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 Hirobriz Breezhaler inhaler is indacaterol maleate equivalent to 120 microgram indacaterol.

Excipients:
Each capsule contains 24.8 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Clear colourless capsules containing a white powder, with "IDL 150" printed in black above and company logo (⏻) printed in black below a 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.

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

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

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.

Method of administration
For inhalation use only.

Hirobriz Breezhaler capsules must be administered only using the Hirobriz Breezhaler inhaler (see section 6.6).

Hirobriz Breezhaler capsules must not be swallowed.

4.3 Contraindications

Hypersensitivity to the active substance, to lactose or to any of the other excipients.

4.4 Special warnings and precautions for use

Asthma
Hirobriz Breezhaler should not be used in asthma due to the absence of long-term outcome data in asthma with Hirobriz Breezhaler.

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 and ST segment depression, although the clinical significance of these observations is unknown.

Clinically relevant effects on prolongation of the QT_c-interval have not been observed in clinical studies of Hirobriz Breezhaler at recommended therapeutic doses (see section 5.1).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetic agents
Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of 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 use with caution (see section 4.4).

Beta-adrenergic blockers
Beta-adrenergic blockers may weaken or antagonise the effect of $beta_2$-adrenergic agonists. 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 co-medications. *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 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.

Lactation
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 (9.1%), cough (6.8%), upper respiratory tract infection (6.2%) and headache (4.8%). 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. 2,154 patients were exposed to indacaterol up to one year at doses up to twice the maximum recommended dose. Of these patients, 627 were on treatment with 150 microgram once daily and 853 on treatment with 300 microgram once daily. Approximately 40% of patients had severe COPD. The mean age of patients was 63 years, with 47% of patients aged 65 years or older, and the majority (89%) 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 (CIOMS III): Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse Reactions	Frequency category
Infections and infestations	
Nasopharyngitis	Common
Upper respiratory tract infection	Common
Sinusitis	Common
Metabolism and nutrition disorders	
Diabetes mellitus and hyperglycaemia	Common
Nervous system disorders	
Headache	Common
Paraesthesia	Uncommon
Cardiac disorders	
Ischaemic heart disease	Common
Atrial fibrillation	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Pharyngolaryngeal pain	Common
Rhinorrhoea	Common
Respiratory tract congestion	Common
Musculoskeletal and connective tissue disorders	
Muscle spasm	Common
General disorders and administration site conditions	
Peripheral oedema	Common
Non-cardiac chest pain	Uncommon

At twice the maximum recommended dose, the safety profile of Hirobriz Breezhaler was overall similar to that of recommended doses. Additional adverse reactions were tremor (common) and anaemia (uncommon).

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 was generally well tolerated and did not lead to any patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 6.8% of patients overall 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.

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: Long-acting $beta_2$-adrenergic agonist, ATC code: not yet assigned

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. Therefore, this shows no concern for a pro-arrhythmic potential related to QT-interval prolongations at recommended therapeutic doses or at twice the maximum recommended dose. 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%. Systemic exposure results from a composite of pulmonary and intestinal 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

18 months.

6.4 Special precautions for storage

Do not store above 30°C.

Hirobriz Breezhaler capsules must always be stored in the blister to protect from moisture and only removed 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 packs, containing 10 hard capsules, with an inhaler made from plastic materials provided in each pack.

Carton containing 10 capsules (1x10 capsule blister strips) and one Hirobriz Breezhaler inhaler.
Carton containing 30 capsules (3x10 capsule blister strips) and one Hirobriz Breezhaler inhaler.

