NOVARTIS

onbrez® breezhaler®

Hard capsules containing inhalation powder

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Onbrez Breezhaler®

Hard capsules containing inhalation powder

Composition

Active substance: Indacaterol

Pharmaceutical form and quantity of active substance per unit

Pharmaceutical form

Hard capsules containing 150 µg of inhalation powder

Hard capsules containing 300 µg of inhalation powder

Quantity of active substance

Hard capsules containing 150 µg indacaterol, corresponding to 194 µg indacaterol maleate

The delivered dose (i.e. the dose discharged through the mouthpiece of the Onbrez Breezhaler® inhaler) is 120 µg indacaterol maleate.

Hard capsules containing 300 µg indacaterol, corresponding to 389 µg indacaterol maleate

The delivered dose (i.e. the dose discharged through the mouthpiece of the Onbrez Breezhaler® inhaler) is 240 µg indacaterol maleate.

Indications / Potential uses

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

Dosage and Administration

Dosage

Adults

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

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

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

Dosage in special patient populations

Elderly patients

No dose adjustment is required in elderly patients.

Children

COPD is not a disease that is relevant to the paediatric population (under 18 years of age). Onbrez Breezhaler has therefore not been investigated in children.

Hepatic or renal impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment or with renal impairment. There are no data are available for use of Onbrez Breezhaler in patients with severe hepatic impairment (Child C; see **Clinical pharmacology** in **Properties and Actions**).

Administration

Onbrez Breezhaler capsules must be administered only by oral inhalation, and only using the Onbrez Breezhaler inhaler. Onbrez Breezhaler capsules must not be swallowed. Onbrez Breezhaler capsules must always be stored in the blister pack, and only removed IMMEDIATELY BEFORE USE. If a dose is missed, the next dose should be taken at the usual time the next day.

Contraindications

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

Warnings and Precautions

Asthma

Onbrez Breezhaler must not be used in asthma.

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 must 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 rescue therapy. In the event of deterioration of COPD during treatment with Onbrez Breezhaler, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. An increase in the daily dose of Onbrez Breezhaler beyond the maximum dose is not appropriate.

Systemic effects

Although no clinically relevant effects on the cardiovascular system are usually seen after the administration of Onbrez Breezhaler at the recommended dose, indacaterol – like other beta$_2$-adrenergic agonists – should be used with caution in patients with cardiovascular disorders. This is particularly valid for patients with coronary insufficiency, cardiac arrhythmias and hypertension, in patients with epilepsy or thyrotoxicosis and in patients who are unusually responsive to beta$_2$-adrenergic agonists. Onbrez Breezhaler has not been studied extensively in patients with these conditions.

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

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient and does not require supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see **Interactions**), which may increase the susceptibility to cardiac arrhythmias.

Clinically notable changes in blood glucose were rare during clinical studies with Onbrez Breezhaler at the recommended doses. Onbrez Breezhaler has not been investigated in patients with type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus. It is known that beta$_2$-adrenergic agonists may cause blood glucose levels to rise. In patients with diabetes mellitus, blood glucose levels should be closely monitored following initiation of treatment with Onbrez Breezhaler.

As with other inhaled beta$_2$-adrenergic medicinal products, Onbrez Breezhaler must not be used more often, or at higher doses, than recommended.

Onbrez Breezhaler must not be used in conjunction with other long-acting beta$_2$-adrenergic agonists, or with medicinal products containing long-acting beta$_2$-adrenergic agonists (see **Interactions**).

Onbrez Breezhaler contains lactose and should therefore not be used in patients with lactose intolerance.

