1 PRODUCT NAME

ONBREZ® BREEZHALER® 150 microgram inhalation powder, hard capsules
ONBREZ® BREEZHALER® 150 microgram inhalation powder, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ONBREZ® hard capsules is supplied with a BREEZHALER® inhalation device.

150 microgram inhalation powder hard capsules

Each capsule contains 194 microgram indacaterol maleate equivalent to 150 microgram indacaterol.

The delivered dose leaving the mouthpiece of the BREEZHALER® device is equivalent to 120 microgram indacaterol.

300 microgram inhalation powder hard capsules

Each capsule contains 389 microgram indacaterol maleate equivalent to 300 microgram indacaterol.

The delivered dose leaving the mouthpiece of the BREEZHALER® device is equivalent to 240 microgram indacaterol.

Excipients:

Lactose monohydrate and gelatin

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

150 microgram: Black product code “IDL 150” printed above and black company logo printed under black bar on clear colourless hard capsule.

300 microgram: Blue product code “IDL 300” printed above and blue company logo printed under blue bar on clear colourless hard capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ONBREZ® BREEZHALER® is a long-acting β2-agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease (See section 5.1).

4.2 Dose and method of administration

Dosage

Adults with COPD

The recommended and usual dosage of ONBREZ® BREEZHALER® is the once-daily inhalation of the content of one 150 microgram ONBREZ® capsule using the BREEZHALER® inhaler. The dosage should only be increased on medical advice.

Once-daily inhalation of the content of one 300 microgram ONBREZ® capsule, using the BREEZHALER® inhaler, has only been shown to provide additional clinical benefit to some patients. The maximum dose is 300 microgram once-daily. This dose should not be exceeded.

Patients with COPD who require corticosteroids should retain this treatment. (See section 4.4 - Patients who require corticosteroids).

Special populations

Patients with renal impairment

No dosage adjustment is required for renally impaired patients.

Patients with hepatic impairment

No dosage adjustment is required for patients with mild and moderate hepatic impairment. There is no data available for subjects with severe hepatic impairment (See section 5.2).

Paediatric population

ONBREZ® BREEZHALER® should not be used in patients under 18 years of age.

Elderly patients

No dose adjustment is needed for elderly patients.

Method of Administration

ONBREZ® capsules must be administered only by the oral inhalation route and only using the BREEZHALER® inhaler. ONBREZ® capsules must not be swallowed. 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. ONBREZ® capsules must always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

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.

4.3 Contraindications

Hypersensitivity to any ingredients of the preparation (See section 2).

4.4 Special warnings and precautions for use

Asthma and mixed airways disease

In the absence of long-term outcome data in asthma with indacaterol, ONBREZ® should not be used in asthma. Indacaterol, the active ingredient of ONBREZ®, belongs to the class of long-acting β2-adrenoceptor agonists. In a study with salmeterol, a different long-acting β2- agonist, a higher rate of severe asthma episodes and death due to asthma was observed in the patients treated with salmeterol than in the placebo group. 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. A differential diagnosis should be made to exclude asthma or mixed airways disease before initiating ONBREZ®. See section 5.1 for clinical experience to date.

Hypersensitivity reactions

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

Patients who require corticosteroids

COPD patients being treated with long-term inhaled glucocorticoids therapy should continue this therapy when initiating ONBREZ®.

Paradoxical bronchospasm

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

Deterioration of disease

ONBREZ® is not indicated for the initial treatment of acute episodes of symptomatic exacerbations, i.e., as a rescue therapy. In case of deterioration of COPD whilst on treatment with ONBREZ®, a re-evaluation of the patient and the COPD treatment regimen should be undertaken. An increase in the daily dose of ONBREZ® beyond the maximum dose is not appropriate. The patient's COPD management plan should make this clear.

Systemic effects

Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of ONBREZ® at the recommended doses, as with other β2-adrenergic agonists, ONBREZ®, 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 β2-adrenergic agonists.

As with other inhaled beta2-adrenergic drugs, ONBREZ® BREEZHALER® should not be used more often or at higher doses than recommended.

ONBREZ® BREEZHALER® should not be used in conjunction with other long-acting beta2-adrenergic agonists or medications containing long-acting beta2-adrenergic agonists.

Cardiovascular effects

Like other β2-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, the drug may need to be discontinued. In addition, β-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT interval and ST segment depression, although the clinical significance of these findings is unknown.

Clinically relevant effects on prolongation of the QTc-interval have not been observed in clinical studies of ONBREZ® BREEZHALER® at recommended therapeutic doses (see section 5.1).

