours with inhalational administration at doses up to 160 µg/kg/day in a 19-month study in mice and at up to 67 µg/kg/day in a 2-year study in rats. These doses are approximately 2 times that in patients at the maximum recommended clinical dose of 260 µg/day (delivered dose), adjusted for body surface area.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule fill: Lactose monohydrate, Magnesium stearate.

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

Colourants: Iron oxide yellow, Indigotine.

Printing ink black: Purified water, Irone oxide black, Isopropyl alcohol, Propylene Glycol, Hypromellose.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C.

Store in the original package in order to protect from light and moisture.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl metacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

PA/Alu/PVC – Alu perforated unit-dose blister. Each blister contains 10 hard capsules.

Pack sizes:
Carton containing 30 Enerzair capsules, together with 1 Breezhaler inhaler.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

For correct administration/use of the product, please refer to section 4 Posology and Method of administration and the Instruction for use (IFU) in patient leaflet.

Each inhaler should be disposed of after all capsules have been used.

7 REGISTRATION HOLDER AND IMPORTER

Novartis Israel Ltd.,
POB 7126, Tel Aviv.

8. MARKETING AUTHORISATION NUMBER(S)

168-70-36695

Revised in Jul2022 according to MOHs guidelines