Interactions

Medicinal products known to prolong the QTc interval

As with other beta$_2$ agonists, there is a theoretical risk that medicinal products known to prolong the QTc interval may have pharmacodynamic interactions with indacaterol and increase the potential risk of ventricular arrhythmia. Examples of such medicinal products are certain antihistamines (e.g. terfenadine, mizolastine), certain antiarrhythmic agents (e.g. quinidine), phenothiazines, erythromycin and tricyclic antidepressants. Concomitant administration of other sympathomimetic agents may exacerbate adverse cardiovascular effects. Caution is required when giving Onbrez Breezhaler to patients receiving concomitant treatment with MAO inhibitors or tricyclic antidepressants since the action of beta$_2$-stimulants on the cardiovascular system may be potentiated.

Concomitant administration of levodopa, levothyroxine and oxytocin may have a negative impact on cardiac tolerance to beta$_2$-sympathomimetic agents.

Sympathomimetics

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of Onbrez Breezhaler (see **Warnings and Precautions**).

Hypokalaemia

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics might potentiate the possible hypokalaemic effects of beta$_2$-adrenergic agonists (see **Warnings and Precautions**).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonize the effect of beta$_2$-adrenergic agonists. Therefore Onbrez Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling clinical 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 interactions

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (Pgp), raises the systemic exposure of indacaterol by up to 2-fold. The magnitude of exposure increases due to interactions does not raise any

safety concerns given the safety experience of treatment with Onbrez Breezhaler in clinical studies of up to one year at doses up to twice the maximum recommended therapeutic dose.
Indacaterol has not been shown to cause drug interactions with co-medications. In vitro investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medicinal products at the systemic exposure levels achieved in clinical practice.

Pregnancy and Lactation

Pregnancy

No clinical data are available on pregnant COPD patients treated with Onbrez Breezhaler. Studies in animals have shown reproductive toxicity associated with an increased incidence of one particular skeletal variation in rabbits (see **Preclinical 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 beta$_2$-adrenergic agonists, Onbrez Breezhaler may inhibit labour due to a relaxant effect on uterine smooth muscle.

Lactation

It is not known whether indacaterol is excreted in human milk. The substance has been detected in the milk of lactating rats. Because many drugs are excreted in human milk, as with other inhaled beta$_2$-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 and other data from animal studies did not reveal a problem or potential problem concerning fertility in either males or females.

Effects on ability to drive and use machines

There have been no studies of the effects of Onbrez Breezhaler on the ability to drive or use machines.

Adverse effects

Summary of the safety profile

The most common adverse effects at the recommended doses were nasopharyngitis (16.7%), cough, upper respiratory tract infections and headache. These were in the vast majority mild or moderate and became less frequent when treatment was continued.
At the recommended doses, the adverse drug reaction profile of Onbrez Breezhaler in patients with COPD shows clinically non-relevant systemic effects of beta$_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per minute. Tachycardia was infrequent and reported at a similar rate as under placebo treatment. No relevant prolongation of the QTcF interval was detected, as compared with placebo. The frequency of notable QTcF intervals (i.e. > 450 ms [males] and > 470 ms [females]) and of reports of hypokalaemia were similar to placebo. Mean maximum changes in blood glucose were similar for Onbrez Breezhaler and placebo.

Description of population

The Onbrez Breezhaler phase III clinical development programme consisted of 6 key studies in 4460 patients with a clinical diagnosis of moderate to severe COPD. Safety data from these studies were pooled from 2154 patients who were given up to 600 µg indacaterol once daily. Of these 2154 patients, 627 were given 150 µg once daily and 853 were given 300 µg once daily. Approximately 40% of the patients had severe COPD. The mean age of the patients was 63 years; 47% were at least 65 years of age. The majority (89%) was Caucasian.

Adverse drug reactions in clinical studies

Adverse drug reactions are listed according to MedDRA system organ class in the following table. Safety profiles in the COPD safety databases were similar after 3, 6 and 12 months of treatment. The sequence of system organ classes presented here reflects decreasing rates of adverse reactions in these organ systems. Within each system organ class, adverse effects are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category is also provided for each adverse reaction using the following convention (CIOMS III):
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000to < 1/1000); very rare (< 1/10 000), including isolated cases.

