1. NAME OF THE MEDICINAL PRODUCT

Onbrez ® Breezhaler ® 150 microgram, inhalation powder, hard capsules

Onbrez ® Breezhaler ® 300 microgram, inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Onbrez Breezhaler 150 mcg: Each capsule contains 194 microgram indacaterol maleate equivalent to 150 microgram indacaterol.

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

Onbrez Breezhaler 300 mcg: Each capsule contains 389 microgram indacaterol maleate equivalent to 300 microgram indacaterol.

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

Excipients with known effect:

Onbrez Breezhaler 150 mcg: Each capsule contains 24.806 mg lactose monohydrate.

Onbrez Breezhaler 300 mcg: Each capsule contains 24.611 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Onbrez Breezhaler 150 mcg: Yellowish transparent (uncoloured) capsules containing a white powder, with “IDL 150” printed in black above a black bar and company logo () printed in black below the black bar.

Onbrez Breezhaler 300 mcg: Yellowish transparent (uncoloured) capsules containing a white powder, with “IDL 300” printed in blue above a blue bar and company logo () printed in blue below the blue bar.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maintenance of bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology

The recommended dosage of Onbrez Breezhaler is the once-daily inhalation of the content of one 150 microgram capsule using the Onbrez Breezhaler inhaler. The dosage should only be increased on medical advice.

Once-daily inhalation of the content of one 300 microgram capsule, using the Onbrez Breezhaler inhaler, has been shown to provide additional clinical benefit to some patients, e.g. with regard to breathlessness, particularly for patients with severe COPD. The maximum dose is 300 microgram once-daily.

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

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

Special populations

Elderly population
No dose adjustment is required in elderly patients.

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

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

Paediatric population

Onbrez Breezhaler should not be used in patients under 18 years of age.

Method of administration

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

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

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

Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.
For instructions on use of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Asthma

Onbrez Breezhaler is a long-acting beta2-adrenergic agonist, which is only indicated for COPD and should not be used in asthma due to the absence of long-term outcome data in asthma.

Long-acting beta2-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

Hypersensitivity

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

Paradoxical bronchospasm

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

Deterioration of disease

Onbrez 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 Onbrez Breezhaler, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. An increase in the daily dose of Onbrez 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 Onbrez Breezhaler at the recommended doses, as with other beta$_2$-adrenergic agonists, indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

Cardiovascular effects

Like other beta$_2$-adrenergic agonists, indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of QT interval, and ST segment

depression, although the clinical significance of these observations is unknown. Therefore, long-acting beta$_2$-adrenergic agonists (LABA) or LABA containing products such as Onbrez Breezhaler should be used with caution in patients with known or suspected prolongation of the QT interval or treated with medicinal products affecting the QT interval.

Hypokalaemia

Beta$_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalemia 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 Onbrez 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 Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetic medicinal products

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

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

Hypokalaemic treatment

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

Beta-adrenergic blockers

Beta-adrenergic blockers and beta$_2$-adrenergic agonists may weaken or antagonise the effect of each other when administered concurrently. Therefore indacaterol should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling

reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Metabolic and transporter based interactions

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is not known whether indacaterol/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of indacaterol/metabolites in milk (see section 5.3). A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Onbrez 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

Onbrez Breezhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

At the recommended doses, the adverse reaction profile of Onbrez 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 Onbrez Breezhaler and on placebo.

Tabulated summary of adverse reactions

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

Adverse reactions in Table1 are listed according to MedDRA system organ class in the COPD safety database. Within each system organ class, adverse reactions are ranked by frequency in descending order according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse Reactions	Frequency category Onbrez Breezhaler 150 mcg	Frequency category Onbrez Breezhaler 300 mcg
Infections and infestations		
- Upper respiratory tract infection	Common	Very common
- Nasopharyngitis	Common	Very common
- Sinusitis	Common	Common
Immune System Disorders		
- Hypersensitivity[1]	Uncommon	Uncommon
Metabolism and nutrition disorders		
- Diabetes mellitus and hyperglycemia	Uncommon	Common
Nervous system disorders		
- Headache	Common	Common
- Dizziness	Common	Common