Hypokalaemia

β2-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-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with ONBREZ® plasma glucose should be monitored more closely in diabetic patients.

During clinical studies, clinically notable changes in blood glucose (>9.99 mmol/L) were generally more frequent by 1-2% on ONBREZ® at the recommended doses than on placebo. ONBREZ® 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, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Drugs known to prolong QTc interval

ONBREZ®, as other β2-adrenergic agonists, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs that are known to prolong the QTc-interval may have an increased the risk of ventricular arrhythmia (see section 4.4).

Sympathomimetic agents

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of ONBREZ® (see section 4.4).

Hypokalaemia

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium- sparing diuretics may potentiate the possible hypokalaemic effect of β2-adrenergic agonists (see section 4.4).

β-adrenergic blockers

β-adrenergic blockers may weaken or antagonise the effect of β2-adrenergic agonists ONBREZ®. Therefore ONBREZ® should not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective β-adrenergic blockers should be preferred, although they should be administered with caution.

Metabolic and transporter based drug interaction

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of ONBREZ®. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in Cmax. Co-administration of erythromycin with ONBREZ® resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for Cmax. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and Cmax, respectively. Taken together, the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Given the safety data of [D] and of the pivotal studies (which both confirmed safe use of a 600 microgram dosage regimen). The magnitude of exposure increases due to drug- interactions does not raise any safety concerns for therapeutic doses of 150 microgram or 300 microgram. given the safety experience of treatment with ONBREZ® in clinical trials of up to one year at doses two- to four-fold the recommended therapeutic doses.

Indacaterol has not been shown to cause drug interactions with co-medications. In vitro investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medications at the systemic exposure levels achieved in clinical practice.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy (Category B3)

No clinical data on exposed pregnancies in COPD patients are available. Indacaterol was not teratogenic at subcutaneous doses up to 1 mg/kg/day in rats and 3 mg/kg/day in rabbits (up to 43- and 248-times, respectively, the AUC in humans at 300 µg/day). An increase in the incidence of a rib skeletal variation and retarded ossification were observed in the rabbit at 3 mg/kg/day, possibly secondary to maternal toxicity; embryofetal development was unaffected in the species at 1 mg/kg/day (relative exposure, 98). Impaired learning and decreased fertility were observed in the pups of rats given indacaterol at a subcutaneous dose of 1mg/kg/day during pregnancy and lactation (relative exposure, 37; unaffected at 0.3 mg/kg/day, associated with a relative exposure level of 15). The potential risk for humans is unknown. Because there are no adequate and well-controlled studies in pregnant women, indacaterol should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Labour and delivery

Like other β2-adrenergic agonists, ONBREZ® may inhibit labour due to a relaxant effect on uterine smooth muscle.

Use in Lactation

It is not known whether indacaterol passes into human breast milk. Indacaterol and several of its metabolites have been detected in the milk of lactating rats, and reduced body weight gain, impaired learning and decreased fertility were observed in pups of rats treated with indacaterol during pregnancy and lactation. Because many drugs are excreted in human milk, as with other inhaled β2-adrenergic drugs, the use of ONBREZ® by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Fertility

No adverse effects on fertility were observed in male and female rats given indacaterol by subcutaneous injection at doses up to 2 mg/kg/day (yielding approximately 114-times [males] and 86-times [females] the serum AUC in humans at the maximum recommended dose of 300 µg/day.

4.7 Effects on ability to drive and use machines

There are no data to suggest that indacaterol affects the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety experience with ONBREZ® BREEZHALER® comprises exposure of up to one year at doses two- to four-fold the recommended therapeutic doses.

The most common adverse drug reactions at the recommended doses were nasopharyngitis, cough, upper respiratory tract infection headache and muscle spasms. These were in the vast majority mild or moderate.

At the recommended doses, the adverse drug reaction profile of indacaterol in patients with COPD shows clinically insignificant systemic effects of β2-adrenergic stimulation. Mean heart rate changes were less than one beat per min, and tachycardia was infrequent and reported at a similar rate as under placebo treatment. Relevant prolongations of QTcF were not detectable in comparison to placebo. The frequency of notable QTcF 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 on indacaterol and on placebo.

Description of population

The ONBREZ® BREEZHALER® Phase III clinical development program consisted of 8 key studies and enrolled 5,430 patients with a clinical diagnosis of moderate to severe COPD. Safety data from five of these studies with treatment durations of 12 weeks or longer were pooled from 2,484 exposed to indacaterol up to 600 microgram once-daily, of which 957 were on treatment with 150 microgram once-daily (for up to six months) and 853 on treatment with 300 microgram once-daily. Approximately 41% of patients had severe COPD. The mean age of patients was 63 years, with Treatment durations in the three trials were 3, 6 and 12 months, respectively. 47% of patients were aged 65 years of older, and the majority (86%) was Caucasian. (See section 5.1 for further information.)

