ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipient with known effect

Each capsule contains 25 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule (inhalation powder)

Capsule with green transparent cap and uncoloured transparent body containing a white powder, with the product code “IGM150-50-160” 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zimbus 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 a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

4.2 Posology and method of administration

Posology

The recommended dose is one capsule to be inhaled once daily.

The maximum recommended dose is 114 mcg/46 mcg/136 mcg once daily.

Treatment should be administered at the same time of the day each day. It can be administered irrespective of the time of the day. 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.

Special populations
Elderly
No dose adjustment is required in elderly patients (65 years of age or older) (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment. Caution should be observed in patients with severe renal impairment or end-stage renal disease requiring dialysis (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for the use of the medicinal product in patients 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).

Paediatric population
The safety and efficacy of Zimbus Breezhaler in paediatric patients below 18 years of age have not been established. No data are available.

Method of administration

For inhalation use only. The capsules must not be swallowed.

The capsules must be administered only using the inhaler provided (see section 6.6) with each new prescription.

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 medicinal product rather than inhaling it.

The capsules must only be removed from the blister immediately before use.

After inhalation, patients should rinse their mouth with water without swallowing (see sections 4.4 and 6.6).

For instructions on use of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

This medicinal product 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 treatment without physician supervision since symptoms may recur after discontinuation.

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 this medicinal product. 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, treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

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

Cardiovascular effects

Like other medicinal products containing beta$_2$-adrenergic agonists, this medicinal product 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.

This medicinal product 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 beta$_2$-adrenergic agonists (LABA) or LABA-containing combination products such as Zimbus 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.

Hypokalaemia with beta agonists

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe asthma, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias (see section 4.5).

Clinically relevant hypokalaemia has not been observed in clinical studies of indacaterol/glycopyrronium/mometasone furoate at the recommended therapeutic dose.

Hyperglycaemia

Inhalation of high doses of beta$_2$-adrenergic agonists and corticosteroids may produce increases in plasma glucose. Upon initiation of treatment, 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, this medicinal product 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 treatment 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, caution should be observed (see sections 4.2 and 5.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies were conducted with indacaterol/glycopyrronium/mometasone furoate. Information on the potential for interactions is based on the potential for each of the monotherapy components.

Medicinal products known to prolong the QTc interval

Like other medicinal products containing a beta$_2$-adrenergic agonist, this medicinal product 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 sections 4.4 and 5.1).

Hypokalaemic treatment

Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists (see section 4.4).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore, this medicinal product 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 Zimbus 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.

Due to the very low plasma concentration achieved after inhaled dosing, clinically significant interactions with mometasone furoate are unlikely. However, there may be a potential for increased systemic exposure to mometasone furoate when strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, nelfinavir, ritonavir, cobicistat) are co-administered.

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 this medicinal product 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 4.8 and 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data from the use of Zimbus 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 section 5.3). In animal reproduction studies with pregnant mice, rats and rabbits, mometasone furoate caused increased foetal malformations and decreased foetal survival and growth.

Like other medicinal products containing beta$_2$-adrenergic agonists, indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

This medicinal product should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding

There is no information available on the presence of indacaterol, glycopyrronium or mometasone furoate in human milk, on the effects on a breast-fed infant, 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.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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%).

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA system organ class (Table 1). The frequency of the adverse reactions is based on the IRIDIUM study. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse 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 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 disorders	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 disorders	Gastroenteritis*[8]	Common
	Dry mouth*[9]	Uncommon
Skin and subcutaneous tissue disorders	Rash*[10]	Uncommon
	Pruritus*[11]	Uncommon
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*[12]	Common
	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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

An overdose will likely produce signs, symptoms or adverse effects associated with the pharmacological actions of the individual components (e.g. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, increased intraocular pressure [causing pain, vision disturbances or reddening of the

eye], constipation or 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 hospitalised.

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

This medicinal product 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).

Indacaterol
The pharmacological effects of $beta_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to increased cyclic-3', 5'-adenosine monophosphate (cyclic AMP) levels, which cause relaxation of bronchial smooth muscle.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial 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.

