ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hirobriz Breezhaler 150 microgram inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains indacaterol maleate equivalent to 150 microgram indacaterol.

The delivered dose leaving the mouthpiece of the inhaler is indacaterol maleate equivalent to 120 microgram indacaterol.

Excipient with known effect

Each capsule contains 24.8 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Transparent (uncoloured) capsules containing a white powder, with "IDL 150" printed in black above a black bar and company logo (⏻) printed in black below the black bar.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hirobriz Breezhaler is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology

The recommended dose is the inhalation of the content of one 150 microgram capsule once a day, using the Hirobriz Breezhaler inhaler. The dose should only be increased on medical advice.

The inhalation of the content of one 300 microgram capsule once a day, using the Hirobriz Breezhaler inhaler has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The maximum dose is 300 microgram once daily.

Hirobriz Breezhaler should be administered at the same time of the day each day.

If a dose is missed the next dose should be taken at the usual time the next day.

Special populations
Elderly population
Maximum plasma concentration and overall systemic exposure increase with age but no dose adjustment is required in elderly patients.

Hepatic impairment
No dose adjustment is required for patients with mild and moderate hepatic impairment. There are no data available for use of Hirobriz Breezhaler in patients with severe hepatic impairment.

Renal impairment
No dose adjustment is required for patients with renal impairment.

Paediatric population
There is no relevant use of Hirobriz Breezhaler in the paediatric population (under 18 years).

Method of administration

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

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

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

Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Asthma

Hirobriz Breezhaler is a long-acting beta$_2$-adrenergic agonist, which is only indicated for COPD and should not be used in asthma due to the absence of long-term outcome data in asthma.

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

Hypersensitivity

Immediate hypersensitivity reactions have been reported after administration of Hirobriz Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Hirobriz Breezhaler should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

As with other inhalation therapy, administration of Hirobriz Breezhaler may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs Hirobriz Breezhaler should be discontinued immediately and alternative therapy substituted.

Deterioration of disease

Hirobriz Breezhaler is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. In the event of deterioration of COPD during treatment with Hirobriz Breezhaler, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. An increase in the daily dose of Hirobriz Breezhaler beyond the maximum dose of 300 microgram is not appropriate.

Systemic effects

Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of Hirobriz Breezhaler at the recommended doses, as with other beta$_2$-adrenergic agonists, indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

Cardiovascular effects

Like other beta$_2$-adrenergic agonists, indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of QT interval and ST segment depression, although the clinical significance of these observations is unknown. Therefore, long-acting beta$_2$-adrenergic agonists (LABA) or LABA containing products such as Hirobriz Breezhaler should be used with caution in patients with known or suspected prolongation of the QT interval or treated with medicinal products affecting the QT interval.

Hypokalaemia

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 COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia

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

During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1-2% on Hirobriz Breezhaler at the recommended doses than on placebo. Hirobriz Breezhaler has not been investigated in patients with not well controlled diabetes mellitus.

Excipients

The capsules contain 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

Sympathomimetic medicinal products

Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) may potentiate adverse reactions to Hirobriz Breezhaler.

Hirobriz Breezhaler should not be used in conjunction with other long-acting beta$_2$-adrenergic agonists or medicinal products containing long-acting beta$_2$-adrenergic agonists.

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, therefore caution is required (see section 4.4).

Beta-adrenergic blockers

Beta-adrenergic blockers and beta$_2$-adrenergic agonists may weaken or antagonise the effect of each other when administered concurrently. Therefore indacaterol should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Metabolic and transporter based interactions

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp) raises the systemic exposure of indacaterol by up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with Hirobriz Breezhaler in clinical studies of up to one year at doses up to twice the maximum recommended therapeutic dose.

Indacaterol has not been shown to cause interactions with medicinal products administered concomitantly. *In vitro* investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medicinal products at the systemic exposure levels achieved in clinical practice.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of indacaterol in pregnant women available. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3). Like other beta$_2$-adrenergic agonists, indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Hirobriz Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding

It is not known whether indacaterol/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of indacaterol/metabolites in milk (see section 5.3). A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Hirobriz Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

A decreased pregnancy rate has been observed in rats. Nevertheless, it is considered unlikely that indacaterol will affect reproductive or fertility performance in humans following inhalation of the maximum recommended dose (see section 5.3).

4.7 Effects on ability to drive and use machines

Hirobriz Breezhaler 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 at the recommended doses were nasopharyngitis (14.3%), upper respiratory tract infection (14.2%), cough (8.2%), headache (3.7%) and muscle spasms (3.5%). These were in the vast majority mild or moderate and became less frequent if treatment was continued.

At the recommended doses, the adverse reaction profile of Hirobriz Breezhaler in patients with COPD shows clinically insignificant systemic effects of $beta_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per minute, and tachycardia was infrequent and reported at a similar rate as under placebo treatment. Relevant prolongations of QT_cF were not detectable in comparison to placebo. The frequency of notable QT_cF intervals [i.e. >450 ms (males) and >470 ms (females)] and reports of hypokalaemia were similar to placebo. The mean of the maximum changes in blood glucose were similar between Hirobriz Breezhaler and placebo.

Tabulated summary of adverse reactions

The Hirobriz Breezhaler Phase III clinical development programme involved patients with a clinical diagnosis of moderate to severe COPD. 4,764 patients were exposed to indacaterol up to one year at doses up to twice the maximum recommended dose. Of these patients, 2,611 were on treatment with 150 microgram once daily and 1,157 on treatment with 300 microgram once daily. Approximately 41% of patients had severe COPD. The mean age of patients was 64 years, with 48% of patients aged 65 years or older, and the majority (80%) was Caucasian.

Adverse reactions in Table 1 are listed according to MedDRA system organ class in the COPD safety database. Within each system organ class, adverse reactions are ranked by frequency in descending order according to the following convention: 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), not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse reactions	Frequency category
Infections and infestations	
Upper respiratory tract infection	Common
Nasopharyngitis	Common
Sinusitis	Common
Immune system disorders	
Hypersensitivity[1]	Uncommon
Metabolism and nutrition disorders	
Diabetes mellitus and hyperglycaemia	Uncommon
Nervous system disorders	
Headache	Common
Dizziness	Common
Paraesthesia	Uncommon
Cardiac disorders	
Ischaemic heart disease	Uncommon
Atrial fibrillation	Uncommon
Palpitations	Uncommon
Tachycardia	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Oropharyngeal pain including throat irritation	Common
Rhinorrhoea	Common
Paradoxical bronchospasm	Uncommon
Skin and subcutaneous tissue disorders	
Pruritus/rash	Uncommon
Musculoskeletal and connective tissue disorders	
Muscle spasm	Common
Myalgia	Uncommon
Musculoskeletal pain	Uncommon
General disorders and administration site conditions	
Chest pain	Common
Peripheral oedema	Common

[1] Reports of hypersensitivity have been received from post-approval marketing experience in association with the use of Hirobriz Breezhaler. These were reported voluntarily from a population of uncertain size, and it is therefore not always possible to reliably estimate the frequency or establish a causal relationship to exposure to the medicinal product. Therefore the frequency was calculated from clinical trial experience.