Adverse reactions from clinical trials

Adverse drug reactions in Table 2 are from this pooled COPD safety database, listed according to MedDRA system organ class and sorted in descending order of frequency on indacaterol 150 microgram once-daily. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Table 2 Adverse Drug Reactions

Adverse Drug Reactions	Indacaterol 150 microgram o.d. n (%)	Indacaterol 300 microgram o.d. n (%)	Placebo n (%)	Frequency category
Infections and infestations				
- Nasopharyngitis	57 (7.6)	82 (9.6)	90 (7.6)	Common
- Upper respiratory tract infection	42(5.6)	45 (5.3)	46 (3.9)	Common
- Sinusitis	13 (1.7)	23 (2.7)	14 (1.2)	Common
Respiratory, thoracic and mediastinal disorders				
- Cough	40 (5.4)	56 (6.6)	53 (4.5)	Common
- Oropharyngeal pain	14 (1.9)	15 (1.8)	13 (1.1)	Common
- Rhinorrhoea	5 (0.7)	13 (1.5)	1 (0.1)	Common
Nervous system disorders				
- Vertigo	6 (0.8)	3 (0.4)	3 (0.3)	Uncommon
- Paraesthesia	5 (0.7)	1 (0.1)	2 (0.2)	Uncommon
Musculoskeletal and connective tissue disorders				
- Muscle spasm	16 (2.4)	32 (3.8)	12 (1.0)	Common
- Myalgia	12 (1.6)	5 (0.6)	6 (0.5)	Common
- Musculoskeletal pain	4 (0.5)	11 (1.3)	7 (0.6)	Common
Cardiac disorders				
Ischaemic heart disease*	10 (1.3)	12 (1.4)	6 (0.5)	Common
Atrial fibrillation	7 (0.9)	5 (0.6)	6 (0.5)	Uncommon

General disorders and administration site conditions				
- Peripheral oedema	11 (1.5)	8 (0.9)	6 (0.5)	Common
- Chest pain	3 (0.4)	10 (1.2)	5 (0.4)	Common
- Chest discomfort	6 (0.8)	1 (0.1)	1 (0.1)	Uncommon
Metabolism and nutrition disorders				
- Diabetes mellitus and hyperglycaemia*	9 (1.2)	11 (1.3)	9 (0.8)	Common
Gastrointestinal disorders				
- Dry mouth	9 (1.2)	5 (0.6)	5 (0.4)	Common

Adverse drug reactions (ADRs) selected based on pooled COPD safety database; frequency of individual ADRs based on 6-month COPD database; frequency category based on 150 microgram or 300 microgram dose, whichever had higher rate. Terms marked with * are Standard MedDRA Query terms.

At a higher dose, i.e., 600 microgram once-daily, the safety profile of indacaterol was overall similar to that of recommended doses. Additional adverse drug reactions were tremor and anaemia. Nasopharyngitis and muscle spasm occurred more frequently than at the recommended doses.

Selected adverse drug reactions

In Phase III clinical studies, health care 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. 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 of COPD and only 6.6% of patients overall reported cough as an adverse event). Phase III studies did not demonstrate an association between cough experienced post inhalation and bronchospasm, exacerbations, deteriorations of disease, or loss of efficacy.

Post-marketing experience - Adverse drug reactions from spontaneous reports and literature cases

The following adverse drug reactions have been derived from post-marketing experience with ONBREZ® BREEZHALER® via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing numbers of spontaneous reports.

Table 3 Adverse Drug Reactions from spontaneous reports (frequency not known)

Nervous system disorders: Headache, dizziness
Cardiac disorders: Tachycardia, palpitation
Respiratory, thoracic and mediastinal disorders: Paradoxical bronchospasm
Skin and subcutaneous tissue disorders: Rash, pruritus

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 increase and QTc interval.

An overdose of indacaterol is likely to lead to exaggerated effects typical of β2-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 β-blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of β-adrenergic blockers may provoke bronchospasm.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Indacaterol is an 'ultra' long-acting β2-adrenergic agonist for once-daily administration. The pharmacological effects of β2-adrenoceptor agonists, including indacaterol, 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 has more than 24-fold greater agonist activity at β2-receptors compared to β1-receptors and 20-fold greater agonist activity compared to β3-receptors. This selectivity profile is similar to eformoterol.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human β2-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although β2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and β1-receptors are the predominant receptors in the human heart, there are also β2-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of β2-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective β2-adrenergic agonists may have cardiac effects.