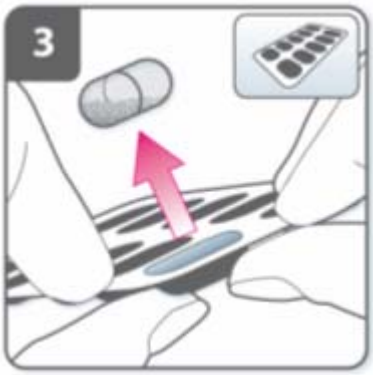
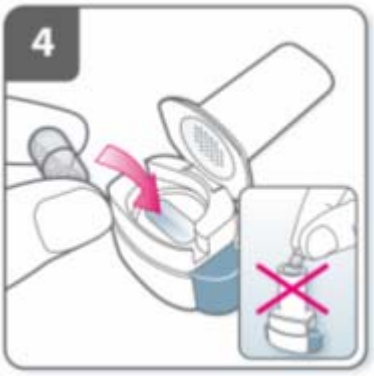
Multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

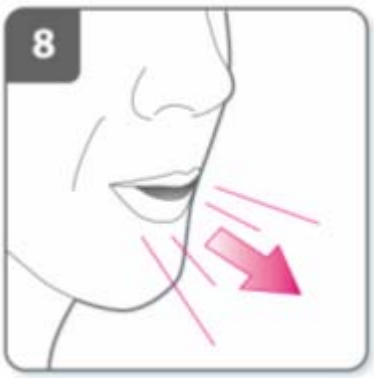
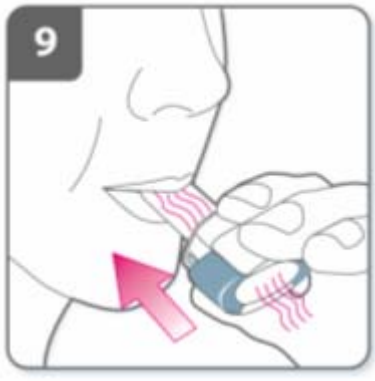
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The Hirobriz Breezhaler inhaler provided with each new prescription should be used. Dispose of each inhaler after 30 days of use.

Instructions for handling and use

	**Pull off the cap.**
	**Open inhaler:** Hold the base of the inhaler firmly and tilt the mouthpiece. This opens the inhaler.
	**Prepare capsule:** **Immediately before use,** with dry hands, remove one capsule from the blister.
	**Insert capsule:** Place the capsule into the capsule chamber. **Never place a capsule directly into the mouthpiece.**

	**Close the inhaler:** Close the inhaler until you hear a “click”.
	**Pierce the capsule:** • Hold the inhaler upright with the mouthpiece pointing up. • Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.** • You should hear a “click” as the capsule is being pierced.
	**Release the side buttons fully.**
	**Breathe out:** Before placing the mouthpiece in your mouth, breathe out fully. **Do not blow into the mouthpiece.**
	**Inhale the medicine** To breathe the medicine deeply into your airways: • Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons. • Place the mouthpiece in your mouth and close your lips firmly around it. • Breathe in rapidly but steadily and as deeply as you can.

	**Note:** As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavour as the medicine goes into your lungs. **Additional information** Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is accidentally pierced more than once (step 6). **If you do not hear a whirring noise:** The capsule may be stuck in the capsule chamber. If this happens: • Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons. • Inhale the medicine again by repeating steps 8 and 9.
	**Hold breath:** After you have inhaled the medicine: • Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth. • Then breathe out. • 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 8, 9, 10 and 11. Most people are able to empty the capsule with one or two inhalations. **Additional information** Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don't worry. As long as the capsule is empty, you have received enough of your medicine.

	**After you have finished taking** your medicine: • Open the mouthpiece again, and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste. • Close the inhaler and replace the cap. **Do not store the capsules in the Hirobriz Breezhaler inhaler.**
	**Mark daily dose tracker:** On the inside of the pack there is a daily dose tracker. Put a mark in today's box if it helps to remind you of when your next dose is due.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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 Hirobriz Breezhaler inhaler is indacaterol maleate equivalent to 240 microgram indacaterol.

Excipients:
Each capsule contains 24.6 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Clear colourless capsules containing a white powder, with "IDL 300" printed in blue above and company logo (⏻) printed in blue below a 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.

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

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

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.

Method of administration
For inhalation use only.

Hirobriz Breezhaler capsules must be administered only using the Hirobriz Breezhaler inhaler (see section 6.6).

Hirobriz Breezhaler capsules must not be swallowed.