At 600 microgram once-daily, the safety profile of Hirobriz Breezhaler was overall similar to that of recommended doses. An additional adverse reaction was tremor (common).

Description of selected adverse reactions

In Phase III clinical studies, healthcare providers observed during clinic visits that on average 17-20% of patients experienced a sporadic cough that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds (about 10 seconds in current smokers). It was observed with a higher frequency in female than in male patients and in current smokers than in ex-smokers. This cough experienced post inhalation did not lead to any patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 8.2% of patients reported cough as an adverse event). There is no evidence that cough experienced post inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy.

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

In COPD patients, single doses of 10 times the maximum recommended therapeutic dose were associated with a moderate increase in pulse rate, systolic blood pressure and QT_c interval.

An overdose of indacaterol is likely to lead to exaggerated effects typical of $beta_2$-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. Use of cardioselective beta blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, selective beta-2-adrenoreceptor agonists, ATC code: R03AC18

Mechanism of action

The pharmacological effects of $beta_2$-adrenoceptor agonists are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol, a long-acting $beta_2$-adrenergic agonist, has more than 24-fold greater agonist activity at $beta_2$-receptors compared to $beta_1$-receptors and 20-fold greater agonist activity compared to $beta_3$-receptors.

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 $beta_2$-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 10-50% 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.

Pharmacodynamic effects

Hirobriz Breezhaler, administered once a day at doses of 150 and 300 microgram consistently provided clinically significant improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours across a number of clinical pharmacodynamic and efficacy studies. There was a rapid onset of action within 5 minutes after inhalation, with an increase in FEV_1 relative to baseline of 110-160 ml, comparable to the effect of the fast-acting $beta_2$-agonist salbutamol 200 microgram and statistically significantly faster compared to salmeterol/fluticasone 50/500 microgram. Mean peak improvements in FEV_1 relative to baseline were 250-330 ml at steady state.

The bronchodilator effect did not depend on the time of dosing, morning or evening.

Hirobriz Breezhaler was shown to reduce lung hyperinflation, resulting in increased inspiratory capacity during exercise and at rest, compared to placebo.

Effects on cardiac electrophysiology
A double-blind, placebo- and active (moxifloxacin)-controlled study for 2 weeks in 404 healthy volunteers demonstrated maximum mean (90% confidence intervals) prolongations of the QT_cF interval (in milliseconds) of 2.66 (0.55, 4.77) 2.98 (1.02, 4.93) and 3.34 (0.86, 5.82) following multiple doses of 150 microgram, 300 microgram and 600 microgram, respectively. There was no evidence of a concentration-delta QT_c relationship in the range of doses evaluated.

As demonstrated in 605 patients with COPD in a 26-week, double-blind, placebo-controlled Phase III study, there was no clinically relevant difference in the development of arrhythmic events monitored over 24 hours, at baseline and up to 3 times during the 26-week treatment period, between patients receiving recommended doses of Hirobriz Breezhaler treatment and those patients who received placebo or treatment with tiotropium.

Clinical efficacy and safety

The clinical development programme included one 12-week, two six-month (one of which was extended to one year to evaluate safety and tolerability) and one one-year randomised controlled studies in patients with a clinical diagnosis of COPD. These studies included measures of lung function and of health outcomes such as dyspnoea, exacerbations and health-related quality of life.

Lung function
Hirobriz Breezhaler, administered once a day at doses of 150 microgram and 300 microgram, showed clinically meaningful improvements in lung function. At the 12-week primary endpoint (24-hour trough FEV_1), the 150 microgram dose resulted in a 130-180 ml increase compared to placebo ($p<0.001$) and a 60 ml increase compared to salmeterol 50 microgram twice a day ($p<0.001$). The 300 microgram dose resulted in a 170-180 ml increase compared to placebo ($p<0.001$) and a 100 ml increase compared to formoterol 12 microgram twice a day ($p<0.001$). Both doses resulted in an increase of 40-50 ml over open-label tiotropium 18 microgram once a day (150 microgram, $p=0.004$; 300 microgram, $p=0.01$). The 24-hour bronchodilator effect of Hirobriz Breezhaler was maintained from the first dose throughout a one-year treatment period with no evidence of loss in efficacy (tachyphylaxis).

Symptomatic benefits

Both doses demonstrated statistically significant improvements in symptom relief over placebo for dyspnoea and health status (as evaluated by Transitional Dyspnoea Index [TDI] and St. George's Respiratory Questionnaire [SGRQ], respectively). The magnitude of response was generally greater than seen with active comparators (Table 2). In addition, patients treated with Hirobriz Breezhaler required significantly less rescue medication, had more days when no rescue medication was needed compared to placebo and had a significantly improved percentage of days with no daytime symptoms.

Pooled efficacy analysis over 6 months' treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparison compared to placebo showed a ratio of rates of 0.68 (95% CI [0.47, 0.98]; p-value 0.036) and 0.74 (95% CI [0.56, 0.96]; p-value 0.026) for 150 microgram and 300 microgram, respectively.

Limited treatment experience is available in individuals of African descent.

Table 2 Symptom relief at 6 months treatment duration

Treatment Dose (microgram)	**Indacaterol 150 once a day**	**Indacaterol 300 once a day**	**Tiotropium 18 once a day**	**Salmeterol 50 twice a day**	**Formoterol 12 twice a day**	**Placebo**
Percentage of patients who achieved MCID TDI†	57 [a] 62 [b]	71 [b] 59 [c]	57 [b]	54 [a]	54 [c]	45 [a] 47 [b] 41 [c]
Percentage of patients who achieved MCID SGRQ†	53 [a] 58 [b]	53 [b] 55 [c]	47 [b]	49 [a]	51 [c]	38 [a] 46 [b] 40 [c]
Reduction in puffs/day of rescue medication use vs. baseline	1.3 [a] 1.5 [b]	1.6 [b]	1.0 [b]	1.2 [a]	n/e	0.3 [a] 0.4 [b]
Percentage of days with no rescue medication use	60 [a] 57 [b]	58 [b]	46 [b]	55 [a]	n/e	42 [a] 42 [b]

Study design with [a]: indacaterol 150 microgram, salmeterol and placebo; [b]: indacaterol 150 and 300 microgram, tiotropium and placebo; [c]: indacaterol 300 microgram, formoterol and placebo
† MCID = minimal clinically important difference (≥1 point change in TDI, ≥4 point change in SGRQ)
n/e= not evaluated at six months

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Hirobriz Breezhaler in all subsets of the paediatric population in chronic obstructive pulmonary disease (COPD) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Indacaterol is a chiral molecule with R-configuration.