Long-acting β2-adrenergic agonists are not a disease modifying agents. There are no data available on the long term morbidity and mortality benefits of indacaterol in patients with COPD.

Primary Pharmacodynamic Effects

Indacaterol provided consistently significant improvement in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours in a number of clinical pharmacodynamic and efficacy trials. There was a rapid onset of action within 5 minutes after inhalation of indacaterol comparable to the effect of the fast-acting β2-agonist salbutamol and a peak effect occurring between 2-4 hours following the dose. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing for up to 52 weeks. The bronchodilator effect did not depend on the time of dosing (morning or evening).

Indacaterol reduced both dynamic and resting hyperinflation in patients with moderate to severe COPD. Peak inspiratory capacity during constant, sub-maximal exercise increased by 317 mL compared

to placebo after administration of 300 microgram once-daily over 14 days. A statistically significant increase in resting inspiratory capacity, exercise endurance and FEV_1 were also demonstrated as well as a significant improvement in measures of dyspnoea.

Secondary Pharmacodynamic Effects

The characteristic adverse effects of inhaled β2-adrenergic agonists occur as a result of activation of systemic β-adrenergic receptors. The most common adverse effects include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium and increases in plasma glucose.

Effects on cardiac electrophysiology

The effect of indacaterol on the QT interval was evaluated in a double-blind, placebo- and active (moxifloxacin)-controlled study following multiple doses of indacaterol 150 microgram, 300 microgram or 600 microgram once-daily for 2 weeks in 404 healthy volunteers. Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QTcF). Maximum mean prolongation of QTcF intervals were <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time-matched comparisons versus placebo. This shows that there is no concern for a pro-arrhythmic potential related to QT-interval prolongations at recommended therapeutic doses. There was no evidence of a concentration-delta QTc relationship in the range of doses evaluated.

Electrocardiographic monitoring in patients with COPD

The effect of indacaterol on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 605 patients with COPD from a 26-week, double-blind, placebo-controlled Phase III study (see section 5.1). Holter monitoring occurred once at baseline and up to 3 times during the 26-week treatment period (at weeks 2, 12 and 26).

A comparison of the mean heart rate over 24 hours showed no increase from baseline for both doses evaluated, 150 microgram once-daily and 300 microgram once-daily. The hourly heart rate analysis was similar for both doses compared to placebo and tiotropium. The pattern of diurnal variation over 24 hours was maintained and was similar to placebo.

No difference from placebo or tiotropium was seen in the rates of atrial fibrillation, time spent in atrial fibrillation and also the maximum ventricular rate of atrial fibrillation.

No clear patterns in the rates of single ectopic beats, couplets or runs were seen across visits.

Because the summary data on rates of ventricular ectopic beats can be difficult to interpret, specific pro-arrhythmic criteria were analysed. In this analysis, baseline occurrence of ventricular ectopic beats was compared to change from baseline, setting certain parameters for the change to describe the pro-arrhythmic response. The number of patients with a documented pro-arrhythmic response was very similar across both indacaterol doses compared to placebo and tiotropium.

Overall, there was no clinically relevant difference in the development of arrhythmic events in patients receiving indacaterol treatment over those patients who received placebo or treatment with tiotropium.

Effects on serum potassium and plasma glucose

Changes in serum potassium and plasma glucose were evaluated in a 26-week, double-blind, placebo-controlled Phase III study (see section 5.1). At 1 hour post-dose at week 12, mean changes compared to placebo in serum potassium ranging from 0.03 to 0.05 mmol/L and in mean plasma glucose ranging from 0.25 to 0.31 mmol/L were observed.

Clinical efficacy and safety

The ONBREZ® BREEZHALER® Phase III clinical development program consisted of 8 key studies and enrolled 5,430 patients with a clinical diagnosis of COPD, who were 40 years old or older, had a smoking history of at least 20 pack years, had a post-bronchodilator FEV_1 <80% and ≥30% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio of less than 70%. The Phase III program includes 3 large, pivotal efficacy and safety studies of up to 52 weeks duration (B2334, B2335S and B2336), a 26 weeks extension study of B2335S (B2335SE), a 12 weeks efficacy and safety study B2346 and 3 small, short-term profiling crossover studies (B2305, B2307, B2340) in patients with COPD.