4.3 Contraindications

Hypersensitivity to the active substance, to lactose or to any of the other excipients.

4.4 Special warnings and precautions for use

Asthma
Hirobriz Breezhaler should not be used in asthma due to the absence of long-term outcome data in asthma with Hirobriz Breezhaler.

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 and ST segment depression, although the clinical significance of these observations is unknown.

Clinically relevant effects on prolongation of the QT_c-interval have not been observed in clinical studies of Hirobriz Breezhaler at recommended therapeutic doses (see section 5.1).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetic agents
Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of 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 use with caution (see section 4.4).

Beta-adrenergic blockers
Beta-adrenergic blockers may weaken or antagonise the effect of $beta_2$-adrenergic agonists. 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 co-medications. *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 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.

Lactation
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 (9.1%), cough (6.8%), upper respiratory tract infection (6.2%) and headache (4.8%). 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. 2,154 patients were exposed to indacaterol up to one year at doses up to twice the maximum recommended dose. Of these patients, 627 were on treatment with 150 microgram once daily and 853 on treatment with 300 microgram once daily. Approximately 40% of patients had severe COPD. The mean age of patients was 63 years, with 47% of patients aged 65 years or older, and the majority (89%) 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 (CIOMS III): Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse Reactions	Frequency category
Infections and infestations	
Nasopharyngitis	Common
Upper respiratory tract infection	Common
Sinusitis	Common
Metabolism and nutrition disorders	
Diabetes mellitus and hyperglycaemia	Common
Nervous system disorders	
Headache	Common
Paraesthesia	Uncommon
Cardiac disorders	
Ischaemic heart disease	Common
Atrial fibrillation	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Pharyngolaryngeal pain	Common
Rhinorrhoea	Common
Respiratory tract congestion	Common
Musculoskeletal and connective tissue disorders	
Muscle spasm	Common
General disorders and administration site conditions	
Peripheral oedema	Common
Non-cardiac chest pain	Uncommon

At twice the maximum recommended dose, the safety profile of Hirobriz Breezhaler was overall similar to that of recommended doses. Additional adverse reactions were tremor (common) and anaemia (uncommon).

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 was generally well tolerated and did not lead to any patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 6.8% of patients overall 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.

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: Long-acting $beta_2$-adrenergic agonist, ATC code: not yet assigned

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. Therefore, this shows no concern for a pro-arrhythmic potential related to QT-interval prolongations at recommended therapeutic doses or at twice the maximum recommended dose. 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%. Systemic exposure results from a composite of pulmonary and intestinal 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

18 months.

6.4 Special precautions for storage

Do not store above 30°C.

Hirobriz Breezhaler capsules must always be stored in the blister to protect from moisture and only removed 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 packs, containing 10 hard capsules, with an inhaler made from plastic materials provided in each pack.

Carton containing 10 capsules (1x10 capsule blister strips) and one Hirobriz Breezhaler inhaler.
Carton containing 30 capsules (3x10 capsule blister strips) and one Hirobriz Breezhaler inhaler.

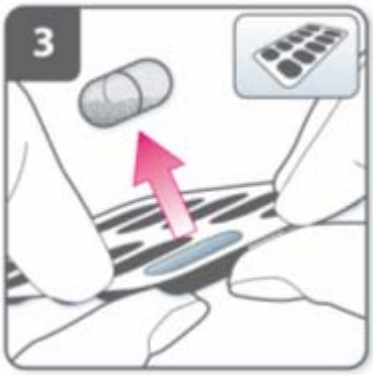
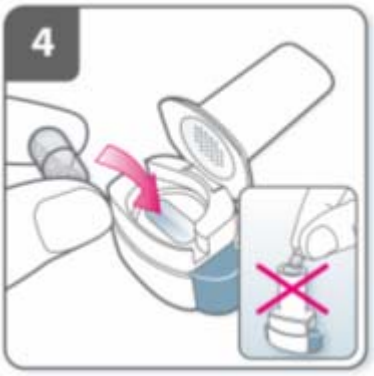
Multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

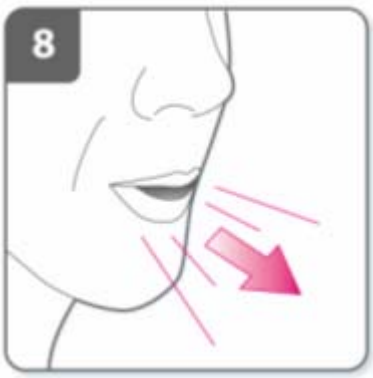
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The Hirobriz Breezhaler inhaler provided with each new prescription should be used. Dispose of each inhaler after 30 days of use.