- Paraesthesia	Uncommon	Uncommon
Cardiac disorders		
- Ischaemic heart disease	Uncommon	Common
- Atrial fibrillation	Uncommon	Uncommon
- Palpitations	Uncommon	Common
- Tachycardia	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
- Cough	Common	Common
- Oropharyngeal pain including throat irritation	Common	Common
- Rhinorrhoea	Common	Common
- Paradoxical bronchospasm	Uncommon	Uncommon
Skin and subcutaneous tissue disorders		
Pruritus/rash	Uncommon	Common
Musculoskeletal and connective tissue disorders		
- Muscle spasm	Common	Common
- Myalgia	Uncommon	Uncommon
- Musculoskeletal pain	Uncommon	Common
General disorders and administration site conditions		
- Chest pain	Common	Common
- Peripheral oedema	Common	Common

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

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

Description of selected adverse reactions

In Phase III clinical studies, healthcare providers observed during clinic visits that on average 17-20% of patients experienced a sporadic cough that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds (about 10 seconds in current smokers). It was observed with a higher frequency in female than in male patients and in current smokers than in ex-smokers. This cough experienced post inhalation did not lead to any

patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 8.2% of patients reported cough as an adverse event). There is no evidence that cough experienced post inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy.

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial agonist at the human $beta_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the human heart, there are also $beta_2$-adrenergic receptors in the human heart comprising 10-50% of the total adrenergic receptors. The precise function of $beta_2$-adrenergic receptors in the heart is not known, but

their presence raises the possibility that even highly selective beta$_2$-adrenergic agonists may have cardiac effects.

Pharmacodynamic effects

Onbrez 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 FEV1 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.

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

Effects on cardiac electrophysiology

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

Onbrez 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 Onbrez 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 Onbrez 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

5.2 Pharmacokinetic properties

Indacaterol is a chiral molecule with R-configuration.

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

Absorption

The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 microgram to 600 microgram) in a dose proportional manner. Absolute bioavailability of indacaterol after an inhaled dose was on average 43% to 45%. Systemic exposure results from a composite of pulmonary and gastrointestinal absorption; about 75% of systemic exposure was from pulmonary absorption and about 25% from gastrointestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 14 days. The mean accumulation ratio of indacaterol, i.e. AUC over the 24-h dosing interval on Day 14 compared to Day 1, was in the range of 2.9 to 3.5 for once-daily inhaled doses between 150 microgram and 600 microgram.

Distribution

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

Biotransformation

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

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

Elimination

In clinical studies which included urine collection, the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 litres/hour. When compared with the serum clearance of indacaterol of 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the faecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human faeces primarily as unchanged parent substance (54% of the dose) and, to a lesser extent, hydroxylated

indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.

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

Special populations

A population pharmacokinetic analysis showed that there is no clinically relevant effect of age (adults up to 88 years), sex, weight (32 [1]- 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 beta2-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 F1 offspring was observed in the peri- and post-developmental rat study at an exposure 14-fold higher than in humans treated with Onbrez 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 beta2-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 Onbrez 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
Printing ink black (150mcg only)
Printing ink blue (300mcg only)

Printing ink black
Shellac (E904), Iron oxide black (E172, C.I. 77499), N-butyl alcohol, Water purified, Propylene glycol (E1520), Ethanol, anhydrous, Isopropyl alcohol, Ammonia solution, concentrated

Printing ink blue

Shellac (E904), FD&C Blue #1/Brilliant Blue FCF Aluminium Lake (E133, C.I. 42090), N-butyl alcohol, Propylene glycol (E1520), Titanium dioxide (E171, C.I. 77891), Iron oxide black (E172, C.I. 77499), Industrial methylated spirit 74 OP, Isopropyl alcohol, Water purified, Ethanol, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

Carton containing 30 capsules and one Onbrez Breezhaler inhaler.

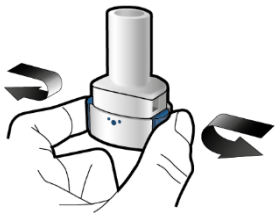
6.6 Special precautions for disposal and other handling

Each inhaler should be disposed after 30 days of use.