The three pivotal studies, (B2334, B2335 and B2336), used the trough 24 hour FEV_1 as the primary endpoint to reflect the efficacy of study drug in COPD over 24 hours. A difference of 120 mL in trough FEV_1 between indacaterol and placebo was considered to be a clinically important difference for COPD patients. Numerous secondary endpoints were reported. These included the St. Georges' Respiratory Questionnaire, the transitional dyspnoea index, COPD exacerbations, use of rescue medication, days of poor control and daytime and night-time symptoms. These were tested according to a complex series of statistical analyses – the reporting of statistical significance may not relate to predefined clinical significance, unlike the primary endpoint.

The registration clinical trial program enrolled a diverse patient group. The mean age in the clinical trial program was 63 years. Of the total number of patients who received indacaterol in the clinical studies from the pooled 6-month database, 1,014 were <65 years, 710 were 65–74 years and 219 were ≥75 years of age. The estimated median number of smoking pack-years was around 42 pack years. Approximately 40% of patients had severe COPD and 40% of patients had three or more CV risk factors at enrolment. ICS use occurred in 35% of patients treated with the 150 microgram and 47% of patients treated with the 300 μg. Exclusion criteria included asthma, use of anticholinergics or long acting LABAs during the study, other excluded medications were non-potassium sparing diuretics, non-selective beta-blockers, quinidine-like medications, tricyclic antidepressants, monoamino-oxidase inhibitors, terfenadine, astemizole and any other drugs contraindicated for QT prolongation; concomitant pulmonary disease including lung cancer, active pulmonary tuberculosis, bronchiectasis, hospitalization for an exacerbation of airway disease in the prior 6 weeks, type I or uncontrolled type II diabetes (consistent HbA1c >8%), history or family history of long QT syndrome, other clinically relevant laboratory abnormality or clinical condition which might compromise the patient's safety.

In these studies, indacaterol, administered once-daily at doses of 150 microgram and 300 microgram, showed clinically meaningful improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours. At the 12-week primary endpoint (24-hour trough FEV_1), the 150 microgram dose resulted in a 0.13-0.18 L increase compared to placebo ($p<0.001$) and a 0.06 L increase compared to salmeterol 50 microgram twice a day ($p<0.001$). The 300 microgram dose resulted in a 0.17-0.18 L increase compared to placebo ($p<0.001$) and a 0.1 L increase compared to formoterol 12 microgram twice a day ($p<0.001$). Both doses resulted in an increase of 0.04-0.05 L over open-label tiotropium 18 microgram once-daily (150 microgram, $p=0.004$; 300 microgram, $p=0.01$)

Indacaterol administered once-daily at the same time each day, either in the morning or evening, had a rapid onset of action within 5 minutes similar to that of salbutamol 200 microgram and statistically significantly faster compared to salmeterol/fluticasone 50/500 μg, and a mean peak improvements in FEV_1 relative to baseline of 0.25-0.33 L at steady-state occurring between 2-4 hours following the dose. The 24-hour bronchodilator effect of ONBREZ BREEZHALER was maintained from the first dose throughout a one-year period with no evidence of loss of efficacy (tachyphylaxis).

In the 3 smaller, crossover Phase III studies, indacaterol, administered once-daily at the same time each day, either in the morning or evening, provided significant improvement in lung function (FEV_1 over 24 hours)

In a 26-week, placebo- and active (open label tiotropium)-controlled study in 2,059 patients, the mean improvement relative to baseline in FEV_1 at 5 minutes was 0.12 L and 0.13 L for indacaterol 150 microgram and 300 microgram once-daily, respectively, and the mean peak improvement, relative to baseline, after the first dose (Day 1) was 0.19 L and 0.24 L, respectively, and improved to 0.23 L and 0.26 L, respectively, when pharmacodynamic steady-state was reached (Day 14) . At the primary end point (Week 12), both indacaterol 150 microgram and 300 microgram once-daily treatment groups showed a significantly higher trough FEV_1 value compared to placebo (both 0.18 L, $p<0.001$). The non-inferiority of indacaterol (150 microgram and 300 microgram) to tiotropium (18 microgram od) was also established in this study.

In this study, 12-hour serial spirometric measurements were performed in a subset of patients throughout daytime hours (12 hours). Serial FEV_1 values over 12 hours at Day 1 and trough FEV_1 values at Day 2 are shown in Figure 1, and at Day 182/183 in Figure 2, respectively. Improvement of lung function was maintained for 24 hours after the first dose and consistently maintained over the 26-week treatment period with no evidence of tolerance.