Instructions for handling and use

	**Pull off the cap.**
	**Open inhaler:** Hold the base of the inhaler firmly and tilt the mouthpiece. This opens the inhaler.
	**Prepare capsule:** **Immediately before use,** with dry hands, remove one capsule from the blister.
	**Insert capsule:** Place the capsule into the capsule chamber. **Never place a capsule directly into the mouthpiece.**

	**Close the inhaler:** Close the inhaler until you hear a “click”.
	**Pierce the capsule:** • Hold the inhaler upright with the mouthpiece pointing up. • Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.** • You should hear a “click” as the capsule is being pierced.
	**Release the side buttons fully.**
	**Breathe out:** Before placing the mouthpiece in your mouth, breathe out fully. **Do not blow into the mouthpiece.**
	**Inhale the medicine** To breathe the medicine deeply into your airways: • Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons. • Place the mouthpiece in your mouth and close your lips firmly around it. • Breathe in rapidly but steadily and as deeply as you can.

	**Note:** As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavour as the medicine goes into your lungs. **Additional information** Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is accidentally pierced more than once (step 6). **If you do not hear a whirring noise:** The capsule may be stuck in the capsule chamber. If this happens: • Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons. • Inhale the medicine again by repeating steps 8 and 9.
	**Hold breath:** After you have inhaled the medicine: • Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth. • Then breathe out. • 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 8, 9, 10 and 11. Most people are able to empty the capsule with one or two inhalations. **Additional information** Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don't worry. As long as the capsule is empty, you have received enough of your medicine.

	**After you have finished taking** your medicine: • Open the mouthpiece again, and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste. • Close the inhaler and replace the cap. **Do not store the capsules in the Hirobriz Breezhaler inhaler.**
	**Mark daily dose tracker:** On the inside of the pack there is a daily dose tracker. Put a mark in today's box if it helps to remind you of when your next dose is due.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nürnberg
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder (MAH) shall ensure, at launch, that physicians who are expected to prescribe/use Hirobriz Breezhaler and pharmacists are provided with an information card containing the following elements:

- Indication is for maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD.

- Hirobriz Breezhaler should not be used in asthma due to the absence of long-term outcome data in asthma with Hirobriz Breezhaler.

- 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.

All materials will refer to summary of product characteristics for full prescribing information.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 4 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version version 4 (23 September 2009) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

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 monohydrate (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

10 capsules + 1 inhaler
30 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Lift here to open.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000	10 capsules + 1 inhaler
EU/0/00/000/000	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

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 monohydrate (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

60 capsules + 2 inhalers
90 capsules + 3 inhalers
300 capsules + 30 inhalers

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).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use only with the inhaler provided in the pack.
Do not swallow capsules.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000	60 capsules + 2 inhalers
EU/0/00/000/000	90 capsules + 3 inhalers
EU/0/00/000/000	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

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 monohydrate (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

10 capsules
30 capsules

Component of a multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Component of a multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Component of a multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Lift here to open.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000	60 capsules + 2 inhalers
EU/0/00/000/000	90 capsules + 3 inhalers
EU/0/00/000/000	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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF OUTER CARTON OF UNIT PACK AND OF INTERMEDIATE CARTON OF MULTIPACK

1. OTHER

See package leaflet for pictures and information on using Hirobriz Breezhaler.