Pharmacokinetic data were obtained from a number of clinical studies, from healthy volunteers and COPD patients.

Absorption

The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 microgram to 600 microgram) in a dose proportional manner. Absolute bioavailability of indacaterol after an inhaled dose was on average 43% to 45%. 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.

Indacaterol serum 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 3.5 for once-daily inhaled doses between 150 microgram and 600 microgram.

Distribution

After intravenous infusion the volume of distribution of indacaterol during the terminal elimination phase was 2557 litres indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1-95.3% and 95.1-96.2%, respectively.

Biotransformation

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, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 is 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.

Elimination

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. When compared with the serum clearance of indacaterol of 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 5% 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 12-14 days.

Special populations

A population pharmacokinetic analysis showed that there is no clinically relevant effect of age (adults up to 88 years), sex, weight (32-168 kg) or race on the pharmacokinetics of indacaterol. It did not suggest any difference between ethnic subgroups in this population.

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.

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

5.3 Preclinical safety data

Effects on the cardiovascular system attributable to the $beta_2$-agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritancy of the nasal cavity and larynx were seen in rodents. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F_1 offspring was observed in the peri- and post-developmental rat study at an exposure 14-fold higher than in humans treated with Hirobriz Breezhaler. Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

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. Systemic exposures (AUC) in rats and mice at the no-observed adverse effect levels in these studies were at least 7- and 49-fold higher, respectively, than in humans treated with Hirobriz Breezhaler once a day at a dose of 300 microgram.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate

Capsule shell

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the blister in order to protect from moisture and only remove immediately before use.

6.5 Nature and contents of container

Hirobriz Breezhaler is a single-dose inhalation device. Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl methacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

PA/Alu/PVC - Alu blister containing 10 hard capsules.

Carton containing 10 capsules and one Hirobriz Breezhaler inhaler.
Carton containing 30 capsules and one Hirobriz Breezhaler inhaler.

Multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

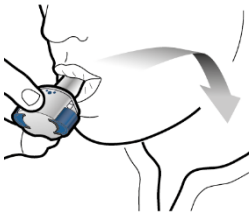
Each inhaler should be disposed of after all capsules have been used.

Instructions for handling and use

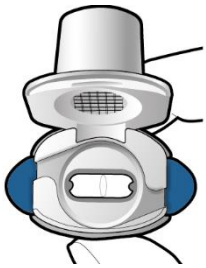
Please read the full **Instructions for Use** before using the Hirobriz Breezhaler.

Insert

Pierce and release

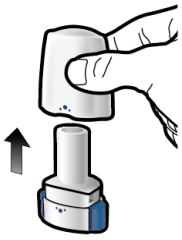


Inhale deeply

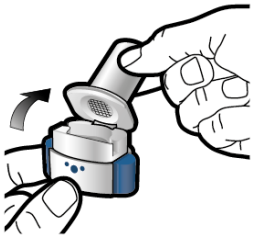


Check capsule is empty

1

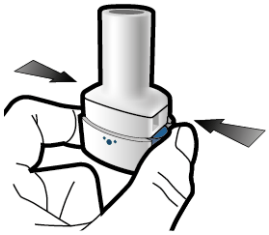


Step 1a:
Pull off cap

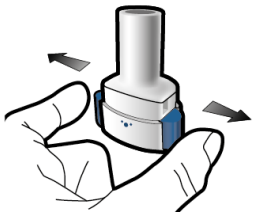


Step 1b:
Open inhaler

2



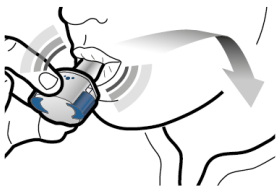
Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced.
Only pierce the capsule once.



Step 2b:
Release side buttons

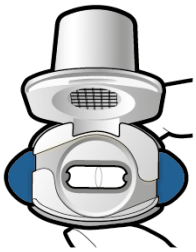
3

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.

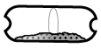
Check



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

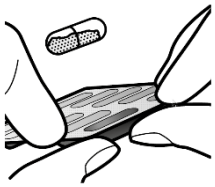
If there is powder left in the capsule:

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



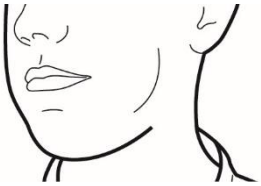
Powder remaining

Empty

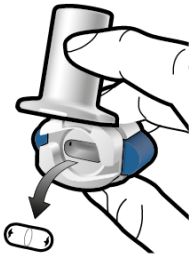


Step 1c:
Remove capsule
Remove one capsule from the blister.
Do not swallow the capsule.

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.

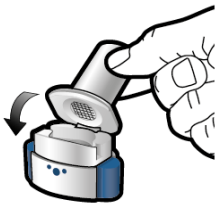


Step 3c:
Hold breath
Hold your breath for up to 5 seconds.



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.



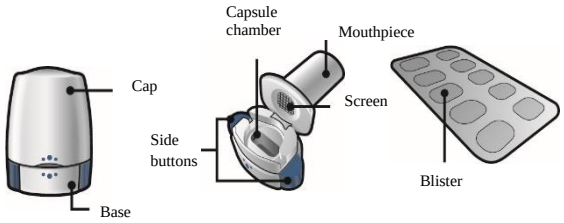
Step 1e:
Close inhaler

Important Information

- Hirobriz Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not swallow the capsule.
- Do not use the Hirobriz Breezhaler capsules with any other inhaler.
- Do not use the Hirobriz 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 Hirobriz Breezhaler Inhaler pack contains:

- One Hirobriz Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Hirobriz 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 3c.

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 3c.

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/1/09/594/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 November 2009
Date of latest renewal: 18 September 2014

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Hirobriz Breezhaler 300 microgram inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains indacaterol maleate equivalent to 300 microgram indacaterol.

The delivered dose leaving the mouthpiece of the inhaler is indacaterol maleate equivalent to 240 microgram indacaterol.

Excipient with known effect

Each capsule contains 24.6 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Transparent (uncoloured) capsules containing a white powder, with “IDL 300” printed in blue above a blue bar and company logo (⏻) printed in blue below the blue bar.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hirobriz Breezhaler is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology

The recommended dose is the inhalation of the content of one 150 microgram capsule once a day, using the Hirobriz Breezhaler inhaler. The dose should only be increased on medical advice.

The inhalation of the content of one 300 microgram capsule once a day, using the Hirobriz Breezhaler inhaler has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The maximum dose is 300 microgram once daily.

Hirobriz Breezhaler should be administered at the same time of the day each day.