Figure 1 Serial least square mean FEV_1 over 12 h at Day 1 and trough FEV_1 at Day 2 (ITT subset with 12 hour serial spirometry)

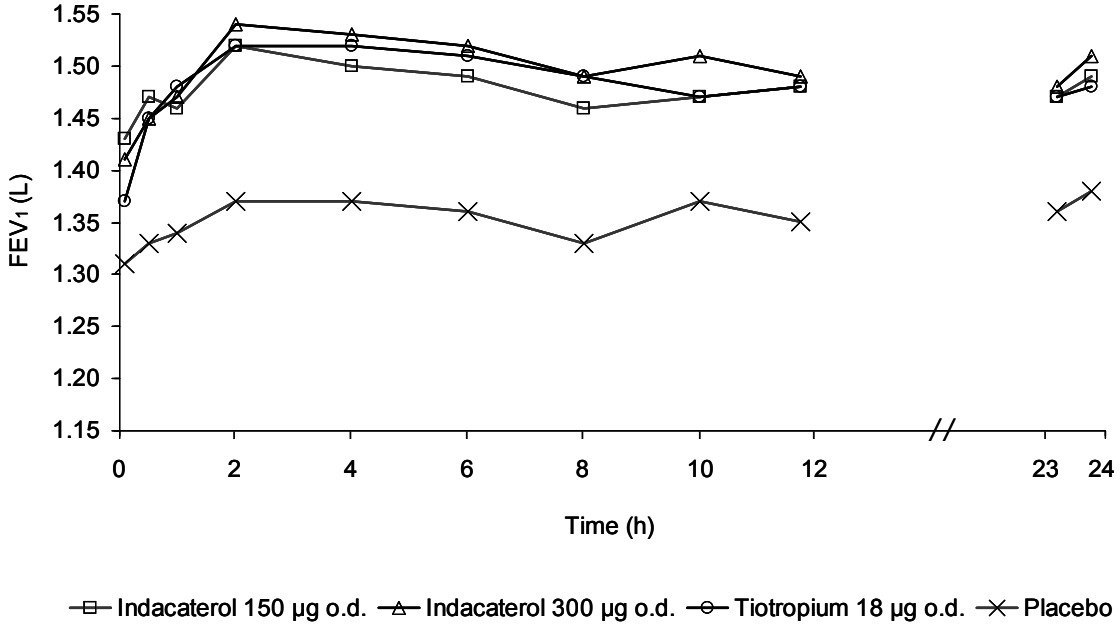
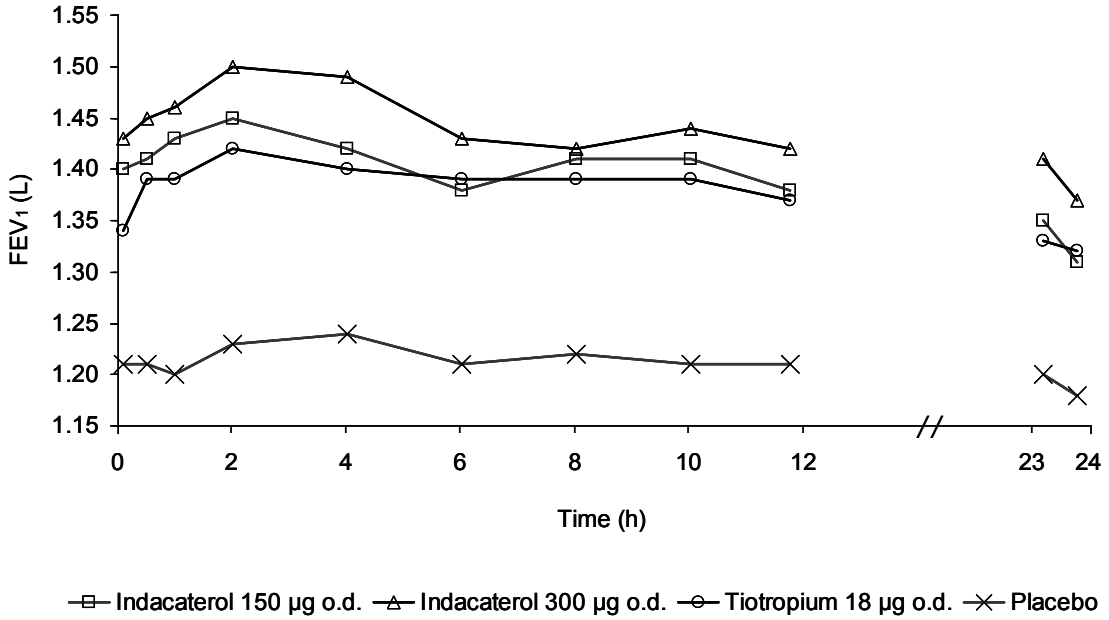


Figure 2 Serial least square mean FEV_1 over 12 h at Day 182 and trough FEV_1 at Day 183 (ITT subset with 12 hour serial spirometry)



In a 26-week, placebo-controlled safety extension to this study in 414 patients, efficacy was not a primary endpoint, however at the secondary end point (Week 52) of trough FEV_1, treatment with both ONBREZ BREEZHALER 150 microgram and 300 microgram once-daily resulted in a significantly higher trough FEV_1 value compared to placebo (0.17 L, $p<0.001$ and 0.18L, $p<0.001$, respectively).