Infections and infestations
Very common: Nasopharyngitis (16.7%)[1]
Common: Upper respiratory tract infections[2], sinusitis[2], pneumonia[2].

Respiratory, thoracic and mediastinal disorders
Common: Cough[2], pharyngolaryngeal pain[3], rhinorrhoea[2].

Nervous system disorders
Common: Headache[2], paraesthesia[2].

Skin and subcutaneous tissue disorders[1]
Common: Muscle spasm[2], myalgia[2], neck pain[2].

Cardiac disorders
Common: Atrial fibrillation[2].
Uncommon: Angina pectoris[2].

General disorders and administration site conditions
Common: Chest discomfort[2].

Metabolism and nutrition disorders
Common: Diabetes mellitus[1].

[1] Adverse drug reactions in study B2334. Number of patients given 300 µg indacaterol, or placebo, once daily: n = 437 and 432, respectively.
[2] Adverse drug reactions from 6-month COPD safety database. Includes all adverse drug reactions of study B2335S and those occurring within the first 6 months of B2334. Number of patients given 150 µg or 300 µg indacaterol, or placebo, once daily: n = 416, 853 and 850, respectively.
[3] Adverse drug reactions in study B2335S. Number of patients given 150 µg or 300 µg indacaterol, or placebo, once daily: n = 416, 416 and 418, respectively.

The safety profile of Onbrez Breezhaler at a higher dose, i.e. 600 µg once daily, was similar overall to that of the recommended doses. Additional adverse drug reactions were peripheral oedema and tremor. Nasopharyngitis and muscle spasm occurred more frequently than at the recommended doses.

Selected adverse drug reactions

In phase III clinical studies, healthcare providers observed during clinic visits that, on average, 17–20% of patients experienced a sporadic cough that usually occurred within 15 seconds following inhalation and typically lasted for 5 seconds. This post-inhalation cough was generally well tolerated and did not lead to any patient discontinuing from the studies at the recommended doses. There is no evidence that this post-inhalation cough is associated with bronchospasm, exacerbations, deterioration of disease or loss of efficacy.

Overdose

In COPD patients, single doses of 10 times the maximum recommended therapeutic dose were associated with a moderate increase in pulse rate, systolic blood pressure and QTc interval.
An overdose of indacaterol is likely to lead to exaggerated effects typical of beta$_2$-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, light-headedness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.
Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalized. 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.
Acute intoxication following inadvertent oral ingestion of Onbrez Breezhaler capsules is unlikely because the bioavailability of indacaterol is low.

Properties and Actions

ATC code: R03AC18

Clinical pharmacology

Mechanism of action

Indacaterol is an "ultra" long-acting beta$_2$-adrenergic agonist for once-daily administration. The pharmacological effects of beta$_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl 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.

Pharmacodynamic properties

Significant improvement in lung function (FEV_1) over 24 hours was consistently found in studies of the pharmacodynamics and efficacy of Onbrez Breezhaler. There was a rapid onset of action within 5 minutes of inhalation of Onbrez Breezhaler, comparable to the effect of the fast-acting beta$_2$-agonist salbutamol. Maximum efficacy was attained two to four hours after dose administration. There was no evidence of 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).
In a study in 27 patients, Onbrez Breezhaler reduced both dynamic and resting hyperinflation in patients with moderate to severe COPD. Inspiratory capacity during constant, sub-maximal physical exercise increased by 317 ml, as compared with placebo, after administration of 300 µg once daily for 14 days. A statistically significant increase in resting inspiratory capacity, exercise endurance and FEV_1, and significant improvement in measures of dyspnoea, were also noted.

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 for 2 weeks in 404 healthy volunteers. It was shown that there are no relevant problems of pro-arrhythmic potential relating to QT-interval prolongations when the recommended therapeutic doses are used. There was no evidence of a concentration-delta QTc relationship in the range of doses evaluated.
The effects of Onbrez Breezhaler on heart rate and rhythm were 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 **Clinical studies** below). Holter monitoring was carried out once at baseline and up to 3 times during the 26-week treatment period.
Comparisons of mean heart rates over 24 hours showed no increase from baseline for either of

the recommended doses. The hourly heart rate analysis was similar for the two doses, placebo and tiotropium.

