SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INBROXA 150 mcg Hard Capsule with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains;

Active substance:
Indacaterol maleat…….195 mcg (equivalent to 150 mcg indacaterol)
The delivered dose leaving the mouthpiece is equivalent to 0.12 mg (120 mcg) indacaterol.

Excipient(s):
Lactose monohydrate (Inhalac 230) (from bovine milk)…….18.555 mg
Lactose monohydrate (Inhalac 400) (from bovine milk)……..6.25 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsules
Transparent light blue hard capsule containing white or nearly white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology/frequency and duration of administration
The recommended dose is the inhalation of the content of one 150-microgram capsule once a day, using the INBROXA inhaler. The dose should only be increased on medical advice.

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

INBROXA should be administered at the same time of the day each day.

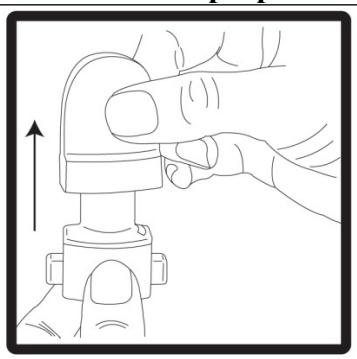
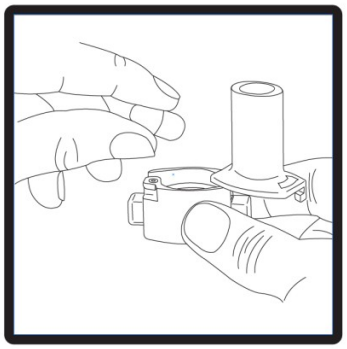
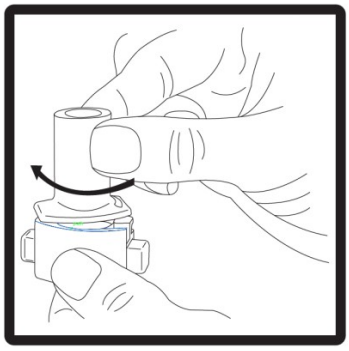
If a dose is missed the next dose should be taken at the usual time the next day.

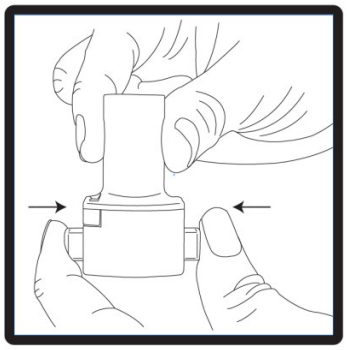
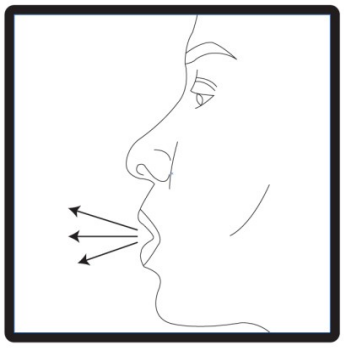
Method of administration:
For inhalation use only. INBROXA capsules should not be swallowed.

INBROXA capsules should only be removed from the blister pack immediately before use.
The capsules should be administered only using the INBROXA inhaler.
The INBROXA inhalation device provided with each new prescription should be used.

Patients should be instructed on how to use the inhaler correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

Instructions for proper use

	1. Pull off the cap.
	2. Hold the base of the inhaler firmly and turn the mouthpiece in the arrow direction to open.
	3. Remove one capsule from the blister just before you use it. Place this capsule in the in the capsule-shaped chamber at the base of the inhaler.
	4. Turn the mouthpiece to close it.