Results of a 12-week, placebo-controlled study in 416 patients which evaluated the 150 microgram once-daily dose, were similar to the results for this dose in the 26-week study. The mean peak improvement in FEV_1, relative to baseline, was 0.23 L after 1 day of once-daily treatment. At the primary end point (Week 12), treatment with indacaterol 150 microgram once-daily resulted in a significantly higher trough FEV_1 value compared to placebo (0.13 L, $p<0.001$).

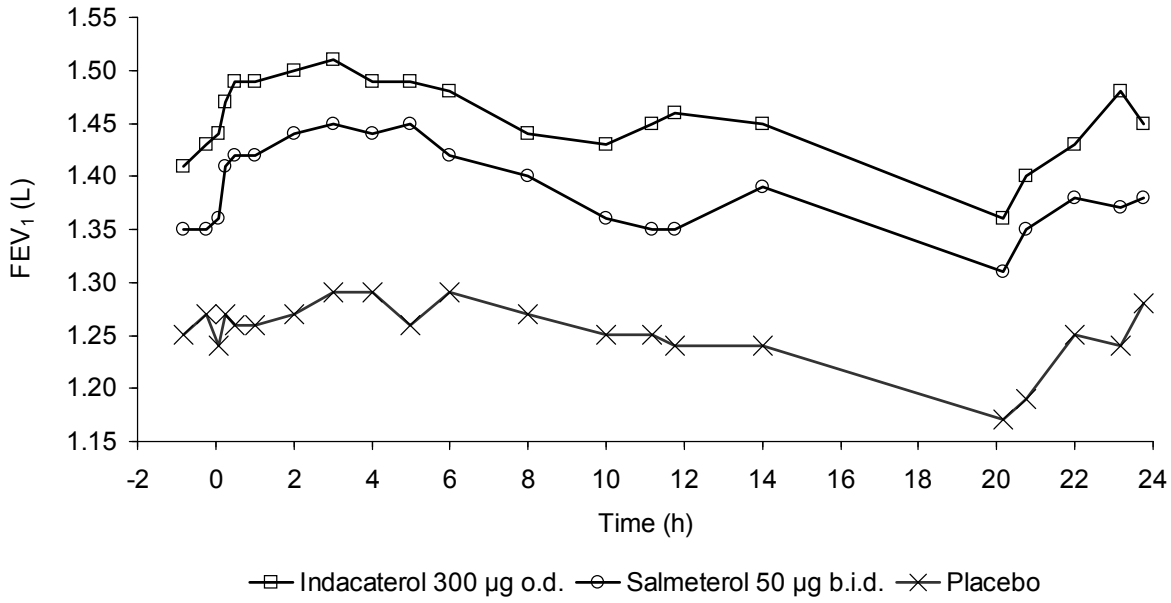
In a 26-week, placebo- and active (blind salmeterol)-controlled study in 1,002 patients which evaluated the ONBREZ BREEZHALER 150 microgram once-daily dose, the mean improvement in FEV_1, relative to baseline, at 5 minutes was 0.11 L with a peak improvement of 0.25 L relative to baseline after the first dose (Day 1). At the primary end point (Week 12), treatment with ONBREZ BREEZHALER 150 microgram once-daily showed a significantly higher trough FEV_1 value compared to both placebo (0.17 L, $p<0.001$) and to salmeterol (0.06 L, $p<0.001$).

In a 52-week, placebo- and active (eformoterol)-controlled study in 1,732 patients which evaluated the indacaterol 300 microgram once-daily dose and a higher dose, the mean improvement in FEV_1, relative to baseline, at 5 minutes was 0.14 L with a peak improvement of 0.20 L relative to baseline after the first dose (Day 1). At the primary end point (Week 12), treatment with indacaterol 300 microgram once-daily resulted in a significantly higher trough FEV_1 value compared to placebo (0.17 L, $p<0.001$) This improvement of lung function was maintained over the 52-week treatment period with no evidence of loss of efficacy over this period.