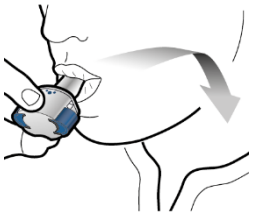
Instructions for handling and use

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

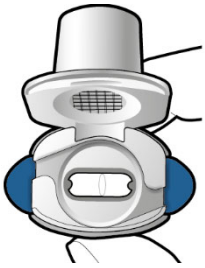
Insert



Pierce and release

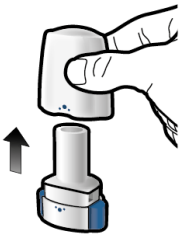


Inhale deeply

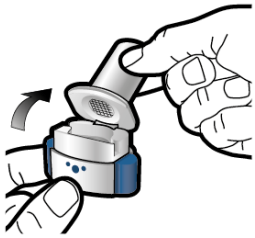


Check capsule is empty

1

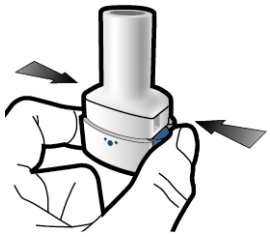


Step 1a:
Pull off cap

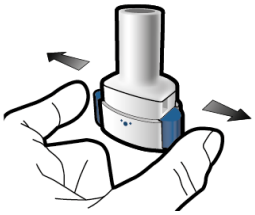


Step 1b:
Open inhaler

2



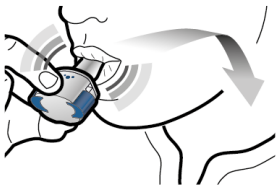
Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced.
Only pierce the capsule once.



Step 2b:
Release side buttons

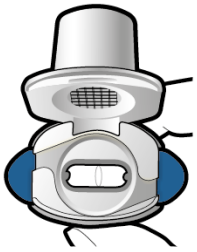
3

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



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

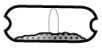
Check



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

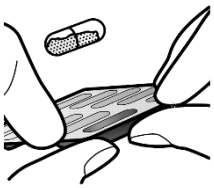
If there is powder left in the capsule:

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



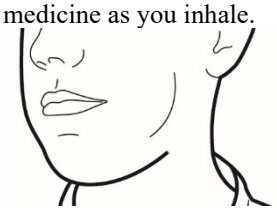
Powder remaining

Empty

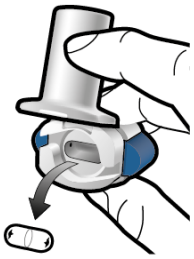


Step 1c:
Remove capsule
Remove one capsule from the blister.
Do not swallow the capsule.

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

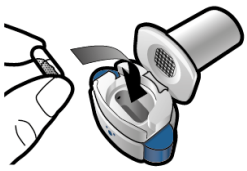


Step 3c:
Hold breath
Hold your breath for up to 5 seconds.

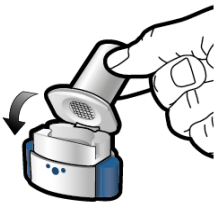


Remove empty capsule
Put the empty capsule in your household waste.

Close the inhaler and replace the cap.



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



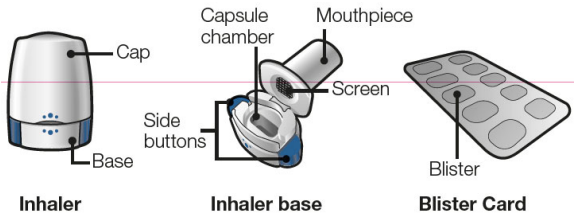
Step 1e:
Close inhaler

Important Information

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

Your Onbrez Breezhaler Inhaler pack contains:

- One Onbrez Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Onbrez Breezhaler capsules to be used in the inhaler



Frequently Asked Questions

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

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

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

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

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

Disposing of the inhaler after use
Each inhaler should be disposed of 30 days of use. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

7. Registration Holder and importer:

Novartis Israel Ltd.,

POB 7126, Tel Aviv.

8. Registration Numbers:

Onbrez Breezhaler 150 MCG : 144 76 33112

Onbrez Breezhaler 300 MCG : 144 75 33111

Revised in Jun2021 according to MOHs guidelines