
Drug Regulatory Affairs

ONBREZ[®] BREEZHALER[®] and related products*
(Indacaterol maleate (QAB149))

150 microgram and 300 microgram inhalation powder hard capsules

Core Data Sheet

Version 1.1

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosing, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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* Additional trade names covered include OSLIF[®] BREEZHALER[®] and HIROBRIZ[®] BREEZHALER[®] in the EEA, ONBRIZE[®] BREEZHALER[®] in Latin America, and ARCAPTA[®] NEOHALER[®] in the US.

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1 Trade names

150 microgram inhalation powder hard capsules

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

300 microgram inhalation powder hard capsules

ONBREZ[®] BREEZHALER[®] 300 microgram, inhalation powder, hard capsules

Additional trade names include ARCAPTA NEOHALER[®], ONBRIZE[®] BREEZHALER[®], OSLIF[®] BREEZHALER[®] and HIROBRIZ[®] BREEZHALER[®]

2 Description and Composition

Pharmaceutical form

Inhalation powder, hard capsules.

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

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

Active substance

150 microgram inhalation powder hard capsules

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

The delivered dose (the dose that leaves the mouthpiece of the ONBREZ BREEZHALER inhaler) 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 (the dose that leaves the mouthpiece of the ONBREZ BREEZHALER inhaler) is equivalent to 240 microgram indacaterol.

Active moiety

Indacaterol

Excipients

Lactose monohydrate and gelatin

Note: Information might differ in some countries.

3 Indications

ONBREZ BREEZHALER is a long-acting beta₂-agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) [1].

4 Dosage and administration

Adults

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 [1,2,37].

Dosing in special populations

No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or renally impaired patients. No data is available for subjects with severe hepatic impairment (see section 11 Clinical Pharmacology) [3].

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

Method of administration

ONBREZ BREEZHALER capsules must be administered only by the oral inhalation route and only using the ONBREZ BREEZHALER inhaler. ONBREZ BREEZHALER 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 BREEZHALER capsules must always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

5 Contraindications

None.

6 Warnings and precautions

Asthma

ONBREZ BREEZHALER should not be used in asthma due to the absence of long-term outcome data in asthma with ONBREZ BREEZHALER [1].

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 instituted.

Deterioration of disease

ONBREZ BREEZHALER is not indicated for the initial treatment of acute episodes of bronchospasm, *i.e.*, as a rescue therapy. In case of deterioration of COPD whilst on treatment with ONBREZ BREEZHALER, a re-evaluation of the patient and the COPD treatment regimen should be undertaken. An increase in the daily dose of ONBREZ BREEZHALER beyond the maximum dose 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 beta₂-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 beta₂-adrenergic agonists [4].

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 beta₂-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, beta-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave 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 11 Clinical pharmacology).

Hypokalaemia

Beta₂-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, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 8 Interactions) which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia

Inhalation of high doses of beta₂-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 [4].

7 Adverse drug reactions

Summary of 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 [4].

The most common adverse drug reactions at the recommended doses were nasopharyngitis, cough, upper respiratory tract infection, and muscle spasms. These were in the vast majority mild or moderate and became less frequent when treatment was continued [4,38].

At the recommended doses, the adverse drug reaction profile of ONBREZ BREEZHALER in patients with COPD shows clinically insignificant systemic effects of beta₂-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 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 on ONBREZ BREEZHALER and on placebo [4].

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 patients exposed to indacaterol up to 600 microgram once-daily, of which 957 were on treatment with 150 microgram once-daily 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 47% of patients aged 65 years or older, and the majority (86%) was Caucasian [4,38].