If a dose is missed the next dose should be taken at the usual time the next day.

Special populations
Elderly population
Maximum plasma concentration and overall systemic exposure increase with age but no dose adjustment is required in elderly patients.

Hepatic impairment
No dose adjustment is required for patients with mild and moderate hepatic impairment. There are no data available for use of Hirobriz Breezhaler in patients with severe hepatic impairment.

Renal impairment
No dose adjustment is required for patients with renal impairment.

Paediatric population
There is no relevant use of Hirobriz Breezhaler in the paediatric population (under 18 years).

Method of administration

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

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

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

Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Asthma

Hirobriz Breezhaler is a long-acting $beta_2$-adrenergic agonist, which is only indicated for COPD and should not be used in asthma due to the absence of long-term outcome data in asthma.

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

Hypersensitivity

Immediate hypersensitivity reactions have been reported after administration of Hirobriz Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Hirobriz Breezhaler should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

As with other inhalation therapy, administration of Hirobriz Breezhaler may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs Hirobriz Breezhaler should be discontinued immediately and alternative therapy substituted.

Deterioration of disease

Hirobriz Breezhaler is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. In the event of deterioration of COPD during treatment with Hirobriz Breezhaler, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. An increase in the daily dose of Hirobriz Breezhaler beyond the maximum dose of 300 microgram is not appropriate.

Systemic effects

Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of Hirobriz Breezhaler at the recommended doses, as with other beta$_2$-adrenergic agonists, indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

Cardiovascular effects

Like other beta$_2$-adrenergic agonists, indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of QT interval and ST segment depression, although the clinical significance of these observations is unknown. Therefore, long-acting beta$_2$-adrenergic agonists (LABA) or LABA containing products such as Hirobriz Breezhaler should be used with caution in patients with known or suspected prolongation of the QT interval or treated with medicinal products affecting the QT interval.

Hypokalaemia

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 COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia

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

During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1-2% on Hirobriz Breezhaler at the recommended doses than on placebo. Hirobriz Breezhaler has not been investigated in patients with not well controlled diabetes mellitus.

Excipients

The capsules contain 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

Sympathomimetic medicinal products

Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) may potentiate adverse reactions to Hirobriz Breezhaler.

Hirobriz Breezhaler should not be used in conjunction with other long-acting beta$_2$-adrenergic agonists or medicinal products containing long-acting beta$_2$-adrenergic agonists.

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, therefore caution is required (see section 4.4).

Beta-adrenergic blockers

Beta-adrenergic blockers and beta$_2$-adrenergic agonists may weaken or antagonise the effect of each other when administered concurrently. Therefore indacaterol should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Metabolic and transporter based interactions

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp) raises the systemic exposure of indacaterol by up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with Hirobriz Breezhaler in clinical studies of up to one year at doses up to twice the maximum recommended therapeutic dose.

Indacaterol has not been shown to cause interactions with medicinal products administered concomitantly. *In vitro* investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medicinal products at the systemic exposure levels achieved in clinical practice.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of indacaterol in pregnant women available. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3). Like other beta$_2$-adrenergic agonists, indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Hirobriz Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding

It is not known whether indacaterol/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of indacaterol/metabolites in milk (see section 5.3). A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Hirobriz Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

A decreased pregnancy rate has been observed in rats. Nevertheless, it is considered unlikely that indacaterol will affect reproductive or fertility performance in humans following inhalation of the maximum recommended dose (see section 5.3).

4.7 Effects on ability to drive and use machines

Hirobriz Breezhaler 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 at the recommended doses were nasopharyngitis (14.3%), upper respiratory tract infection (14.2%), cough (8.2%), headache (3.7%) and muscle spasms (3.5%). These were in the vast majority mild or moderate and became less frequent if treatment was continued.

At the recommended doses, the adverse reaction profile of Hirobriz Breezhaler in patients with COPD shows clinically insignificant systemic effects of $beta_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per minute, and tachycardia was infrequent and reported at a similar rate as under placebo treatment. Relevant prolongations of QT_cF were not detectable in comparison to placebo. The frequency of notable QT_cF intervals [i.e. >450 ms (males) and >470 ms (females)] and reports of hypokalaemia were similar to placebo. The mean of the maximum changes in blood glucose were similar between Hirobriz Breezhaler and placebo.

Tabulated summary of adverse reactions

The Hirobriz Breezhaler Phase III clinical development programme involved patients with a clinical diagnosis of moderate to severe COPD. 4,764 patients were exposed to indacaterol up to one year at doses up to twice the maximum recommended dose. Of these patients, 2,611 were on treatment with 150 microgram once daily and 1,157 on treatment with 300 microgram once daily. Approximately 41% of patients had severe COPD. The mean age of patients was 64 years, with 48% of patients aged 65 years or older, and the majority (80%) was Caucasian.

Adverse reactions in Table 1 are listed according to MedDRA system organ class in the COPD safety database. Within each system organ class, adverse reactions are ranked by frequency in descending order according to the following convention: 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), not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse reactions	Frequency category
Infections and infestations	
Nasopharyngitis	Very common
Upper respiratory tract infection	Very common
Sinusitis	Common
Immune system disorders	
Hypersensitivity[1]	Uncommon
Metabolism and nutrition disorders	
Diabetes mellitus and hyperglycaemia	Common
Nervous system disorders	
Headache	Common
Dizziness	Common
Paraesthesia	Uncommon
Cardiac disorders	
Ischaemic heart disease	Common
Palpitations	Common
Atrial fibrillation	Uncommon
Tachycardia	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Oropharyngeal pain including throat irritation	Common
Rhinorrhoea	Common
Paradoxical bronchospasm	Uncommon
Skin and subcutaneous tissue disorders	
Pruritus/rash	Common
Musculoskeletal and connective tissue disorders	
Muscle spasm	Common
Musculoskeletal pain	Common
Myalgia	Uncommon
General disorders and administration site conditions	
Chest pain	Common
Peripheral oedema	Common

[1] Reports of hypersensitivity have been received from post-approval marketing experience in association with the use of Hirobriz Breezhaler. These were reported voluntarily from a population of uncertain size, and it is therefore not always possible to reliably estimate the frequency or establish a causal relationship to exposure to the medicinal product. Therefore the frequency was calculated from clinical trial experience.

At 600 microgram once-daily, the safety profile of Hirobriz Breezhaler was overall similar to that of recommended doses. An additional adverse reaction was tremor (common).

Description of selected adverse reactions

In Phase III clinical studies, healthcare providers observed during clinic visits that on average 17-20% of patients experienced a sporadic cough that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds (about 10 seconds in current smokers). It was observed with a higher frequency in female than in male patients and in current smokers than in ex-smokers. This cough experienced post inhalation did not lead to any patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 8.2% of patients reported cough as an adverse event). There is no evidence that cough experienced post inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy.