Effects on levels of serum potassium and plasma glucose

No clinically relevant changes in serum potassium or plasma glucose levels were seen in a 26-week, double-blind, placebo-controlled, phase III study

Clinical studies

The Onbrez Breezhaler phase III clinical development programme consisted of 6 key studies in 4460 patients, 40 years of age or older, with a clinical diagnosis of COPD. The duration of the clinical studies was up to 1 year. The patients 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 an FEV_1/FVC ratio below 70%.

In a 26-week, placebo- and active-controlled study (open label tiotropium) in 2059 patients, the mean improvement in FEV_1 at 5 minutes relative to baseline following once-daily use of 150 µg and 300 µg Onbrez Breezhaler was 0.12 litres and 0.13 litres, respectively. The mean peak improvement, relative to baseline, after the first dose (day 1) was 0.19 litres and 0.24 litres, respectively, and improved to 0.23 litres and 0.26 litres, respectively, when pharmacodynamic steady-state was reached (day 14). At the primary end point (week 12), both the 150 µg and 300 µg once-daily Onbrez Breezhaler treatment groups showed significantly higher trough FEV_1 than did those given placebo (both 0.18 litres, $p < 0.001$) or tiotropium (0.05 litres, $p = 0.004$, and 0.04 litres, $p = 0.01$, respectively).

In this study, serial spirometric measurements were performed in a subset of patients during the day (over a 12-hour period in each case). The improvement in 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.

The results of a 12-week, placebo-controlled study in 416 patients which evaluated the 150 µg 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 litres after 1 day of once-daily treatment. At the primary end point (week 12), treatment with 150 µg Onbrez Breezhaler once-daily resulted in significantly higher trough FEV_1 than with placebo (0.13 litres, $p < 0.001$).

In a 52-week, placebo- and active-controlled study (formoterol) in 1732 patients to assess both a once-daily dose of 300 µg Onbrez Breezhaler and a higher dose, the mean improvement in FEV_1 at 5 minutes, relative to baseline, was 0.14 litres with a peak improvement of 0.20 litres relative to baseline after the first dose (day 1). At the primary end point (week 12), treatment with 300 µg Onbrez Breezhaler once daily resulted in significantly higher trough FEV_1 than with placebo (0.17 litres, $p < 0.001$) or formoterol (0.1 litres, $p = 0.001$). This improvement in 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 FEV_1 at all visits.

In a 2-week, placebo- and active-controlled (open label salmeterol) crossover study, 24-hour spirometry was carried out in 68 patients. After 14 days of once-daily treatment, improvement in lung function, as compared with placebo, was maintained for 24 hours. In addition, trough FEV_1 was statistically significantly higher than with salmeterol (0.09 litres, $p = 0.011$). Similar results were obtained with serial spirometry after 26 weeks in a subset of patients (n = 236) from the 26-week study. Both studies further support the improvement in FEV_1 vs. placebo with Onbrez Breezhaler administered once daily,

and demonstrate that bronchodilation was maintained throughout the 24-hour dosing interval, as compared with placebo.

In the 26-week study, Onbrez Breezhaler significantly improved dyspnoea, compared with baseline (as evaluated using the transitional dyspnoea index, TDI). This improvement, as compared with placebo, was maintained for the entire 26 weeks with both the 150 µg and 300 µg doses. Blinded use of 300 µg Onbrez Breezhaler once daily was also statistically superior to open-label tiotropium at all timepoints ($p \leq 0.01$). The percentage of patients who achieved a TDI focal score ≥ 1.0 (signifying a clinically important difference) was significantly higher in the indacaterol group than in the placebo group at all 4 assessment points ($p \leq 0.001$): At 26 weeks, the rates were 62.4% with 150 µg Onbrez Breezhaler once daily and 70.8% with 300 µg Onbrez Breezhaler once daily, as compared with 57.3% with tiotropium and 46.6% with placebo.