Adverse drug reactions from clinical trials

Adverse drug reactions in Table 1 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 [4,38]. Within each system organ class, the adverse 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 reaction: Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Table 1 Adverse drug reactions in pooled COPD safety database

Adverse Drug Reactions	Indacaterol	Indacaterol	Placebo	Frequency category
	150 µg o.d. N= 746 n (%)	300 µg o.d. N= 853 n (%)	N= 1185 n (%)	
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
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
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
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
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
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

Adverse drug reactions (ADRs) selected based on pooled COPD safety database [38]; frequency of individual ADRs based on 6-month COPD database; frequency category based on 150 microgram or 300 microgram dose, whichever had higher rate [4,38]. Terms marked with * are Standard MedDRA Query terms.

At a higher dose, *i.e.*, 600 microgram once-daily, the safety profile of ONBREZ BREEZHALER 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 [4,38].

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). There is no evidence that cough experienced post inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy [4,5,38].

8 Interactions

Drugs known to prolong QTc interval

ONBREZ BREEZHALER, as other beta₂-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 known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see section 6 Warnings and precautions).

Sympathomimetic agents

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of ONBREZ BREEZHALER (see section 6 Warnings and precautions).

Hypokalemia

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta₂-adrenergic agonists (see section 6 Warnings and precautions).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta₂-adrenergic agonists. Therefore ONBREZ BREEZHALER 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 drug interaction

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of ONBREZ BREEZHALER [3]. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (*i.e.*, ketoconazole [8], erythromycin [9] and verapamil [10]). 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 C_{max}. Co-administration of erythromycin with ONBREZ BREEZHALER resulted in an increase of 1.4-

to 1.6-fold for AUC and 1.2 fold for C_{max} . 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 C_{max} , 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. The magnitude of exposure increases due to drug interactions does not raise any safety concerns given the safety experience of treatment with ONBREZ BREEZHALER in clinical trials of up to one year at doses two- to four-fold the recommended therapeutic doses [4].

ONBREZ BREEZHALER 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 [11].

9 Pregnancy and Breast-feeding

Pregnancy

No clinical data on exposed pregnancies in COPD patients are available [4]. Studies in animals have shown reproductive toxicity associated with an increased incidence of one skeletal variation in rabbits (see section 13 Non-clinical safety data). 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 beta₂-adrenergic agonists, ONBREZ BREEZHALER may inhibit labor due to a relaxant effect on uterine smooth muscle.

Breast-feeding

It is not known whether indacaterol passes into human breast milk. The substance has been detected in the milk of lactating rats [12]. Because many drugs are excreted in human milk, as with other inhaled beta₂-adrenergic drugs, the use of ONBREZ BREEZHALER 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

Reproduction studies or other data in animals did not reveal a problem or potential problem concerning fertility in either males or females [13].

10 Overdosage

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 QT_c interval [14].

An overdose of indacaterol is likely to lead to exaggerated effects typical of beta₂-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.

11 Clinical pharmacology

Mechanism of Action

Indacaterol is an 'ultra' long-acting beta₂-adrenergic agonist for once-daily administration [15]. The pharmacological effects of beta₂-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes 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 beta₂-receptors compared to beta₁-receptors and 20-fold greater agonist activity compared to beta₃-receptors. This selectivity profile is similar to formoterol [16].

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human beta₂-adrenergic receptor with nanomolar potency [16]. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action [17].

Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the human heart, there are also beta₂-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of beta₂-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective beta₂-adrenergic agonists may have cardiac effects.

Pharmacodynamic Properties

Primary Pharmacodynamic Effects

ONBREZ BREEZHALER provided consistently significant improvement in lung function (as measured by the forced expiratory volume in one second, FEV₁) over 24 hours in a number of clinical pharmacodynamic and efficacy trials [3]. There was a rapid onset of action within 5 minutes after inhalation of ONBREZ BREEZHALER, comparable to the effect of the fast-acting beta₂-agonist salbutamol [18] and a peak effect occurring between 2-4 hours following the dose [3]. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing for up to 52 weeks [7]. The bronchodilator effect did not depend on the time of dosing (morning or evening) [19].