Glycopyrronium
Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways. Glycopyrronium bromide is a high-affinity muscarinic receptor antagonist. 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).

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 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 leukotriene production and of the production of the Th2 cytokines IL-4 and IL-5 from human CD4+ T-cells.

Pharmacodynamic effects

The pharmacodynamic response profile of this medicinal product is characterised by rapid onset of action within 5 minutes after dosing and sustained effect over the whole 24-hour dosing interval.

The pharmacodynamic response profile is further characterised by increased mean peak forced expiratory volume in the first second (FEV_1) of 172 ml following indacaterol/glycopyrronium/mometasone furoate 114 mcg/46 mcg/136 mcg once daily compared to salmeterol/fluticasone 50 mcg/500 mcg twice daily.

No tachyphylaxis to the lung function benefits of Zimbus Breezhaler was observed over time.

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

Clinical efficacy and safety

Comparison of Zimbus Breezhaler to fixed combinations of LABA/ICS
The safety and efficacy of Zimbus 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 Zimbus 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 Zimbus Breezhaler 114 mcg/46 mcg/68 mcg once daily over indacaterol/mometasone furoate 125 mcg/127.5 mcg once daily or Zimbus 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.

Zimbus 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 2).

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 2.

Exacerbations were a secondary endpoint (not part of confirmatory testing strategy). Zimbus 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 2).

Results for the most clinically relevant endpoints are described in Table 2.

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

Endpoint	Time point/ Duration	Zimbus Breezhaler[1] vs IND/MF[2]	Zimbus Breezhaler[1] vs SAL/FP[3]
Lung function			
Trough FEV_1[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] Zimbus 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 Zimbus 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 Zimbus Breezhaler to the concurrent open-label administration of salmeterol/fluticasone + tiotropium
A randomised, partially-blinded, active-treatment-controlled, non-inferiority study (ARGON) comparing Zimbus 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.

Zimbus 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).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with indacaterol/glycopyrronium/mometasone furoate in one or more subsets of the paediatric population in asthma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following inhalation of Zimbus 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 the indacaterol/glycopyrronium/mometasone furoate combination and the monotherapy products. Steady-state plasma exposure to indacaterol, glycopyrronium and mometasone furoate after inhalation of the combination was similar to the systemic exposure after inhalation of indacaterol maleate, glycopyrronium or mometasone furoate as monotherapy products.

Following inhalation of the combination, 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-h 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 60 and 480 mcg (delivered dose). 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 inhaler. Steady state was achieved after 12 days. The mean accumulation ratio of mometasone furoate, i.e. AUC over the 24-h dosing interval on day 14 compared to day 1, was in the range of 1.28 to 1.40 for once-daily inhaled doses between 68 and 136 mcg as part of the indacaterol/glycopyrronium/mometasone furoate combination.

Following oral administration of mometasone furoate, the absolute oral systemic bioavailability of mometasone furoate was estimated to be very low (<2%).

Distribution

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

Glycopyrronium
After intravenous dosing, the steady-state volume of distribution (V_{ss}) of glycopyrronium was 83 litres and the volume of distribution in the terminal phase (V_z) was 376 litres. The apparent volume of distribution in the terminal phase following inhalation ($V_{z/F}$) was 7 310 litres, 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 peak levels achieved in plasma for a 44 mcg once-daily dosing regimen.

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

Biotransformation

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

In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolised indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6 and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low-affinity substrate for the efflux pump P-gp.

In vitro the UGT1A1 isoform is a major contributor to the metabolic clearance of indacaterol. However, as shown in a clinical study in populations with different UGT1A1 genotypes, systemic exposure to indacaterol is not significantly affected by the UGT1A1-genotype.

Glycopyrronium
In vitro metabolism studies showed consistent metabolic pathways for glycopyrronium bromide 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 catalysed 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 after 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 bromide 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 bromide 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 metabolised by CYP3A4.

Elimination

Indacaterol
In clinical studies which included urine collection, the amount of indacaterol excreted unchanged via urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 litres/hour. Compared with the serum clearance of indacaterol of 18.8 to 23.3 litres/hour, 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 in which 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 bromide 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.