Start date

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 monohydrate (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

10 capsules + 1 inhaler
30 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Lift here to open.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000	10 capsules + 1 inhaler
EU/0/00/000/000	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

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 monohydrate (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

60 capsules + 2 inhalers
90 capsules + 3 inhalers
300 capsules + 30 inhalers

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).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use only with the inhaler provided in the pack.
Do not swallow capsules.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000	60 capsules + 2 inhalers
EU/0/00/000/000	90 capsules + 3 inhalers
EU/0/00/000/000	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

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 monohydrate (see package leaflet for further information) and gelatin.

4. PHARMACEUTICAL FORM AND CONTENTS

10 capsules
30 capsules

Component of a multipack comprising 2 packs (each containing 30 capsules and 1 inhaler).
Component of a multipack comprising 3 packs (each containing 30 capsules and 1 inhaler).
Component of a multipack comprising 30 packs (each containing 10 capsules and 1 inhaler).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Lift here to open.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000	60 capsules + 2 inhalers
EU/0/00/000/000	90 capsules + 3 inhalers
EU/0/00/000/000	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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF OUTER CARTON OF UNIT PACK AND OF INTERMEDIATE CARTON OF MULTIPACK

1. OTHER

See package leaflet for pictures and information on using Hirobriz Breezhaler.

Start date

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 maleate

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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 in adults who have breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD). It helps you breathe more easily and minimise the effects of COPD.

2. BEFORE YOU USE HIROBRIZ BREEZHALER

Follow all the doctor's instructions carefully. They may differ from the general information contained in this leaflet.

Do not use Hirobriz Breezhaler
- if you are allergic (hypersensitive) to indacaterol, to lactose or to gelatin.

If this applies to you, **tell your doctor without taking Hirobriz Breezhaler.** If you think you may be allergic, ask your doctor for advice.

Take special care with 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.

If any of the above applies to you (or you are not sure), **tell your doctor before using Hirobriz Breezhaler**.

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

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.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
In particular, please tell your doctor if you are using:
- medicines for breathing problems that are similar to Hirobriz Breezhaler. 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.

Using Hirobriz Breezhaler with food and drink
You can inhale Hirobriz Breezhaler anytime before or after food or drink.

Pregnancy and breast-feeding
If you are pregnant or think that you may be pregnant, or if you are breast-feeding, tell your doctor before using Hirobriz Breezhaler. 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.

3. HOW TO USE HIROBRIZ BREEZHALER

Always use Hirobriz Breezhaler exactly as your doctor has told you. You should 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 strips) 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 strip 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.

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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Hirobriz Breezhaler can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 patient in 10
- common: affects 1 to 10 patients in 100
- uncommon: affects 1 to 10 patients in 1,000
- rare: affects 1 to 10 patients in 10,000
- very rare: affects less than 1 patient in 10,000
- not known: frequency cannot be estimated from the available data.

Some side effects may be serious. Tell your doctor immediately
- if you get crushing chest pain, or irregular heart beat.
- 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.

Other side effects may include:

<u>Common side effects</u>
- feeling of pressure or pain in the cheeks and forehead (inflammation of the sinuses)
- runny nose
- cough
- sore throat
- headache
- cold-like symptoms. You may get all or most of the following: sore throat, runny nose, blocked nose, sneezing, coughing and a headache.
- muscle spasm
- difficulty to breathe as with bronchitis
- swollen hands, ankles and feet (oedema)

Uncommon side effects
- tingling or numbness
- chest pain

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.

5. HOW TO STORE HIROBRIZ BREEZHALER

Keep out of the reach and sight of children.
Do not use after the expiry date shown on the box and blister strip. 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 Hirobriz Breezhaler if you notice that the pack is damaged or show signs of tampering.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Hirobriz Breezhaler contains
- Each Hirobriz Breezhaler 150 microgram capsule contains 150 microgram indacaterol as indacaterol maleate. The other ingredients are lactose and gelatin.
- Each Hirobriz Breezhaler 300 microgram capsule contains 300 microgram indacaterol as indacaterol maleate. The other ingredients are lactose and gelatin.