In the 52-week study there was a statistically significant reduction in the number of puffs of rescue short-acting $beta_2$-adrenergic agonists with 300 µg Onbrez Breezhaler once daily, as compared with formoterol and placebo (1.69, 1.35 and 0.02 fewer puffs, respectively). Similarly, in the 26-week study, reductions in rescue use in the 150 µg and 300 µg Onbrez Breezhaler once daily groups were statistically significant, as compared with open label tiotropium and placebo (1.45 and 1.56 vs. 0.99 and 0.39 fewer puffs, respectively). In the 12-week study (which had no active comparator), a similar pattern was observed with 150 µg Onbrez Breezhaler once daily.

Patients given 150 µg or 300 µg Onbrez Breezhaler once daily had numerically lower risks of COPD exacerbation than those on placebo in long-term studies with 12, 26 and 52 weeks of treatment. Time to the first COPD exacerbation was significantly longer than with placebo in the 26-week study of treatment with 150 µg once daily and in the 52-week study of treatment with 300 µg once daily ($p = 0.019$ and $p = 0.03$, respectively).

Onbrez Breezhaler also improved health-related quality of life (as measured using the St. George's Respiratory Questionnaire [SGRQ]) in long-term studies with 12, 26 and 52 weeks of treatment. Both of the recommended doses produced a significant lowering (improvement) in the mean total score in the SGRQ, as well as in each component score, as compared with placebo: An improvement, as compared with placebo, exceeding the minimal clinically important difference of 4 units was seen at 8 and 12 weeks in the 12-week study. This was also demonstrated for once-daily treatment with 300 µg at 8, 24, 44 and 52 weeks in the 52-week study. In the 26-week study, patients treated once daily with 150 µg showed a significantly lower mean total SGRQ score than did patients using tiotropium ($p \leq 0.05$).

As compared with placebo, once-daily treatment with 150 µg and 300 µg Onbrez Breezhaler for 26 weeks significantly increased the percentage of days with no daytime symptoms ($p < 0.02$) and the percentage of days on which patients were able to perform their normal daily activities ($p < 0.001$).

Pharmacokinetics

Indacaterol is the pure R-enantiomer of the molecule. Pharmacokinetic data were obtained from a number of clinical studies, from healthy volunteers and COPD patients.

Absorption and bioavailability

Inhalation

Following inhalation of indacaterol, the average time to reach peak serum concentrations of indacaterol was approximately 15 minutes after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 µg to 600 µg) in a dose-proportional manner. The 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 levels 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-hour dosing interval on day 14 compared with day 1, was in the range of 2.9 to 3.5 for once-daily inhaled doses between 150 µg and 600 µg. Systemic exposure following inhalation results from a composite of oral and pulmonary absorption, with pulmonary absorption accounting for the principal amount.

Oral administration

The oral bioavailability of indacaterol when swallowed from a capsule is approximately 25% when the orogastrointestinal absorption rate of 30–50%. C_{max} is reached within 0.5–2 hours.

Distribution

The volume of distribution (V_z) of indacaterol after intravenous infusion was 2557 litres, indicating extensive distribution. Human serum and plasma protein binding *in vitro* was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Biotransformation / Metabolism

After oral administration of radiolabelled indacaterol in an ADME (absorption, distribution, metabolism, excretion) study in humans, unchanged indacaterol was the main component detectable in serum, accounting for about one-third of total drug-related AUC over 24 hours. The most common serum metabolite was a hydroxylated derivative. A phenolic O-glucuronide of indacaterol and hydroxylated indacaterol were other common metabolites. A diastereomer of the hydroxylated derivative, an N-glucuronide of indacaterol, and C- and N-dealkylated products were also identified as metabolites.

In vitro investigations indicated that UGT1A1 was 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 considered to be the most important isoenzyme in the hydroxylation of indacaterol. *In vitro* studies further indicated that indacaterol is a low-affinity substrate for the efflux pump, Pgp.