Mean renal clearance of glycopyrronium was in the range of 17.4 and 24.4 litres/hour. 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 $T_{½}$ of approximately 4.5 hours. A radiolabelled, orally inhaled dose is excreted mainly in the faeces (74%) and to a lesser extent in the urine (8%).

Interactions

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.

Special populations

A population pharmacokinetic analysis in patients with asthma after inhalation of Zimbus 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.

Patients with renal impairment
The effect of renal impairment on the pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate has not been evaluated in dedicated studies with Zimbus Breezhaler. In a population pharmacokinetic analysis, estimated glomerular filtration rate (eGFR) was not a statistically significant covariate for systemic exposure of indacaterol, glycopyrronium and mometasone furoate following administration of Zimbus 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 (see sections 4.2 and 4.4).

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 Zimbus Breezhaler administration, AUC_{0-24h} 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. Based on a population pharmacokinetic 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.

Patients with 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 Zimbus Breezhaler. However, studies have been conducted with the monotherapy components indacaterol and mometasone furoate (see section 4.2).

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. 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 mcg 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 50 pcg/ml) were few.

Other special populations
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. Total systemic exposure (AUC) for glycopyrronium may be up to 1.8-fold higher in asthma patients with low body weight (35 kg) and up to 2.5-fold higher in asthma patients with low body weight (35 kg) and low absolute GFR (45 ml/min).

5.3 Preclinical safety data

No animal studies were performed with the combination of indacaterol, glycopyrronium and mometasone furoate. The non-clinical assessments of each monotherapy and of indacaterol/mometasone and indacaterol/glycopyrronium combination products are presented below:

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 was 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.

Following subcutaneous administration in a rabbit study, adverse effects of indacaterol with respect to pregnancy and embryonal/foetal development could only be demonstrated at doses more than 500-fold those achieved following daily inhalation of 150 mcg in humans (based on $AUC_{0\text{-}24\ h}$).

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 at an exposure 14-fold higher than in humans treated with indacaterol. Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

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.

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

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.

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 studies of reproductive function, subcutaneous mometasone furoate at 15 mcg/kg prolonged gestation and difficult labour occurred, with a reduction in offspring survival and body weight.

Environmental risk assessment (ERA)
Environmental risk assessment studies have shown that mometasone may pose a risk to surface water (see section 6.6).

Indacaterol and glycopyrronium combination

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

The effect on heart rate for indacaterol/glycopyrronium was increased in magnitude and duration 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate
Magnesium stearate

Capsule shell

Hypromellose
Carrageenan
Potassium chloride
Iron oxide, yellow (E172)
Indigo carmine (E132)
Water, purified

Printing ink

Water, purified
Iron oxide, black (E172)
Isopropyl alcohol
Propylene glycol (E1520)
Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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.

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.

Single pack containing 10 x 1, 30 x 1 or 90 x 1 hard capsules, together with 1 inhaler.
Multipacks containing 150 (15 packs of 10 x 1) hard capsules and 15 inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The inhaler provided with each new prescription should be used. The inhaler in each pack should be disposed of after all capsules in that pack have been used.

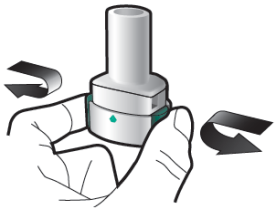
This medicinal product may pose a risk to the environment (see section 5.3).

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

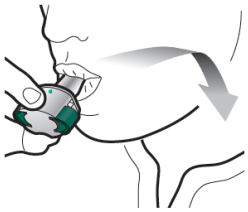
Instructions for handling and use

Please read the full **Instructions for Use** before using the Zimbus Breezhaler.