ONBREZ BREEZHALER reduced both dynamic and resting hyperinflation in patients with moderate to severe COPD. 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 FEV₁ were also demonstrated as well as a significant improvement in measures of dyspnoea [20].

Secondary Pharmacodynamic Effects

The characteristic adverse effects of inhaled beta₂-adrenergic agonists occur as a result of activation of systemic beta-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 ONBREZ BREEZHALER 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 (QT_cF). Maximum mean prolongation of QT_cF 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 QT_c relationship in the range of doses evaluated [21].

Electrocardiographic monitoring in patients with COPD

The effect of ONBREZ BREEZHALER 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 12 Clinical studies). Holter monitoring occurred once at baseline and up to 3 times during the 26-week treatment period (at weeks 2, 12 and 26) [6].

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 [6].

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 analyzed. In this analysis, baseline occurrence of ventricular ectopic beats were 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 [6].

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 12 Clinical studies) [6]. 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 [6].

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 [3].

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 [3,21].

Distribution

After intravenous infusion the volume of distribution (V_z) 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 [3].

Biotransformation/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, and C- and N-dealkylated products were further metabolites identified [3,22].

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 [11]. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp [3].

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 [3].

In a human ADME study where indacaterol was given orally, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose) [3]. Mass balance was complete with $\geq 90\%$ of the dose recovered in the excreta [22].

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 [23] ranged from 40 to 52 hours which is consistent with the observed time-to-steady state of approximately 12 to 14 days [3].

Special Populations

A population analysis of the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated that ONBREZ BREEZHALER 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. Limited treatment experience is available for the black population [3,4,24].

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 C_{max} 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 [25].

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 [3]. 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 [3].

12 Clinical studies

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 FEV₁ <80% and $\geq 30\%$ of the predicted normal value and a post-bronchodilator FEV₁/FVC ratio of less than 70% [1,38-40].

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, FEV₁) over 24 hours. At the 12-week primary

endpoint (24-hour trough FEV₁), 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) [1,38-40].

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 microgram [18], and mean peak improvements in FEV₁ relative to baseline of 0.25-0.33 L at steady-state occurring between 2-4 hours following the dose [2]. 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) [7].

In a 26-week, placebo- and active (open label tiotropium)-controlled study in 2,059 patients, the mean improvement relative to baseline in FEV₁ at 5 minutes was 0.12 L and 0.13 L for ONBREZ BREEZHALER 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 ONBREZ BREEZHALER 150 microgram and 300 microgram once-daily treatment groups showed a significantly higher trough FEV₁ value compared to placebo (both 0.18 L, p<0.001) and to tiotropium (0.05 L, p=0.004, and 0.04 L, p=0.01, respectively).

In this study, 12-hour serial spirometric measurements were performed in a subset of patients throughout daytime hours (12 hours). Serial FEV₁ values over 12 hours at Day 1 and trough FEV₁ 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 [6].

Figure 1 Serial least square mean FEV₁ over 12 h at Day 1 and trough FEV₁ at Day 2 (ITT subset with 12 hour serial spirometry)