	5. Hold the device in the upright position (with the mouthpiece facing upward) and press both side buttons ONLY ONCE at the same time. After the capsule is pierced in this way, release the side buttons. Please note: During this procedure, the gelatin capsule might fragment and small pieces of gelatin might reach the mouth and throat during inhalation. Fragments of gelatin are harmless and are digested after ingestion. This can be minimized by removing the capsule from the blister just before use and pressing the side buttons only once (see step 3).
	6. Breathe out fully.
	7. Place the mouthpiece in your mouth and tilt your head slightly backwards. Close your lips firmly around the mouthpiece and breathe in quickly and deeply as you can. As the powder dispersed, you will hear a whirring noise from the capsule spinning in its chamber. If you do not hear this noise, it might have been stuck in the capsule chamber. In this case, open the capsule chamber and loosen the capsule by moving it in the chamber. DO NOT PRESS the side buttons repeatedly to loosen the capsule.
8. Hold your breath. While removing the inhaler from the mouth, hold your breath for 5-10 seconds or as long as possible. Then breathe out. Open the inhaler to check for any powder remaining in the capsule. If powder remains in the capsule, close the inhaler and repeat steps 7 and 8. Most patients can empty the capsule in one or two inhalations. Some people rarely cough for a short time after taking the medicine by inhalation. Do not worry if you cough. As long as the capsule is empty, the medicine will be taken in full dose.	
9. After use, discard the empty capsule and close the mouthpiece.	

Additional information on special populations
Renal impairment
No dose adjustment is required for patients with renal impairment.

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

Pediatric population
There is no relevant use of INBROXA in the pediatric population (under 18 years).

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

4.3 Contraindications

It is contraindicated in hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Asthma
INBROXA is a long-acting beta$_2$-adrenergic agonist, which is only indicated for COPD and should not be used in asthma due to the absence of long-term outcome data in asthma.

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

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

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

Deterioration of disease
INBROXA is not indicated for the treatment of acute episodes of bronchospasm (i.e. as rescue therapy). In the event of deterioration of COPD during treatment with INBROXA, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. An increase in the daily dose of INBROXA beyond the maximum dose of 300 microgram is not appropriate.

Systemic effects
Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of indacaterol at the recommended doses, as with other beta$_2$-adrenergic agonists, indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

Cardiovascular effects

Like other beta$_2$-adrenergic agonists, INBROXA may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of QT interval and ST segment depression, although the clinical significance of these observations is unknown. Therefore, long-acting beta$_2$-adrenergic agonists such as INBROXA should be used with caution in patients with known or suspected prolongation of the QT interval or treated with medicinal products affecting the QT interval.

No clinically relevant effects on QTc-interval prolongation have been observed in clinical studies with indacaterol at recommended therapeutic doses (see section 5.1).

Hypokalemia
Beta$_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see section 4.5), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycemia
Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with INBROXA 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 indacaterol at the recommended doses than on placebo. Indacaterol has not been investigated in patients with not well-controlled diabetes mellitus.

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

4.5 Interactions with other medicinal products and other forms of interaction

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

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

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

Beta-adrenergic blockers
Beta-adrenergic blockers and beta$_2$-adrenergic agonists may weaken or antagonize the effect of each other when administered concurrently. Therefore, indacaterol should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be

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

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

4.6 Fertility, pregnancy and lactation

General principles
Pregnancy category is C

Women of child-bearing potential/Contraception
Like other beta$_2$-adrenergic stimulants, INBROXA may inhibit labor due to a relaxant effect on uterine smooth muscle.

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

Studies on animals are insufficient in terms of effects on pregnancy/and-or/embryonal/fetal development/and-or/birth/and-or/postpartum development (see section 5.3). The potential risk for humans is unknown.

INBROXA should not be used during pregnancy unless absolutely necessary.

Breast-feeding
It is not known whether indacaterol/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of indacaterol/metabolites in milk (see section 5.3). A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from INBROXA therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Reproductive ability / Fertility
A decreased pregnancy rate has been observed in rats. Nevertheless, it is considered unlikely that indacaterol will affect reproductive or fertility performance in humans following inhalation of the maximum recommended dose (see section 5.3).

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

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

At the recommended doses, the adverse reaction profile of indacaterol in patients with COPD shows clinically insignificant systemic effects of beta$_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per minute, and tachycardia was infrequent and reported at a similar rate as under placebo treatment. Relevant prolongations of QT_cF were not detectable in comparison to placebo. The frequency of notable QT_cF intervals [i.e. >450 ms (males) and >470 ms (females)] and reports of hypokalemia were similar to placebo. The mean of the maximum changes in blood glucose were similar between indacaterol and placebo.