Insert



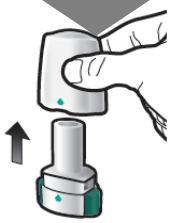
Pierce and release



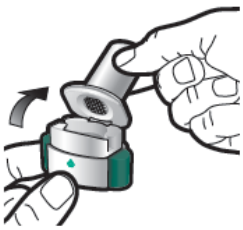
Inhale deeply

Check capsule is empty

1

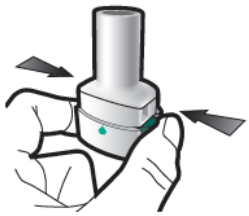


Step 1a:
Pull off cap



Step 1b:
Open inhaler

2



Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time.

You should hear a noise as the capsule is pierced. Only pierce the capsule once.

Step 2b:
Release side buttons

3

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

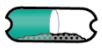
Step 3b:
Inhale medicine deeply
Hold the inhaler as shown in the picture. Place the mouthpiece in your mouth and close your lips firmly around it.
Do not press the side buttons.

Check

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

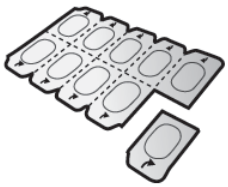
If there is powder left in the capsule:

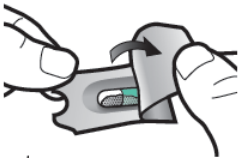
- Close the inhaler.
- Repeat steps 3a to 3d.



Powder remaining

Empty





Step 1c:
Remove capsule
Separate one of the blisters from the blister card.
Peel open the blister and remove the capsule.
Do not push the capsule through the foil.
Do not swallow the capsule.

Breathe in quickly and as deeply as you can.
During inhalation you will hear a whirring noise.
You may taste the medicine as you inhale.

Step 3c:
Hold breath
Hold your breath for up to 5 seconds.

Step 3d:
Rinse mouth
Rinse your mouth with water after each dose and spit it out.

Remove empty capsule
Put the empty capsule in your household waste.
Close the inhaler and replace the cap.

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

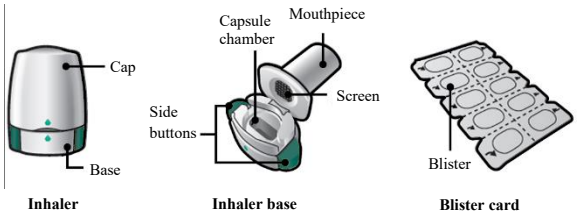
Step 1e:
Close inhaler

Important Information

- Zimbus Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the Zimbus Breezhaler capsules with any other inhaler.
- Do not use the Zimbus Breezhaler inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Do not blow into the mouthpiece.
- Do not press the side buttons while inhaling through the mouthpiece.
- Do not handle capsules with wet hands.
- Never wash your inhaler with water.

Your Zimbus Breezhaler Inhaler pack contains:

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



Frequently Asked Questions

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

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

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1440/001
EU/1/20/1440/002
EU/1/20/1440/004
EU/1/20/1440/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 July 2020
Date of latest renewal: 12 February 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium/mometasone furoate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 114 micrograms indacaterol (as acetate), 46 micrograms glycopyrronium (equivalent to 58 micrograms glycopyrronium bromide) and 136 micrograms mometasone furoate.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate and magnesium stearate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

10 x 1 capsules + 1 inhaler
30 x 1 capsules + 1 inhaler
90 x 1 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Do not swallow capsules.
Inhalation use
Treatment for 90 days.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1440/001	10 x 1 capsules + 1 inhaler
EU/1/20/1440/002	30 x 1 capsules + 1 inhaler
EU/1/20/1440/004	90 x 1 capsules + 1 inhaler

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zimbus Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium/mometasone furoate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 114 micrograms indacaterol (as acetate), 46 micrograms glycopyrronium (equivalent to 58 micrograms glycopyrronium bromide) and 136 micrograms mometasone furoate.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate and magnesium stearate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

Multipack: 150 (15 packs of 10 x 1) capsules + 15 inhalers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Do not swallow capsules.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1440/005 150 (15 packs of 10 x 1) capsules + 15 inhalers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zimbus Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium/mometasone furoate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 114 micrograms indacaterol (as acetate), 46 micrograms glycopyrronium (equivalent to 58 micrograms glycopyrronium bromide) and 136 micrograms mometasone furoate.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate and magnesium stearate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