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

In COPD patients, single doses of 10 times the maximum recommended therapeutic dose were associated with a moderate increase in pulse rate, systolic blood pressure and QT_c interval.

An overdose of indacaterol is likely to lead to exaggerated effects typical of $beta_2$-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. Use of cardioselective beta blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, selective beta-2-adrenoreceptor agonists, ATC code: R03AC18

Mechanism of action

The pharmacological effects of $beta_2$-adrenoceptor agonists are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol, a long-acting $beta_2$-adrenergic agonist, has more than 24-fold greater agonist activity at $beta_2$-receptors compared to $beta_1$-receptors and 20-fold greater agonist activity compared to $beta_3$-receptors.

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 $beta_2$-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 10-50% 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.

Pharmacodynamic effects

Hirobriz Breezhaler, administered once a day at doses of 150 and 300 microgram consistently provided clinically significant improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours across a number of clinical pharmacodynamic and efficacy studies. There was a rapid onset of action within 5 minutes after inhalation, with an increase in FEV_1 relative to baseline of 110-160 ml, comparable to the effect of the fast-acting $beta_2$-agonist salbutamol 200 microgram and statistically significantly faster compared to salmeterol/fluticasone 50/500 microgram. Mean peak improvements in FEV_1 relative to baseline were 250-330 ml at steady state.

The bronchodilator effect did not depend on the time of dosing, morning or evening.

Hirobriz Breezhaler was shown to reduce lung hyperinflation, resulting in increased inspiratory capacity during exercise and at rest, compared to placebo.

Effects on cardiac electrophysiology
A double-blind, placebo- and active (moxifloxacin)-controlled study for 2 weeks in 404 healthy volunteers demonstrated maximum mean (90% confidence intervals) prolongations of the QT_cF interval (in milliseconds) of 2.66 (0.55, 4.77) 2.98 (1.02, 4.93) and 3.34 (0.86, 5.82) following multiple doses of 150 microgram, 300 microgram and 600 microgram, respectively. There was no evidence of a concentration-delta QT_c relationship in the range of doses evaluated.

As demonstrated in 605 patients with COPD in a 26-week, double-blind, placebo-controlled Phase III study, there was no clinically relevant difference in the development of arrhythmic events monitored over 24 hours, at baseline and up to 3 times during the 26-week treatment period, between patients receiving recommended doses of Hirobriz Breezhaler treatment and those patients who received placebo or treatment with tiotropium.

Clinical efficacy and safety

The clinical development programme included one 12-week, two six-month (one of which was extended to one year to evaluate safety and tolerability) and one one-year randomised controlled studies in patients with a clinical diagnosis of COPD. These studies included measures of lung function and of health outcomes such as dyspnoea, exacerbations and health-related quality of life.

Lung function
Hirobriz Breezhaler, administered once a day at doses of 150 microgram and 300 microgram, showed clinically meaningful improvements in lung function. At the 12-week primary endpoint (24-hour trough FEV_1), the 150 microgram dose resulted in a 130-180 ml increase compared to placebo ($p<0.001$) and a 60 ml increase compared to salmeterol 50 microgram twice a day ($p<0.001$). The 300 microgram dose resulted in a 170-180 ml increase compared to placebo ($p<0.001$) and a 100 ml increase compared to formoterol 12 microgram twice a day ($p<0.001$). Both doses resulted in an increase of 40-50 ml over open-label tiotropium 18 microgram once a day (150 microgram, $p=0.004$; 300 microgram, $p=0.01$). The 24-hour bronchodilator effect of Hirobriz Breezhaler was maintained from the first dose throughout a one-year treatment period with no evidence of loss in efficacy (tachyphylaxis).

Symptomatic benefits

Both doses demonstrated statistically significant improvements in symptom relief over placebo for dyspnoea and health status (as evaluated by Transitional Dyspnoea Index [TDI] and St. George's Respiratory Questionnaire [SGRQ], respectively). The magnitude of response was generally greater than seen with active comparators (Table 2). In addition, patients treated with Hirobriz Breezhaler required significantly less rescue medication, had more days when no rescue medication was needed compared to placebo and had a significantly improved percentage of days with no daytime symptoms.

Pooled efficacy analysis over 6 months' treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparison compared to placebo showed a ratio of rates of 0.68 (95% CI [0.47, 0.98]; p-value 0.036) and 0.74 (95% CI [0.56, 0.96]; p-value 0.026) for 150 microgram and 300 microgram, respectively.

Limited treatment experience is available in individuals of African descent.

Table 2 Symptom relief at 6 months treatment duration

Treatment Dose (microgram)	**Indacaterol 150 once a day**	**Indacaterol 300 once a day**	**Tiotropium 18 once a day**	**Salmeterol 50 twice a day**	**Formoterol 12 twice a day**	**Placebo**
Percentage of patients who achieved MCID TDI†	57 [a] 62 [b]	71 [b] 59 [c]	57 [b]	54 [a]	54 [c]	45 [a] 47 [b] 41 [c]
Percentage of patients who achieved MCID SGRQ†	53 [a] 58 [b]	53 [b] 55 [c]	47 [b]	49 [a]	51 [c]	38 [a] 46 [b] 40 [c]
Reduction in puffs/day of rescue medication use vs. baseline	1.3 [a] 1.5 [b]	1.6 [b]	1.0 [b]	1.2 [a]	n/e	0.3 [a] 0.4 [b]
Percentage of days with no rescue medication use	60 [a] 57 [b]	58 [b]	46 [b]	55 [a]	n/e	42 [a] 42 [b]

Study design with [a]: indacaterol 150 microgram, salmeterol and placebo; [b]: indacaterol 150 and 300 microgram, tiotropium and placebo; [c]: indacaterol 300 microgram, formoterol and placebo
† MCID = minimal clinically important difference (≥1 point change in TDI, ≥4 point change in SGRQ)
n/e= not evaluated at six months

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Hirobriz Breezhaler in all subsets of the paediatric population in chronic obstructive pulmonary disease (COPD) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Indacaterol is a chiral molecule with R-configuration.

Pharmacokinetic data were obtained from a number of clinical studies, from healthy volunteers and COPD patients.

Absorption

The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 microgram to 600 microgram) in a dose proportional manner. Absolute bioavailability of indacaterol after an inhaled dose was on average 43% to 45%. 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.

Indacaterol serum 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 3.5 for once-daily inhaled doses between 150 microgram and 600 microgram.

Distribution

After intravenous infusion the volume of distribution of indacaterol during the terminal elimination phase was 2557 litres indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1-95.3% and 95.1-96.2%, respectively.

Biotransformation

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, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 is 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.