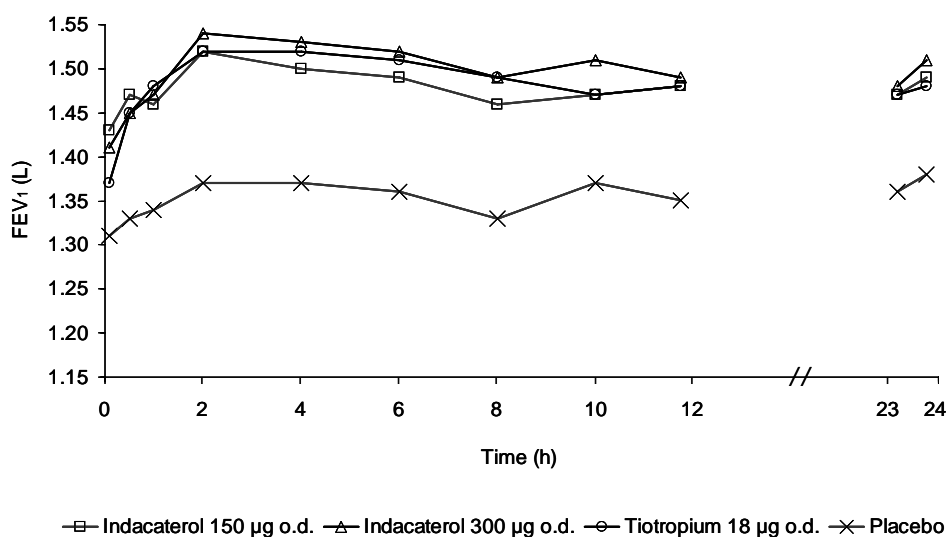
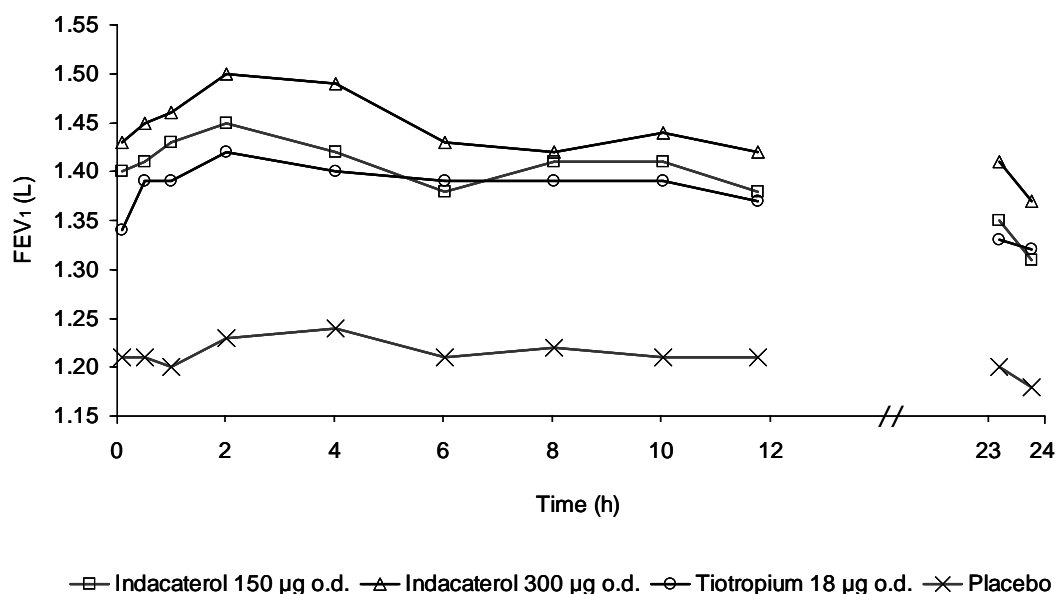


Figure 2 Serial least square mean FEV₁ over 12 h at Day 182 and trough FEV₁ at Day 183 (ITT subset with 12 hour serial spirometry)



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 FEV₁, treatment with both ONBREZ BREEZHALER 150 microgram and 300 microgram once-daily resulted in a significantly higher trough FEV₁ value compared to placebo (0.17 L, $p < 0.001$ and 0.18L, $p < 0.001$, respectively) [38,39].

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 FEV₁, relative to baseline, was 0.23 L after 1 day of once-daily treatment. At the primary end point (Week 12), treatment with ONBREZ BREEZHALER 150 microgram once-daily resulted in a significantly higher trough FEV₁ value compared to placebo (0.13 L, $p < 0.001$) [26].