10 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Do not swallow capsules.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1440/005 150 (15 packs of 10 x 1) capsules + 15 inhalers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zimbus Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF

- **OUTER CARTON OF UNIT PACK**
- **INTERMEDIATE CARTON OF MULTIPACK**

1. OTHER

1	Insert
2	Pierce and release
3	Inhale deeply
Check	Check capsule is empty

Read the leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zimbus Breezhaler 114 mcg/46 mcg/136 mcg inhalation powder
indacaterol/glycopyrronium/mometasone furoate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use only

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium/mometasone furoate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Zimbus Breezhaler is and what it is used for

What Zimbus Breezhaler is and how it works
Zimbus Breezhaler contains three active substances:
- indacaterol
- glycopyrronium
- mometasone furoate

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

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

What Zimbus Breezhaler is used for
Zimbus Breezhaler is used regularly as treatment for asthma in adults.

Asthma is a serious, long-term lung disease where the muscles around the smaller airways become tight (bronchoconstriction) and inflamed. Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough.

You should use Zimbus Breezhaler every day and not only when you have breathing problems or other symptoms of asthma. This will ensure that it controls your asthma properly. Do not use this medicine to relieve a sudden attack of breathlessness or wheezing.

If you have any questions about how Zimbus Breezhaler works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use Zimbus Breezhaler

Follow all the doctor's instructions carefully.

Do not use Zimbus Breezhaler
- if you are allergic to indacaterol, glycopyrronium, mometasone furoate, or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

Warnings and precautions
Talk to your doctor, pharmacist or nurse **before** using Zimbus Breezhaler if any of the following applies to you:
- if you have heart problems, including an irregular or fast heartbeat.
- if you have thyroid gland problems.
- if you have ever been told you have diabetes or high blood sugar.
- if you suffer from seizures or fits.
- if you have severe kidney problems.
- if you have severe liver problems.
- if you have a low level of potassium in your blood.
- if you have an eye problem called angle-closure glaucoma.
- if you have difficulty passing urine.
- if you have tuberculosis (TB) of the lung, or any long standing or untreated infections.

During treatment with Zimbus Breezhaler
Stop using this medicine and get medical help immediately if you have any of the following:
- tightness of the chest, coughing, wheezing or breathlessness immediately after using Zimbus Breezhaler (signs the medicine is unexpectedly tightening the airways, known as paradoxical bronchospasm).
- difficulty breathing or swallowing, swelling of the tongue, lips or face, skin rash, itching and hives (signs of allergic reaction).
- eye pain or discomfort, temporary blurring of vision, visual haloes (seeing bright circles around lights) or coloured images in association with red eyes (signs of an attack of angle-closure glaucoma).

Children and adolescents
Do not give this medicine to children or adolescents (below the age of 18 years) because it has not been studied in this age group.

Other medicines and Zimbus Breezhaler
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular, tell your doctor or pharmacist if you are using:
- medicines that decrease the level of potassium in your blood. These include diuretics (which increase urine production and can be used to treat high blood pressure, e.g. hydrochlorothiazide), other bronchodilators such as methylxanthines used for breathing problems (e.g. theophylline) or corticosteroids (e.g. prednisolone).
- tricyclic antidepressants or monoamine oxidase inhibitors (medicines used in the treatment of depression).
- any medicines that may be similar to Zimbus Breezhaler (contain similar active substances); using them together may increase the risk of possible side effects.
- medicines called beta blockers used to treat high blood pressure or other heart problems (e.g. propranolol) or to treat glaucoma (e.g. timolol).
- ketoconazole or itraconazole (medicines used to treat fungal infections).
- ritonavir, nelfinavir or cobicistat (medicines used to treat HIV infection).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you whether you can use Zimbus Breezhaler.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines.

Zimbus Breezhaler contains lactose
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to use Zimbus Breezhaler

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Zimbus Breezhaler to inhale
The usual dose is to inhale the content of one capsule each day. You only need to use the medicine once a day. Do not use more than your doctor tells you to use.

You should use Zimbus Breezhaler every day, even when your asthma is not troubling you.