Elimination

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. When compared with the serum clearance of indacaterol of 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 5% 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 12-14 days.

Special populations

A population pharmacokinetic analysis showed that there is no clinically relevant effect of age (adults up to 88 years), sex, weight (32-168 kg) or race on the pharmacokinetics of indacaterol. It did not suggest any difference between ethnic subgroups in this population.

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.

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

5.3 Preclinical safety data

Effects on the cardiovascular system attributable to the $beta_2$-agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritancy of the nasal cavity and larynx were seen in rodents. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F_1 offspring was observed in the peri- and post-developmental rat study at an exposure 14-fold higher than in humans treated with Hirobriz Breezhaler. Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

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. Systemic exposures (AUC) in rats and mice at the no-observed adverse effect levels in these studies were at least 7- and 49-fold higher, respectively, than in humans treated with Hirobriz Breezhaler once a day at a dose of 300 microgram.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate

Capsule shell

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the blister in order to protect from moisture and only remove immediately before use.

6.5 Nature and contents of container

Hirobriz Breezhaler is a single-dose inhalation device. Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl methacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

PA/Alu/PVC - Alu blister containing 10 hard capsules.

Carton containing 10 capsules and one Hirobriz Breezhaler inhaler.
Carton containing 30 capsules and one Hirobriz Breezhaler inhaler.

Multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

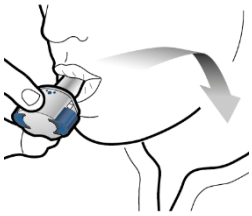
Each inhaler should be disposed of after all capsules have been used.

Instructions for handling and use

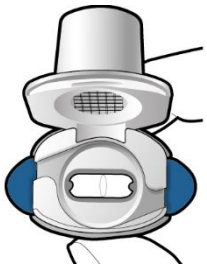
Please read the full **Instructions for Use** before using the Hirobriz Breezhaler.

Insert

Pierce and release

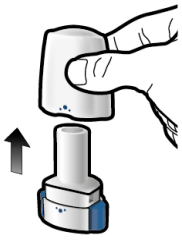


Inhale deeply

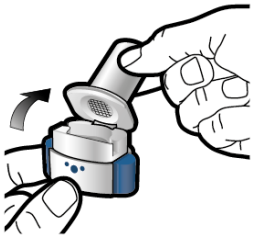


Check capsule is empty

1

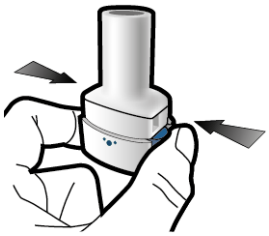


Step 1a:
Pull off cap

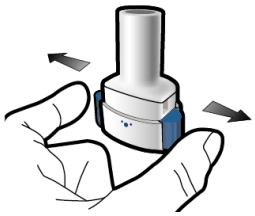


Step 1b:
Open inhaler

2



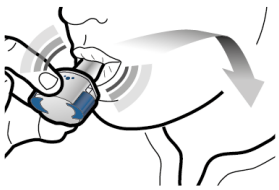
Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced.
Only pierce the capsule once.



Step 2b:
Release side buttons

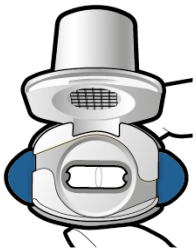
3

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.

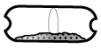
Check



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

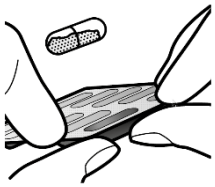
If there is powder left in the capsule:

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



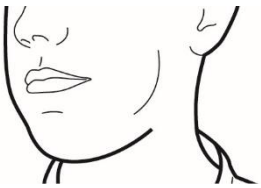
Powder remaining

Empty

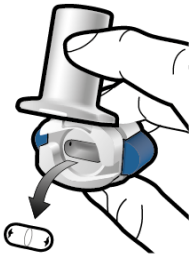


Step 1c:
Remove capsule
Remove one capsule from the blister.
Do not swallow the capsule.

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.

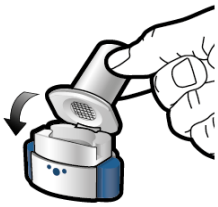


Step 3c:
Hold breath
Hold your breath for up to 5 seconds.



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.



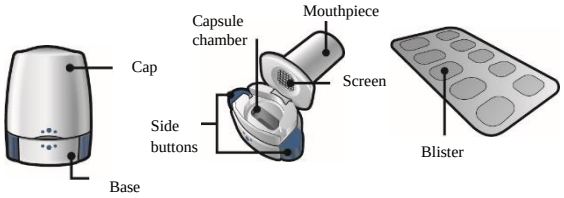
Step 1e:
Close inhaler

Important Information

- Hirobriz Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not swallow the capsule.
- Do not use the Hirobriz Breezhaler capsules with any other inhaler.
- Do not use the Hirobriz 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 Hirobriz Breezhaler Inhaler pack contains:

- One Hirobriz Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Hirobriz 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 3c.

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 3c.

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/1/09/594/006-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 November 2009
Date of latest renewal: 18 September 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER 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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Farmacéutica SA
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

Hirobriz Breezhaler 150 microgram inhalation powder, hard capsules
indacaterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains indacaterol maleate equivalent to 150 microgram indacaterol.

3. LIST OF EXCIPIENTS

Contains lactose (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

10 capsules + 1 inhaler
30 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original blister in order to protect from moisture and do not remove until immediately before use.

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/1/09/594/001	10 capsules + 1 inhaler
EU/1/09/594/002	30 capsules + 1 inhaler

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hirobriz Breezhaler 150

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

Hirobriz Breezhaler 150 microgram inhalation powder, hard capsules
indacaterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains indacaterol maleate equivalent to 150 microgram indacaterol.

3. LIST OF EXCIPIENTS

Contains lactose (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

Multipack: 60 (2 packs of 30 capsules and 1 inhaler).
Multipack: 90 (3 packs of 30 capsules and 1 inhaler).
Multipack: 300 (30 packs of 10 capsules and 1 inhaler).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original blister in order to protect from moisture and do not remove until immediately before use.

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/1/09/594/003	60 capsules + 2 inhalers
EU/1/09/594/004	90 capsules + 3 inhalers
EU/1/09/594/005	300 capsules + 30 inhalers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hirobriz Breezhaler 150

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

Hirobriz Breezhaler 150 microgram inhalation powder, hard capsules
indacaterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains indacaterol maleate equivalent to 150 microgram indacaterol.

3. LIST OF EXCIPIENTS

Contains lactose (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

10 capsules and 1 inhaler. Component of a multipack. Not to be sold separately.
30 capsules and 1 inhaler. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original blister in order to protect from moisture and do not remove until immediately before use.