In a 2-week, placebo- and active (open label salmeterol)-controlled crossover study, 24-hour spirometry was assessed in 68 patients. Serial spirometry values over 24 hours are displayed in Figure 3. After 14 days of once-daily treatment, improvement of lung function compared to placebo was maintained for 24 hours. Similar results from 24-hour serial spirometry were observed after 26 weeks in a subset of patients (n=236) from the 26-week study. Both studies further support the improvement

in FEV_1 over placebo with indacaterol administered once-daily, and that bronchodilation was maintained throughout the 24-hour dosing interval, in comparison to placebo.

Figure 3 24 h profile of least squares means of FEV_1 (L) after 14 days treatment (Modified ITT population)



In terms of the evaluation of indacaterol 300 microgram was compared to eformoterol in the 52 week study and indacaterol was significantly better than eformoterol on 24 hour trough FEV_1 at week 12 (0.10 mL, $p<0.01$), though this was not the primary endpoint of the study. Efficacy and safety data to support the registration of the of 150 microgram indacaterol maleate dose were limited to 6 months' experience in the Phase 3 studies. Post registration study extension 2335SE provides efficacy and safety data up to 12 months.

The following health outcome effects were demonstrated in the long-term studies of 12-, 26- and 52-week treatment duration. These health outcomes were multiple measured secondary endpoints and the type 1 error were not formally controlled a priori for these comparisons.

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 1).

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 show a ratio of rates of 0.68 (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 1 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

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 (Vz) of indacaterol was 2,557 L indicating an extensive distribution. The in vitro human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Metabolism

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 h. A hydroxylated derivative was the most prominent metabolite in serum. A phenolic O-glucuronide of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, a carboxylic acid and a N-dealkylated product were further metabolites identified.
In vitro investigations indicated that UGT1A1 is the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant

CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. In vitro investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

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 L/h. When compared with the serum clearance of indacaterol of 23.3 L/h, 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 drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.
Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 52 hours which is consistent with the observed time-to-steady state of approximately 12 to 14 days.

Pharmacokinetics in special patient groups

A population analysis of the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated that indacaterol can be used safely in all age and weight groups and regardless of gender. It did not suggest any difference between ethnic subgroups in this population.

The pharmacokinetics of indacaterol was investigated in two different UGT1A1 genotypes – the fully functional [(TA)6, (TA)6] genotype and the low activity [(TA)7, (TA)7] genotype (Gilbert's syndrome genotype). The study demonstrated that steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

Patients with mild and moderate hepatic impairment showed no relevant changes in Cmax 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.

Carcinogenicity

The carcinogenic potential of indacaterol has been evaluated in a 26-week oral gavage study in transgenic mice (CB6F1/TgrasH2) and a 2-year inhalation study in rats. No carcinogenicity was observed in mice at doses up to 600mg/kg/day (49-times in males and 106-times in females the AUC in humans at the maximum recommended clinical dose of 300 µg/day). Lifetime treatment of rats at 2.1 mg/kg/day (relative exposure, 14) resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females. Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other β2-adrenergic agonist drugs. Their development is consistent with proliferation in response to prolonged relaxation of the smooth muscle (pharmacologically mediated), and the finding is not considered to indicate a carcinogenic hazard to patients. Squamous metaplasia was observed in the upper respiratory tract tissues of mice, rats and dogs following inhalation administration of indacaterol. This finding is consistent with an adaptive response to irritation and occurred at large multiples of the human dose. It is not considered to indicate a carcinogenic hazard to humans with the therapeutic use of indacaterol. No data are available to determine whether exposure to tobacco smoke enhances the respiratory tract toxicity of indacaterol.

Genotoxicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose monohydrate

Capsule shell
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C.
Protect from moisture.

6.5 Nature and contents of container

ONBREZ® BREEZHALER® (indacaterol maleate) hard capsules are supplied in blister packs of 30 with a BREEZHALER® inhalation device to allow oral inhalation of the content of the capsule shell.

Pack sizes:

Carton containing 10 capsules and a Breezhaler device
Carton containing 30 capsules and a Breezhaler device
Carton containing 60 capsules and two Breezhaler devices.
**Not all pack sizes may be marketed.*

6.6 Special precautions for disposal and handling

For correct administration/use of the product please refer to section 4.2.
Detailed instructions for use are provided in the package leaflet.

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

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Novartis New Zealand Limited
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AUCKLAND 1023

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Auckland 1149
Telephone: 0800 354 335

® = Registered Trademark

9 DATE OF FIRST APPROVAL

18 August 2011

10 DATE OF REVISION OF THE TEXT

15 September 2017

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
All	Adoption of SPC format
6.3	Updated shelf-life to 30 months

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