When to inhale Zimbus Breezhaler
Inhale Zimbus Breezhaler at the same time each day. This will help control your symptoms throughout the day and night. It will also help you to remember to use it.

How to inhale Zimbus Breezhaler
- Zimbus Breezhaler is for inhalation use.
- In this pack, you will find an inhaler and capsules that contain the medicine. The inhaler enables you to inhale the medicine in the capsule. Only use the capsules with the inhaler provided in this pack. The capsules should remain in the blister until you need to use them.
- Peel the backing away from the blister to open it, **do not push the capsule through the foil**.
- When you start a new pack, use the new inhaler supplied in this new pack.
- Dispose of the inhaler in each pack after all capsules in that pack have been used.
- Do not swallow the capsules.
- **Please read the instructions for use on the other side of this leaflet for more information on how to use the inhaler.**

If your symptoms do not improve
If your asthma is not getting better or if it gets worse after you have started using Zimbus Breezhaler, talk to your doctor.

If you use more Zimbus Breezhaler than you should
If you accidently inhale too much of this medicine, contact your doctor or hospital for advice immediately. You may need medical attention.

If you forget to use Zimbus Breezhaler
If you forget to inhale a dose at the usual time, inhale one as soon as possible on that day. Then inhale the next dose at the usual time on the next day. Do not inhale two doses on the same day.

If you stop using Zimbus Breezhaler
Do not stop using Zimbus Breezhaler unless your doctor tells you to. Your asthma symptoms may come back if you stop using it.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious
Stop using Zimbus Breezhaler and get medical help immediately if you have any of the following:

Common: may affect up to 1 in every 10 people
- difficulty breathing or swallowing, swelling of the tongue, lips or face, skin rash, itching and hives (signs of allergic reaction).

Other side effects
Other side effects include the following listed below. If these side effects become severe, please tell your doctor, pharmacist or nurse.

Very common: may affect more than 1 in 10 people
- sore throat, runny nose (nasopharyngitis)
- sudden difficulty breathing and feeling of tightness in chest with wheezing or coughing (asthma exacerbation)

Common: may affect up to 1 in every 10 people
- oral thrush (sign of candidiasis). After you have finished taking your dose, rinse your mouth with water or a mouthwash solution and then spit this out. This will help to prevent thrush.
- a frequent urge to urinate and pain or burning when urinating (signs of urinary tract infection)
- headache
- fast heart beat
- cough
- voice alteration (hoarseness)
- diarrhoea, abdominal cramps, nausea, and vomiting (gastroenteritis)
- pain in muscles, bones or joints (signs of musculoskeletal pain)
- muscle spasm
- fever
- upper respiratory tract infection
- oropharyngeal pain

Uncommon: may affect up to 1 in every 100 people
- dry mouth
- rash
- high level of sugar in the blood (hyperglycaemia)
- skin itching
- difficulty and pain when passing urine (signs of dysuria)
- clouding of the lens of your eyes (signs of cataract)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zimbus Breezhaler

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Store the capsules in the original blister, in order to protect from light and moisture, and do not remove until immediately before use.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zimbus Breezhaler contains

- The active substances are indacaterol (as acetate), glycopyrronium (as bromide) and mometasone furoate. Each capsule contains 150 micrograms indacaterol (as acetate), 63 micrograms 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 micrograms indacaterol (as acetate), 58 micrograms glycopyrronium bromide (equivalent to 46 micrograms glycopyrronium) and 136 micrograms mometasone furoate.
- The other ingredients of the capsule are lactose monohydrate and magnesium stearate (see "Zimbus Breezhaler contains lactose" in section 2).
- The ingredients of the capsule shell are hypromellose, carrageenan, potassium chloride, iron oxide, yellow (E172), indigo carmine (E132), water, purified and printing ink.
    - The ingredients of the printing ink are iron oxide, black (E172), isopropyl alcohol, propylene glycol (E1520), hypromellose (E464) and water, purified.

What Zimbus Breezhaler looks like and contents of the pack

In this pack, you will find an inhaler together with capsules in blisters. The capsules are transparent and contain a white powder. They have a black product code "IGM150-50-160" printed above two black bars on the body with a logo printed in black and surrounded by a black bar on the cap.