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

- Hirobriz Breezhaler 150 microgram capsules are clear and colourless. They have a **black** product code "**IDL 150**" printed above and a **black** company logo (⏻) printed below a **black** bar.
- Hirobriz Breezhaler 300 microgram capsules are clear and colourless. They have a **blue** product code "**IDL 300**" printed above and a **blue** company logo (⏻) printed below a **blue** bar.

The following pack sizes are available:
Carton containing 10 capsules (1x10 capsule blister strips) and 1 inhaler.
Carton containing 30 capsules (3x10 capsule blister strips) 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 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 Pharma Services Inc.
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
Novartis Pharma Services Inc.
Tel: +372 66 30 810

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

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

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

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

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

Malta
Novartis Pharma Services Inc.
Tel: +356 2298 3217

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

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

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 550 8888

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

România
Novartis Pharma Services Inc.
Tel: +40 21 31299 01

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
Δημητριάδης και Παπαέλληνας Λτδ
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

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

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last approved in

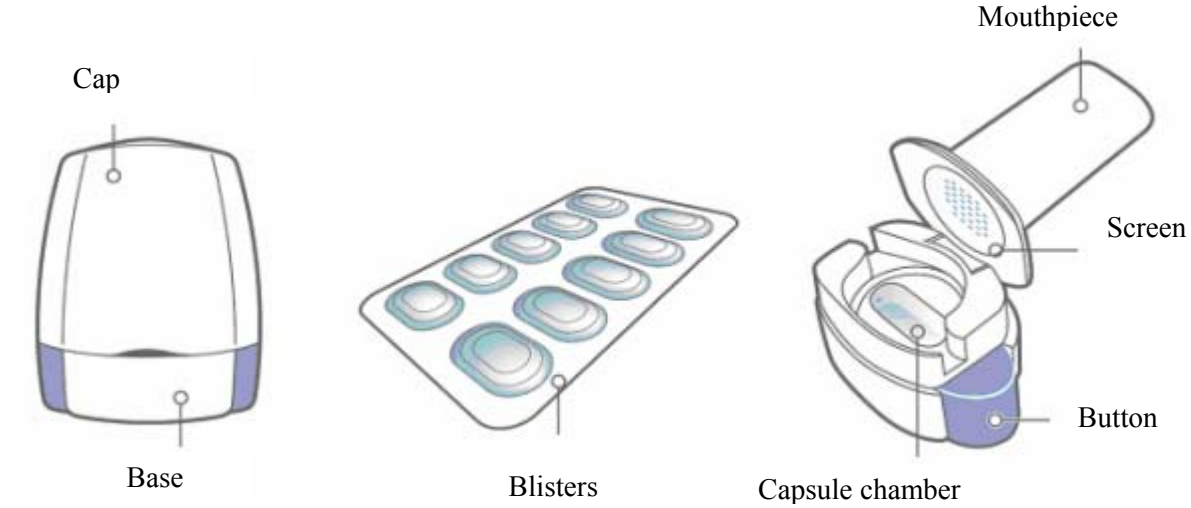
INSTRUCTIONS FOR USE OF HIROBRIZ BREEZHALER INHALER

Please read the following instructions carefully to learn how to use and care for your Hirobriz Breezhaler inhaler.

- **Only use the Hirobriz Breezhaler inhaler contained in this pack.** Do not use Hirobriz Breezhaler capsules with any other inhaler, and do not use Hirobriz Breezhaler inhaler to take any other capsule medicine.
- When you start a new pack, only use the new Hirobriz Breezhaler inhaler that is supplied in the pack.
- Dispose of each inhaler after 30 days of use.
- Ask your pharmacist how to dispose of medicines and inhalers no longer required.
- **Do not swallow the capsules.** The powder in the capsules is for you to inhale.

Your Hirobriz Breezhaler pack:
Each Hirobriz Breezhaler pack contains:
– one Hirobriz Breezhaler inhaler
– one or more blister strips containing Hirobriz Breezhaler capsules to be used in the inhaler.

The Hirobriz Breezhaler inhaler enables you to inhale the medicine contained in an Hirobriz Breezhaler capsule.