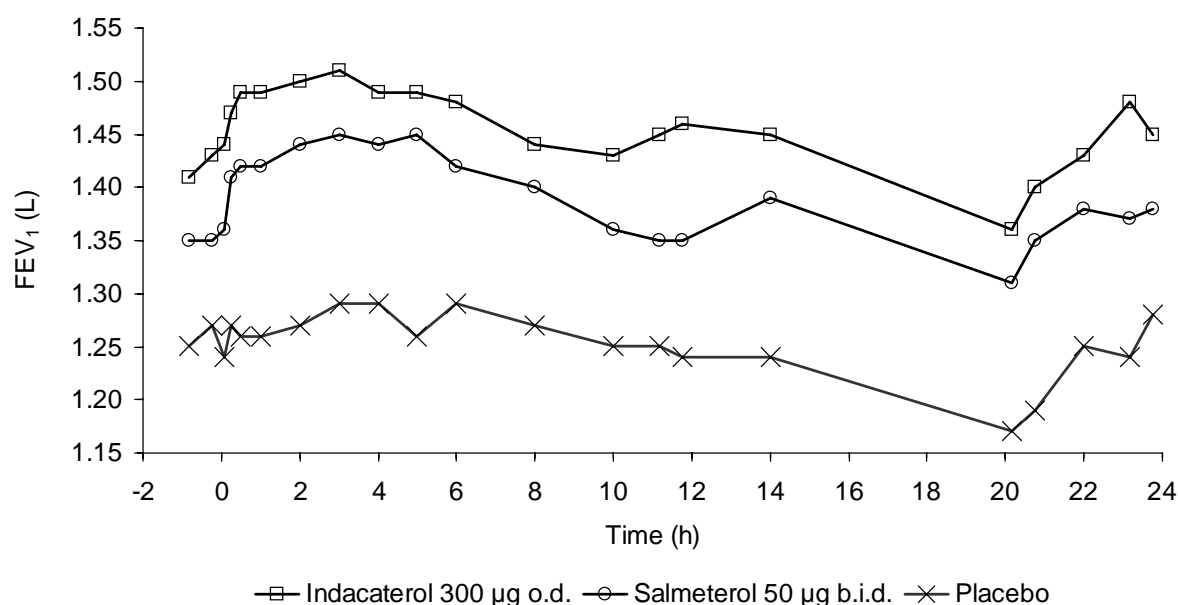
In a 26-week, placebo- and active (blind salmeterol)-controlled study in 1,002 patients which evaluated the ONBREZ BREEZHALER 150 microgram once-daily dose, the mean improvement in FEV₁, relative to baseline, at 5 minutes was 0.11 L with a peak improvement of 0.25 L relative to baseline after the first dose (Day 1). At the primary end point (Week 12), treatment with ONBREZ BREEZHALER 150 microgram once-daily showed a significantly higher trough FEV₁ value compared to both placebo (0.17 L, $p < 0.001$) and to salmeterol (0.06 L, $p < 0.001$) [38,40].

In a 52-week, placebo- and active (formoterol)-controlled study in 1,732 patients which evaluated the ONBREZ BREEZHALER 300 microgram once-daily dose and a higher dose, the mean improvement in FEV₁, 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 ONBREZ BREEZHALER 300 microgram once-daily resulted in a significantly higher trough FEV₁ value compared to placebo (0.17 L, $p < 0.001$) and to formoterol (0.1 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. ONBREZ BREEZHALER was superior to formoterol with regard to trough FEV₁ at all visits [7].

In a 2-week, placebo- and active (open label salmeterol)-controlled crossover study, 24-hour spirometry was assessed in 68 patients [27]. 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, and in addition, the trough FEV₁ value was statistically significantly higher compared to salmeterol (0.09 L, p=0.011). Similar results from 24-hour serial spirometry were observed after 26 weeks in a subset of patients (n=236) from the 26-week study [6]. Both studies further support the improvement in FEV₁ over placebo with ONBREZ BREEZHALER administered once-daily, and that bronchodilation was maintained throughout the 24-hour dosing interval, in comparison to placebo [6,27].