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/1/09/594/003	60 capsules + 2 inhalers
EU/1/09/594/004	90 capsules + 3 inhalers
EU/1/09/594/005	300 capsules + 30 inhalers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hirobriz Breezhaler 150

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 AND OF 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

Hirobriz Breezhaler 150 microgram inhalation powder, hard capsules
indacaterol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use only. Do not swallow.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Hirobriz Breezhaler 300 microgram inhalation powder, hard capsules
indacaterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains indacaterol maleate equivalent to 300 microgram indacaterol.

3. LIST OF EXCIPIENTS

Contains lactose (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

10 capsules + 1 inhaler
30 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original blister in order to protect from moisture and do not remove until immediately before use.

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/1/09/594/006	10 capsules + 1 inhaler
EU/1/09/594/007	30 capsules + 1 inhaler

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hirobriz Breezhaler 300

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

Hirobriz Breezhaler 300 microgram inhalation powder, hard capsules
indacaterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains indacaterol maleate equivalent to 300 microgram indacaterol.

3. LIST OF EXCIPIENTS

Contains lactose (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

Multipack: 60 (2 packs of 30 capsules and 1 inhaler).
Multipack: 90 (3 packs of 30 capsules and 1 inhaler).
Multipack: 300 (30 packs of 10 capsules and 1 inhaler).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original blister in order to protect from moisture and do not remove until immediately before use.

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/1/09/594/008	60 capsules + 2 inhalers
EU/1/09/594/009	90 capsules + 3 inhalers
EU/1/09/594/010	300 capsules + 30 inhalers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hirobriz Breezhaler 300

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

Hirobriz Breezhaler 300 microgram inhalation powder, hard capsules
indacaterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains indacaterol maleate equivalent to 300 microgram indacaterol.

3. LIST OF EXCIPIENTS

Contains lactose (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

10 capsules and 1 inhaler. Component of a multipack. Not to be sold separately.
30 capsules and 1 inhaler. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original blister in order to protect from moisture and do not remove until immediately before use.

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/1/09/594/008	60 capsules + 2 inhalers
EU/1/09/594/009	90 capsules + 3 inhalers
EU/1/09/594/010	300 capsules + 30 inhalers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hirobriz Breezhaler 300

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 AND OF 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

Hirobriz Breezhaler 300 microgram inhalation powder, hard capsules
indacaterol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use only. Do not swallow.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Hirobriz Breezhaler 150 microgram inhalation powder, hard capsules
Hirobriz Breezhaler 300 microgram inhalation powder, hard capsules
indacaterol

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 further questions, ask your doctor or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

What Hirobriz Breezhaler is
Hirobriz Breezhaler contains the active substance indacaterol which belongs to a group of medicines called bronchodilators. When you inhale it, it relaxes the muscles in the walls of the small air passages in the lungs. This helps open up the airways, making it easier to get air in and out.

What Hirobriz Breezhaler is used for
Hirobriz Breezhaler is used to make breathing easier for adult patients who have breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD). In COPD the muscles around the airways tighten. This makes breathing difficult. This medicine relaxes these muscles in the lungs, making it easier for air to get in and out of the lungs.

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

Do not use Hirobriz Breezhaler
- if you are allergic to indacaterol or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using Hirobriz Breezhaler
- if you have asthma (in this case you should not use Hirobriz Breezhaler).
- if you have heart problems.
- if you have epilepsy.
- if you have thyroid gland problems (thyrotoxicosis).
- if you have diabetes.

During treatment with Hirobriz Breezhaler,
- **Stop using the medicine and tell your doctor immediately** if you get tightness of the chest, coughing, wheezing or breathlessness immediately after using the medicine. These may be signs of a condition called bronchospasm.
- **Tell your doctor immediately** if your COPD symptoms (breathlessness, wheezing, cough) do not improve or get worse.

Children and adolescents
Hirobriz Breezhaler **should not** be given to **children or adolescents below the age of 18 years**.

Other medicines and Hirobriz Breezhaler
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, please tell your doctor if you are using:
- medicines for breathing problems that are similar to Hirobriz Breezhaler (i.e. medicines such as salmeterol and formoterol). You may be more likely to get side effects.
- medicines called beta blockers that are used for high blood pressure or other heart problems (such as propranolol), or for the eye problem called glaucoma (such as timolol).
- medicines that lower the amount of potassium in your blood. These include:
  - steroids (e.g. prednisolone),
  - diuretics (water tablets) used for high blood pressure such as hydrochlorothiazide,
  - medicines for breathing problems such as theophylline.

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 or pharmacist for advice before using this medicine.

You should not use Hirobriz Breezhaler unless your doctor tells you so.

Ask your doctor or pharmacist for advice before taking any medicine.

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

Hirobriz Breezhaler contains lactose
This medicine contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicine.

3. How to use Hirobriz Breezhaler

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

How much Hirobriz Breezhaler to use
- The usual dose is to inhale the content of one capsule each day. Your doctor may tell you to use the 150 microgram capsule or the 300 microgram capsule depending on your condition and on how you respond to the treatment. Do not use more than your doctor tells you to use.
- Use your inhaler at the same time each day, the effects last for 24 hours. This ensures that there is always enough medicine in your body to help you breathe more easily throughout the day and night. It will also help you to remember to use it.

How to use Hirobriz Breezhaler
- In this pack, you will find an inhaler and capsules (in blister) that contain the medicine as inhalation powder. The Hirobriz Breezhaler inhaler enables you to inhale the medicine contained in a capsule.
- Only use the capsules with the inhaler provided in this pack (Hirobriz Breezhaler inhaler). The capsules should remain in the blister until you need to use them.
- When you start a new pack, use the new Hirobriz Breezhaler inhaler that is supplied in the pack.
- Dispose of each inhaler after 30 days of use.
- Do not swallow the capsules.
- **Please read the instructions at the end of this leaflet for more information about how to use the inhaler.**

If you use more Hirobriz Breezhaler than you should
If you have inhaled too much Hirobriz Breezhaler or if someone else uses your capsules, tell your doctor immediately or go to the nearest emergency unit. Show the pack of Hirobriz Breezhaler. Medical attention may be needed. You may notice that your heart is beating faster than usual, or you may have a headache, feel drowsy, feel nauseous or have to vomit.

If you forget to use Hirobriz Breezhaler
If you forget to inhale a dose, inhale just one dose at the usual time the next day. Do not inhale a double dose to make up for a forgotten dose.

How long to continue your treatment with Hirobriz Breezhaler
– Keep using your treatment with Hirobriz Breezhaler for as long as your doctor tells you.
– COPD is a long-term disease and you should use Hirobriz Breezhaler **every day** and not only when you have breathing problems or other symptoms of COPD.
If you have questions about how long to continue your treatment with Hirobriz Breezhaler, talk to your doctor or pharmacist.