Adverse reactions

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

Adverse reactions are listed according to MedDRA system organ class in the COPD safety database. Within each system organ class, adverse reactions are ranked by frequency in descending order according to the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations
Common: Upper respiratory tract infection, nasopharyngitis, sinusitis

Immune system disorders
Uncommon: Hypersensitivity[1]

Metabolism and nutrition disorders
Uncommon: Diabetes mellitus and hyperglycemia

Nervous system disorders
Common: Headache, dizziness
Uncommon: Paresthesia

Cardiac disorders
Uncommon: Ischemic heart disease, atrial fibrillation, palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders
Common: Cough, oropharyngeal pain including throat irritation, rhinorrhea
Uncommon: Paradoxical bronchospasm

Skin and subcutaneous tissue disorders
Uncommon: Pruritus/rash

Musculoskeletal and connective tissue disorders
Common: Muscle spasm
Uncommon: Myalgia, musculoskeletal pain

General disorders and administration site conditions
Common: Chest pain, peripheral edema

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

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

Description of selected adverse reactions
In Phase III clinical studies, healthcare providers observed during clinic visits that on average 17-20% of patients experienced a sporadic cough that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds (about 10 seconds in current smokers). It was observed with a higher frequency in female than in male patients and in current smokers than in ex-smokers. This cough experienced post inhalation did not lead to any patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 8.2% of patients reported cough as an adverse event). There is no evidence that cough experienced post inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, selective $beta_2$-adrenoreceptor

agonists
ATC code: R03AC18

Mechanism of action
The pharmacological effects of beta$_2$-adrenoceptor agonists are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalysis the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol, a long-acting beta$_2$-adrenergic agonist, has more than 24-fold greater agonist activity at beta$_2$-receptors compared to beta$_1$-receptors and 20-fold greater agonist activity compared to beta$_3$-receptors.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial agonist at the human beta$_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the human heart, there are also beta$_2$-adrenergic receptors in the human heart comprising 10-50% of the total adrenergic receptors. The precise function of beta$_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective beta$_2$-adrenergic agonists may have cardiac effects.

Pharmacodynamic effects
İndacaterol, administered once a day at doses of 150 and 300 micrograms consistently provided clinically significant improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours across a number of clinical pharmacodynamic and efficacy studies. There was a rapid onset of action within 5 minutes after inhalation, with an increase in FEV_1 relative to baseline of 110-160 ml, comparable to the effect of the fast-acting beta$_2$-agonist salbutamol 200 microgram and statistically significantly faster compared to salmeterol/fluticasone 50/500 microgram. Mean peak improvements in FEV_1 relative to baseline were 250-330 ml at steady state. The bronchodilator effect did not depend on the time of dosing (morning or evening).

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

Effects on cardiac electrophysiology
A double-blind, placebo- and active (moxifloxacin)-controlled study for 2 weeks in 404 healthy volunteers demonstrated maximum mean (90% confidence intervals) prolongations of the QT_cF interval (in milliseconds) of 2.66 (0.55, 4.77) 2.98 (1.02, 4.93) and 3.34 (0.86, 5.82) following multiple doses of 150 microgram, 300 microgram and 600 microgram, respectively. This indicates that there is no concern for the proarrhythmic potential associated with QT interval prolongation at recommended therapeutic doses or at twice the maximum recommended dose. There was no evidence of a concentration-delta QT_c relationship in the range of doses evaluated.

As demonstrated in 605 patients with COPD in a 26-week, double-blind, placebo-controlled Phase III study, there was no clinically relevant difference in the development of arrhythmic events monitored over 24 hours, at baseline and up to 3 times during the 26-week treatment period, between patients receiving recommended doses of indacaterol treatment and those patients who received placebo or treatment with tiotropium.

Clinical efficacy and safety

The clinical development program included one 12-week, two 6-month (one of which was extended to one year to evaluate safety and tolerability) and one 1-year randomized controlled studies in patients with a clinical diagnosis of COPD. These studies included measures of lung function and of health outcomes such as dyspnea, exacerbations and health-related quality of life.

Lung function

İndacaterol, administered once a day at doses of 150 microgram and 300 microgram, showed clinically meaningful improvements in lung function. At the 12-week primary endpoint (24-hour trough FEV_1), the 150 microgram dose resulted in a 130-180 ml increase compared to placebo ($p<0.001$) and a 60 ml increase compared to salmeterol 50 microgram twice a day ($p<0.001$). The 300 microgram dose resulted in a 170-180 ml increase compared to placebo ($p<0.001$) and a 100 ml increase compared to formoterol 12 microgram twice a day ($p<0.001$). Both doses resulted in an increase of 40-50 ml over open-label tiotropium 18 microgram once a day (150 microgram, $p=0.004$; 300 microgram, $p=0.01$). The 24-hour bronchodilator effect of indacaterol was maintained from the first dose throughout a one-year treatment period with no evidence of loss in efficacy (tachyphylaxis).