Elimination

In clinical studies that included urine collection, the amount of indacaterol excreted unchanged in the urine was generally lower than 2% of the dose. The mean renal clearance of indacaterol was between 0.46 and 1.20 litres/hour. Given the fact that serum clearance of indacaterol is 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available indacaterol.

In an ADME study in humans, in which indacaterol was given orally, the faecal route of excretion was dominant over the urinary route. Indacaterol was excreted in human faeces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, as hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥ 90% of the dose recovered in the excreta.

Indacaterol serum levels declined in a multiphasic 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. This is consistent with the observed time-to-steady state of approximately 12 to 14 days.

Special patient populations
A population analysis of the effects of age, sex and weight on systemic exposure in COPD patients after inhalation indicated that Onbrez Breezhaler can be used safely in all age and weight groups, regardless of the patient's sex. There was no evidence of any differences between ethnic subgroups in this population.
The pharmacokinetics of indacaterol were 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 the steady-state AUC and C_{max} of indacaterol were 1.2 times higher in the [$(TA)_7$, $(TA)_7$] genotype, indicating that systemic exposure to indacaterol was only insignificantly affected by this UGT1A1 genotypic variation.
There were no relevant changes in the C_{max} or AUC of indacaterol in patients with mild or moderate hepatic impairment, nor did protein binding differ between healthy controls and patients with mild or moderate hepatic impairment. No studies were carried out in patients with severe hepatic impairment.
Due to the very low contribution of the urinary pathway to total body elimination, no study was performed in renally impaired patients.

Preclinical data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity. 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 are known pharmacological effects attributable to the $beta_2$-agonistic properties of indacaterol. During a chronic toxicity study in dogs, elevated levels of creatinine were detected in the blood, but no evidence of altered renal function was seen in the results of either this or any other study. Other relevant effects noted in repeated-dose toxicity studies were mild irritation of the upper respiratory tract in rats, i.e. rhinitis and epithelial changes of the nasal cavity and larynx. All these findings were observed only at exposures sufficiently in excess of the maximum human exposure as to be of little relevance to clinical use.
Adverse effects with respect to fertility, pregnancy, embryonic and fetal development, and prenatal and postnatal development were only seen at doses greater than 195 times the maximum recommended daily inhalation dose (on a mg/m^2 basis) of 300 µg in humans. These effects, i.e. an increased incidence of one skeletal variation, occurred in rabbits. Following subcutaneous administration, indacaterol was not teratogenic in rats or rabbits. Genotoxicity studies showed no evidence of mutagenicity or clastogenicity. The carcinogenic potential of indacaterol was examined in a 2 year inhalation study in rats and a 26 week study of oral administration in transgenic mice. In female rats, lifetime treatment at doses approximately 68 times the maximum recommended daily dose (on a mg/m^2 basis) of 300 µg in humans resulted in an increased incidence of benign ovarian leiomyoma and of focal hyperplasia of ovarian smooth muscle. Increases in leiomyomas of the genital tract in female rats have been similarly ascertained with other $beta_2$-adrenergic agonists. No evidence of tumorigenicity was seen in CB6F1/TgrasH2 hemizygous mice given oral indacaterol (gavage) for 26 weeks at doses approximately 9800 times the maximum recommended daily dose (on a mg/m^2 basis) of 300 µg in humans.

Other information
Shelf-life
See folding box
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
See folding box. Onbrez Breezhaler capsules must always be stored in the blisters to protect them from moisture, and may only be removed from the blisters immediately before use.
Keep out of the reach of children.

Instructions for use and handling
See **Dosage and Administration** for information on correct administration and use of the product. Detailed instructions for use are included in the patient information text. Patients must use the new Onbrez Breezhaler inhaler contained in each newly prescribed pack.

Pack sizes
Country specific pack sizes

Manufacturer
See folding box

Information last revised
January 2010

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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