Figure 3 24 h profile of least squares means of FEV₁ (L) after 14 days treatment (Modified ITT population)



The following health outcome effects were demonstrated in the long-term studies of 12-, 26- and 52-week treatment duration:

ONBREZ BREEZHALER significantly improved dyspnea compared to baseline in the 26-week study (as evaluated using the Transitional Dyspnea Index, TDI) by the first assessment (day 29), and this was maintained for the entire 26 weeks in the 150 microgram and 300 microgram once-daily treatments compared to placebo. ONBREZ BREEZHALER 300 microgram once-daily was also statistically superior to open label tiotropium at all timepoints (p≤0.01). The proportion of patients who achieved a score of ≥1.0 (corresponding to a clinically important difference) in TDI focal score was significantly greater in the indacaterol group at all 4 assessment points compared to the placebo group (p≤0.001). At 26 weeks, the proportions were 62.4% and 70.8% with ONBREZ BREEZHALER 150 microgram once-daily and 300 microgram once-daily, respectively, compared to 57.3% and 46.6% with tiotropium and with placebo, respectively [6]. In the 26-week, placebo- and active (blind salmeterol)-controlled study ONBREZ BREEZHALER 150 microgram once-daily also

significantly improved dyspnea over the entire 26-week treatment period. The proportion of patients who achieved a TDI focal score of ≥ 1.0 (corresponding to a clinically important difference) was significantly greater in the indacaterol group at all four assessment points (Day 29, Day 57, Day 84, and Day 182) than in the placebo group ($p \leq 0.005$) [38,40].

In this study statistically significant differences between either active treatment and placebo were seen for the change from baseline in mean daily, daytime and nighttime number of puffs of rescue medication at every 4-weekly interval of the 26-week treatment period. ONBREZ BREEZHALER-treated patients required numerically fewer daily, daytime and nighttime puffs of rescue medication compared with salmeterol-treated patients at certain 4-week intervals, but none of the differences between active treatments were statistically significant [38,40]. In the 52-week study there was a statistically significant reduction in the number of puffs of rescue short-acting beta₂-adrenergic agonists with ONBREZ BREEZHALER 300 microgram once-daily compared to formoterol and placebo (1.69, 1.35 and 0.02 fewer puffs, respectively) [7]. Similarly, in the 26-week study, reductions in rescue use in the ONBREZ BREEZHALER 150 microgram once-daily and 300 microgram once-daily groups were statistically significant compared to open label tiotropium and placebo (1.45 and 1.56 compared to 0.99 and 0.39 fewer puffs, respectively) [6]. In the 12-week study (which had no active comparator) a similar pattern was observed with ONBREZ BREEZHALER 150 microgram once-daily [26].

Patients treated with ONBREZ BREEZHALER 150 microgram and 300 microgram once-daily had numerically lower risks of COPD exacerbation compared to placebo in long-term trials of 12-, 26- and 52-week treatment duration [2]. Time-to-first-COPD exacerbation as compared to placebo was significantly longer in the 26-week study under treatment with 150 microgram once-daily and in the 52-week study under treatment with 300 microgram once-daily ($p=0.019$ and $p=0.03$, respectively) [6,7]. Pooled analyses showed that patients treated with ONBREZ BREEZHALER 150 microgram and 300 microgram once-daily had statistically lower risks of COPD exacerbations compared to placebo in both the 6-month and 12-month pooled populations. Time-to-first-COPD exacerbation as compared to placebo was significantly longer in the 6-month population under treatment with 150 microgram and 300 microgram doses once-daily ($p=0.005$ and $p=0.006$, respectively) and in the 12-month population under treatment with 300 microgram once-daily ($p=0.022$) [38]. Pooled efficacy analysis over 6 and 12 months of treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparisons to placebo over 6 months showed a ratio of rates of 0.70 (95% CI [0.53,0.94]; p -value 0.014) and 0.74 (95% CI [0.57,0.96]; p -value 0.024) for ONBREZ BREEZHALER 150 microgram and 300 microgram, respectively, and over 12 months the ratio of rates was of 0.78 (95% CI [0.62,0.98]; p -value 0.034) for treatment with 300 microgram once-daily [38].