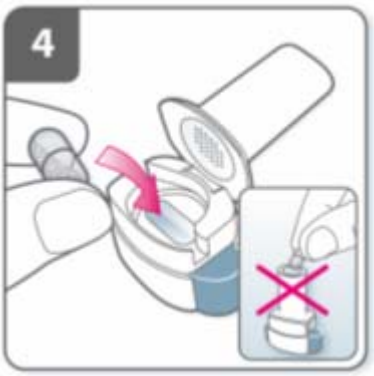
Hirobriz Breezhaler inhaler **Blister** **Inhaler base**

How to use your inhaler

Pull off the cap.

Open inhaler:
Hold the base of the inhaler firmly and tilt the mouthpiece. This opens the inhaler.

Prepare capsule.
Immediately before use, with dry hands, remove one capsule from the blister.



Insert capsule:
Place the capsule into the capsule chamber.

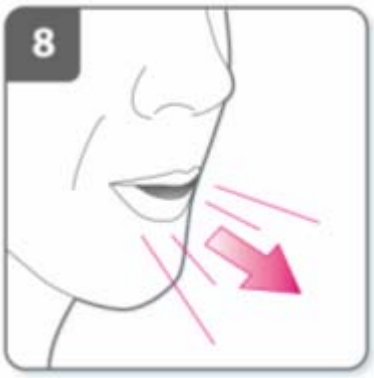
Never place a capsule directly into the mouthpiece.

Close the inhaler:
Close the inhaler until you hear a “click”.

Pierce the capsule:

- Hold the inhaler upright with the mouthpiece pointing up.
- Pierce the capsule by firmly pressing together both side buttons at the same time. Do this only once.
- You should hear a “click” as the capsule is being pierced.

Release the side buttons fully.



Breathe out:
Before placing the mouthpiece in your mouth, breathe out fully.

Do not blow into the mouthpiece.

Inhale the medicine:
To breathe the medicine deeply into your airways:

- Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece.
- Breathe in rapidly but steadily and as deeply as you can.

Note:
As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavour as the medicine goes into your lungs.

Additional information
Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is accidentally pierced more than once (step 6).

If you do not hear a whirring noise:
The capsule may be stuck in the capsule chamber. If this happens:

- Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.
- Inhale the medicine again by repeating steps 8 and 9.

Hold breath:
After you have inhaled the medicine:

- Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.
- Then breathe out.
- 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 8, 9, 10 and 11.

Most people are able to empty the capsule with one or two inhalations.

Additional information
Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don’t worry. As long as the capsule is empty, you have received enough of your medicine.

After you have finished taking your medicine:

- Open the mouthpiece again, remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste.
- Close the inhaler and replace the cap.

Do not store the capsules in the Hirobriz Breezhaler inhaler.

Mark daily dose tracker:
On the inside of the pack there is a daily dose tracker. Put a mark in today's box if it helps to remind you of when your next dose is due.

REMEMBER:

- **Do not swallow Hirobriz Breezhaler capsules.**
- **Only use the Hirobriz Breezhaler inhaler contained in this pack.**
- Hirobriz Breezhaler capsules must always be stored in the blister, and only removed immediately before use.
- Never place a Hirobriz Breezhaler capsule directly into the mouthpiece of the Hirobriz Breezhaler inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the Hirobriz Breezhaler inhaler.
- Always release the push buttons before inhalation.
- Never wash the Hirobriz Breezhaler inhaler with water. Keep it dry. See "How to clean your inhaler".
- Never take the Hirobriz Breezhaler inhaler apart.
- Always use the new Hirobriz Breezhaler inhaler that comes with your new Hirobriz Breezhaler medication pack. Dispose of each inhaler after 30 days of use.
- Do not store the capsules in the Hirobriz Breezhaler inhaler.
- Always keep the Hirobriz Breezhaler inhaler and Hirobriz Breezhaler capsules in a dry place.

How to clean your inhaler
Clean your inhaler once a week.

- Wipe the mouthpiece inside and outside to remove any powder with a clean, dry lint-free cloth.
- Do not wash your inhaler with water. Keep it dry.
- Do not take the inhaler apart.