Symptomatic benefits

Both doses demonstrated statistically significant improvements in symptom relief over placebo for dyspnoea and health status (as evaluated by Transitional Dyspnea 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 indacaterol required significantly less rescue medication, had more days when no rescue medication was needed compared to placebo and had a significantly improved percentage of days with no daytime symptoms.

Pooled efficacy analysis over 6 months' treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparison compared to placebo showed a ratio of rates of 0.68 (95% CI [0.47, 0.98]; p-value 0.036) and 0.74 (95% CI [0.56, 0.96]; p-value 0.026) for 150 microgram and 300 microgram, respectively.

Limited treatment experience is available in individuals of African descent.

Table 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[b]	1.2[a]	n/e	0.3[a] 0.4[b]
Percentage of days with no	60 [a] 57 [b]	58[b]	46[b]	55[a]	n/e	42[a] 42[b]

rescue medication use						

In the study design, the following medicines were used: [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

General properties
Indacaterol is a chiral molecule with R-configuration.
Pharmacokinetic data were obtained from a number of clinical studies, from healthy volunteers and COPD patients.

Absorption
The median time to reach peak serum concentrations of indacaterol was approximately 15 minutes 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 averaged 43-45%. Systemic exposure results from a composite of pulmonary and gastrointestinal absorption; about 75% of systemic exposure was from pulmonary absorption and about 25% from gastrointestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady state was achieved within 12 to 14 days. The mean accumulation ratio of indacaterol (i.e. AUC over the 24-hour 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 and 600 microgram.

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

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

In vitro investigations indicated that UGT1A1 is the only UGT isoform that 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 liters/hour. When compared with the serum clearance of indacaterol of 23.3

liters/hour, it is evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available indacaterol.

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

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

Characteristics in special populations

Hepatic impairment:

Patients with mild and moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Renal impairment:

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

Pediatric population:

There is no relevant use of INBROXA in pediatric populations (under 18 years of age).

Geriatric population:

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

Age, gender, weight, race:

A population pharmacokinetic analysis showed that there is no clinically relevant effect of age (adults up to 88 years), sex, weight (32-168 kg) or race on the pharmacokinetics of indacaterol. It did not suggest any difference between ethnic subgroups in this population.

5.3 Preclinical safety data

Effects on the cardiovascular system attributable to the $beta_2$-agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritancy of the nasal cavity and larynx were seen in rodents. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F1 offspring was observed in the peri- and post-developmental rat study at an exposure 14-fold higher than in humans treated with indacaterol. Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential. Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent

with similar findings reported for other beta$_2$-adrenergic agonists. No evidence of carcinogenicity was seen in mice. Systemic exposures (AUC) in rats and mice at the no-observed adverse effect levels in these studies were at least 7- and 49-fold higher, respectively, than in humans treated with indacaterol once a day at a dose of 300 microgram.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (Inhalac 230) (from bovine milk)
Lactose monohydrate (Inhalac 400) (from bovine milk)

Gelatin capsule composition
Gelatin (bovine gelatin)
Brilliant blue FCF-FD&C Blue 1
Red iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 30°C and in its package.
Hard capsules should be stored in the blister in order to protect them from moisture and should only be removed just before use.

6.5 Nature and contents of container

INBROXA 150 mcg hard capsules with inhalation powder are packaged in blisters consisting of OPA-Alu-PVC film and aluminum foil. Blisters are presented in a cardboard box, together with a monodose dry powder inhaler in a plastic separator and package leaflet.
Each cardboard box contains 30 or 60 capsules and 1 device (monodose dry powder inhaler) in a plastic separator.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkali Merkez Mah. Basin Ekspres Cad. No:1
34303 Küçükçekmece – ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2020/44

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 02.03.2020
Date of last renewal: -

10. DATE OF REVISION OF THE TEXT

12.01.2021