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 may be serious. Tell your doctor immediately
- if you get crushing chest pain, (common).
- if you get high levels of sugar in your blood (diabetes). You will feel tired, very thirsty and hungry (without gaining weight) and will pass more urine than usual (common).
- if you get irregular heart beat (uncommon).
- if you get symptoms of an allergic reaction such as rash, itching, hives, difficulty breathing or swallowing, dizziness (uncommon).
- if you have difficulty breathing with wheezing or coughing (uncommon).

Other side effects may include:

Very common side effects (may affect more than 1 in 10 people)
- cold-like symptoms. You may get all or most of the following: sore throat, runny nose, blocked nose, sneezing, coughing, headache.

Common side effects (may affect up to 1 in 10 people)
- feeling of pressure or pain in the cheeks and forehead (inflammation of the sinuses)
- runny nose
- cough
- sore throat
- headache
- dizziness
- palpitations
- muscle spasm
- swollen hands, ankles and feet (oedema)
- itching/rash
- chest pain
- pain in muscles, bones or joints

Uncommon side effects (may affect up to 1 in 100 people)
- fast heart beat
- tingling or numbness
- muscle pain

Some people occasionally cough soon after inhaling the medicine. Cough is a common symptom in COPD. If you experience coughing briefly after inhaling the medicine, do not worry. Check your inhaler to see if the capsule is empty and that you have received the full dose. If the capsule is empty, there is no need for concern. If the capsule is not empty then inhale again as directed.

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 Hirobriz 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 in the original package in order to protect from moisture and do not remove until immediately before use.
Do not use this medicine if you notice that the pack is damaged or show signs of tampering.
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 Hirobriz Breezhaler contains
- Each Hirobriz Breezhaler 150 microgram capsule contains 150 microgram indacaterol as indacaterol maleate. The other ingredients include lactose and the capsule is made of gelatin.
- Each Hirobriz Breezhaler 300 microgram capsule contains 300 microgram indacaterol as indacaterol maleate. The other ingredients include lactose and the capsule is made of gelatin.

What Hirobriz Breezhaler looks like and content of the pack
In this pack, you will find an inhaler, together with capsules in blister. The capsules are transparent (uncoloured) and contain a white powder.

– Hirobriz Breezhaler 150 microgram capsules have a **black** product code "**IDL 150**" printed above a **black** bar and a **black** company logo (⏻) printed below the **black** bar.
– Hirobriz Breezhaler 300 microgram capsules have a **blue** product code "**IDL 300**" printed above a **blue** bar and a **blue** company logo (⏻) printed below the **blue** bar.

The following pack sizes are available:
Carton containing 10 capsules and 1 inhaler.
Carton containing 30 capsules and 1 inhaler.
Multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

Not all pack sizes or strengths may be available in your country.

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

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

España
Laboratorios Farmacéuticos ROVI, S.A.
Tel.: +34 91 375 62 30

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

This leaflet was last revised in

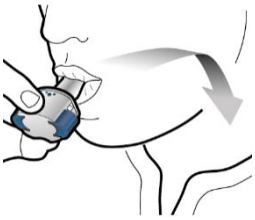
Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

INSTRUCTIONS FOR USE OF HIROBRIZ BREEZHALER INHALER

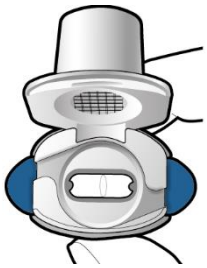
Please read the full **Instructions for Use** before using the Hirobriz Breezhaler.

Insert

Pierce and release

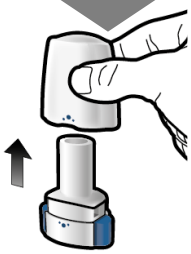


Inhale deeply

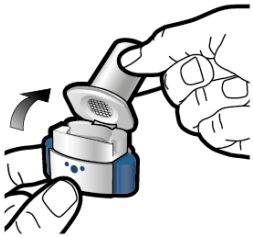


Check capsule is empty

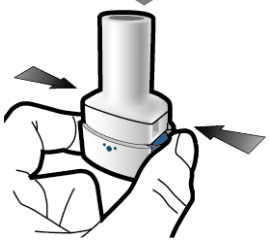
1 **2** **3** **Check**



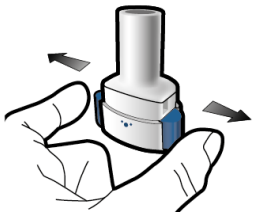
Step 1a:
Pull off cap



Step 1b:
Open inhaler

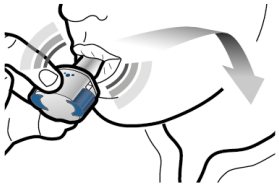


Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced. Only pierce the capsule once.

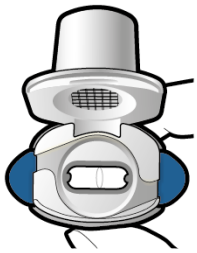


Step 2b:
Release side buttons

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



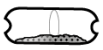
Step 3b:
Inhale medicine deeply
Hold the inhaler as shown in the picture. Place the mouthpiece in your mouth and close your lips firmly around it.
Do not press the side buttons.



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

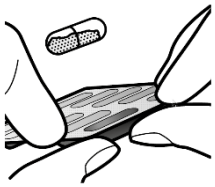
If there is powder left in the capsule:

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



Powder remaining

Empty

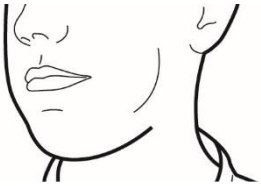


Step 1c:
Remove capsule
Remove one capsule from the blister.
Do not swallow the capsule.

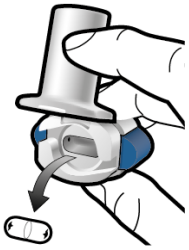
Step 1d:
Insert capsule
Never place a capsule directly into the mouthpiece.

Step 1e:
Close inhaler

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.



Remove empty capsule
Put the empty capsule in your household waste.

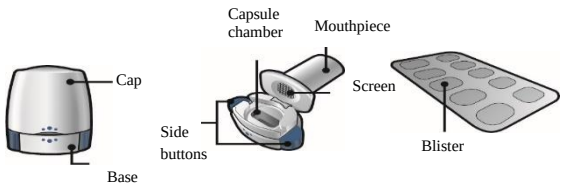
Close the inhaler and replace the cap.

Important Information

- Hirobriz Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not swallow the capsule.
- Do not use the Hirobriz Breezhaler capsules with any other inhaler.
- Do not use the Hirobriz 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 Hirobriz Breezhaler Inhaler pack contains:

- One Hirobriz Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Hirobriz 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 3c.

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 3c.

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.