ONBREZ BREEZHALER also significantly improved health-related quality of life (as measured using the St. George's Respiratory Questionnaire) in long-term trials of 12-, 26- and 52-week treatment duration [2]. Both doses of 150 microgram and 300 microgram once-daily demonstrated a significantly lower (improved) mean total score in the SGRQ, as well as each component score, in comparison to placebo: An improvement compared to placebo exceeding the minimal clinically important difference of 4 units was shown at 8 and 12 weeks in the 12-week study [26], and in the 52-week study this was shown for treatment with 300 microgram once-daily at 8, 24, 44 and 52 weeks [7]. In the 26-week study, patients treated with 150

microgram once-daily showed a significantly lower mean total score in the SGRQ compared to tiotropium ($p \leq 0.05$) [6], and at the end of the 26-week, placebo-controlled safety extension to this study the mean change in SGRQ total score was a decrease (improvement) of 3.2 units for ONBREZ BREEZHALER 150 microgram versus placebo after 52 weeks of treatment [39]. In the other 26-week study, treatment with both ONBREZ BREEZHALER 150 microgram and salmeterol resulted in a significantly lower (improved) mean SGRQ total scores compared to placebo with mean differences of 6.3 units ($p < 0.001$) and 4.2 units ($p < 0.001$), respectively, that exceeded the minimal clinically important difference of 4 units after 12 weeks and thus were also clinically relevant. ONBREZ BREEZHALER also achieved statistical superiority over salmeterol by 2.1 units ($p = 0.033$) [38,40].

ONBREZ BREEZHALER 150 microgram and 300 microgram once-daily treatment over 26 weeks significantly improved the percentage of days with no daytime symptoms ($p < 0.02$) and the percentage of days where patients were able to perform their normal daily activities as compared to placebo ($p < 0.001$) [6].

13 Non-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction. The effects of indacaterol seen in toxicity studies in dogs were mainly on the cardiovascular system and consisted of tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological effects and could be explained by the β_2 -agonistic properties of indacaterol. Other relevant effects noted in repeated-dose toxicity studies were mild irritancy of the upper respiratory tract in rats consisting of rhinitis and epithelial changes of the nasal cavity and larynx. All these findings were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use [28].

Adverse effects with respect to fertility, pregnancy, embryonal/foetal development, pre- and postnatal development could only be demonstrated at doses more than 195-fold the maximum recommended daily inhalation dose of 300 microgram in humans (on a mg/m^2 basis) [29]. The effects, namely an increased incidence of one skeletal variation, were observed in rabbits [29,30]. Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration. Studies on genotoxicity did not reveal any mutagenic or clastogenic potential [31-33]. The carcinogenic potential of indacaterol has been evaluated in a 2-year inhalation study in rats and a 26-week oral transgenic mouse study [34,35]. Lifetime treatment of rats resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females at doses approximately 68-times the maximum recommended dose of 300 microgram once-daily for humans (on a mg/m^2 basis) [34]. Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other β_2 -adrenergic agonist drugs [36]. A 26-week oral (gavage) study in CB6F1/TgrasH2 hemizygous mice with indacaterol did not show any evidence of tumorigenicity at doses approximately 9800-times the maximum recommended dose of 300 microgram once-daily for humans (on a mg/m^2 basis) [35].

14 Pharmaceutical information

Special Precautions for storage

Do not store above 30°C and protect from moisture.

Note: Information might differ in some countries.

ONBREZ BREEZHALER must be kept out of the reach and sight of children.

Instructions for use and Handling

For correct administration/use of the product please refer to section 4.

[This is a non-referenced document.](#)