The following pack sizes are available:
Single pack containing 10 x 1, 30 x 1 or 90 x 1 hard capsules, together with 1 inhaler.
Multipacks comprising 15 cartons, each containing 10 x 1 hard capsules together with 1 inhaler.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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Novartis Pharma GmbH
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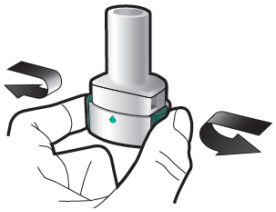
This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

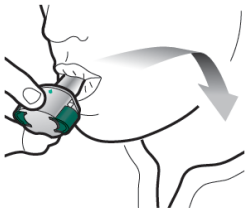
Instructions for Use of Zimbus Breezhaler

Please read full instructions for use of Zimbus Breezhaler inhaler before use.

Insert



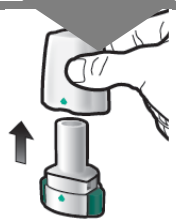
Pierce and release



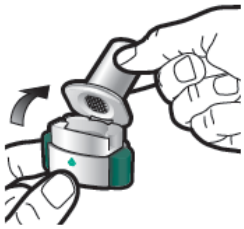
Inhale deeply

Check capsule is empty

1

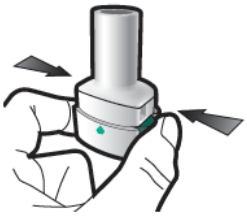


Step 1a:
Pull off cap



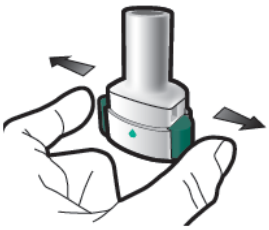
Step 1b:
Open inhaler

2



Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time.

You should hear a noise as the capsule is pierced. Only pierce the capsule once.



Step 2b:
Release side buttons

3

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

Step 3b:
Inhale medicine deeply
Hold the inhaler as shown in the picture. Place the mouthpiece in your mouth and close your lips firmly around it.
Do not press the side buttons.

Check

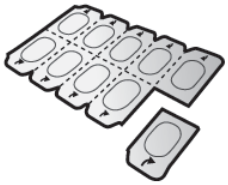
Check capsule is empty
Open the inhaler to see if any powder is left in the capsule.

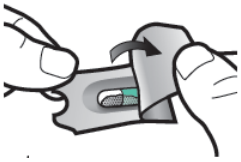
If there is powder left in the capsule:

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

Powder remaining

Empty





Step 1c:
Remove capsule
Separate one of the blisters from the blister card.
Peel open the blister and remove the capsule.
Do not push the capsule through the foil.
Do not swallow the capsule.

Breathe in quickly and as deeply as you can.
During inhalation you will hear a whirring noise.
You may taste the medicine as you inhale.

Step 3c:
Hold breath
Hold your breath for up to 5 seconds.

Step 3d:
Rinse mouth
Rinse your mouth with water after each dose and spit it out.

Remove empty capsule
Put the empty capsule in your household waste.
Close the inhaler and replace the cap.

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

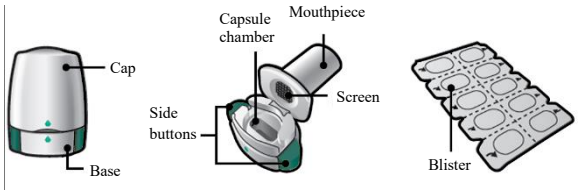
Step 1e:
Close inhaler

Important Information

- Zimbus Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the Zimbus Breezhaler capsules with any other inhaler.
- Do not use the Zimbus Breezhaler inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Do not blow into the mouthpiece.
- Do not press the side buttons while inhaling through the mouthpiece.
- Do not handle capsules with wet hands.
- Never wash your inhaler with water.

Your Zimbus Breezhaler Inhaler pack contains:

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



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

Frequently Asked Questions

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

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

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

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

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

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