SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

COSEBLAR 85 mcg / 43 mcg Hard Capsules with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains:

Active substances:

Indacaterol maleate	143 mcg	(equivalent to 110 mcg indacaterol)
Glycopyrronium bromide	63 mcg	(equivalent to 50 mcg glycopyrronium)

Each delivered dose through the mouthpiece per inhalation is equivalent to 85 mcg indacaterol for indacaterol maleate and 43 mcg glycopyrronium for glycopyrronium bromide.

Excipients with known effect:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for inhalation, hard capsules.
Transparent yellow capsules containing white or whitish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COSEBLAR is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology/frequency and duration of administration

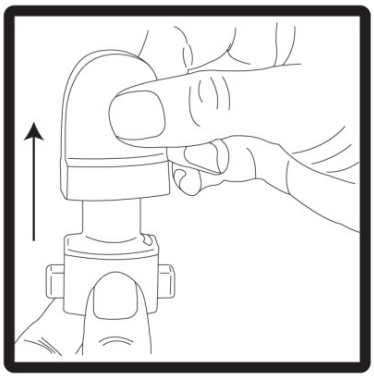
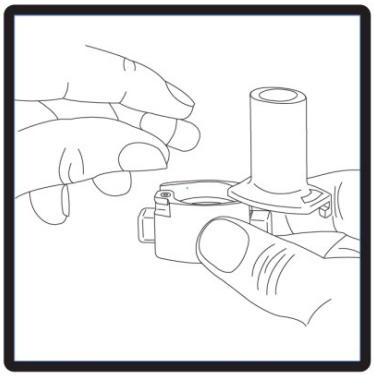
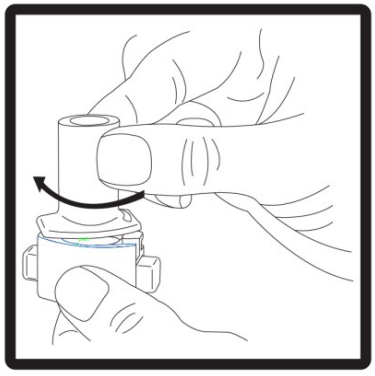
Posology

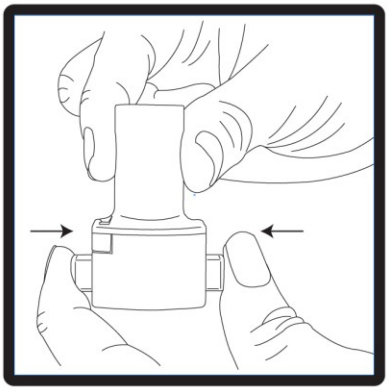
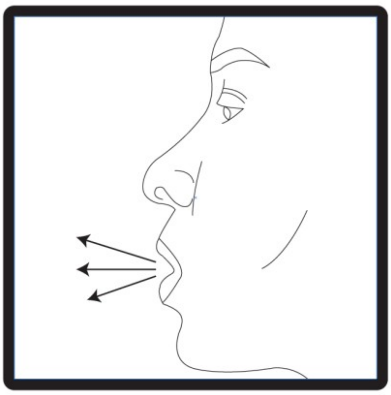
The recommended dose is the inhalation of the content of one capsule once daily using the inhaler. COSEBLAR is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day.

Method of administration

For inhalation use only. The capsules must not be swallowed.
The capsules must be administered only using the inhaler. The inhaler provided with each new prescription should be used.
Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it.

Instructions for use:

	**1.** Pull the cover off.
	**2.** While holding the bottom of the device firmly, open the mouthpiece by turning it in the direction of the arrow.
	**3.** Remove the capsule out of its package right before use. Place a capsule into the capsule shaped chamber at the bottom of the device.
	**4.** Turn the mouthpiece to close it.

	**5.** Hold the device upright (with the mouthpiece up) and press the tabs on the side ONLY ONCE simultaneously. After the capsule is pierced, release the side tabs. Please note: The capsule can be broken into pieces during this process and there is a possibility that small capsule pieces escape into mouth and throat during inhalation. Capsule fragments are harmless. Removing the capsule from its package just before use and pushing the tabs at sides only once for piercing the capsule minimize the risk of capsule being broken into pieces (see Step 3).
	**6.** Blow your breath away strongly.
	**7.** Place the mouthpiece in your mouth and tilt your head back slightly. Close your lips tightly around the mouthpiece and inhale as quickly and deeply as possible. You will hear a "buzz" sound because of the capsule rotating in its chamber during powder dispersion. If you did not hear that sound, the capsule could have been stuck in its chamber. If that is the case, open your device, and dislocate the capsule in its chamber and loosen it. DO NOT PUSH the buttons more than once in order to loosen the capsule.
8. Hold your breath: While removing the inhaler from your mouth, hold your breath for 5 to 10 seconds or for as long as possible. Then exhale. Open the inhaler to check that no powder remains in the capsule. If powder remains in the capsule, turn off the inhaler and repeat the steps 6, 7 and 8. Most patients can empty the capsule in one or two inhalations. Some people rarely cough for a short time after inhaling the medicine. Do not worry if you cough. As long as the capsule is empty, you will receive the full dose of your medicine.	
9. Discard the empty capsule after using it and close the mouthpiece.	

Additional information
Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is pierced more than once (see Step 5).

Cleaning the inhaler
Never wash the inhaler with water. If you want to clean it, wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry.

Additional information on special populations
Renal impairment
COSEBLAR can be used at the recommended dose in patients with mild and moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis, it should be used only if the expected benefit outweighs the potential risk (see sections 4.4 and 5.2).

Hepatic impairment
COSEBLAR can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of indacaterol maleate/glycopyrronium bromide in patients with severe hepatic impairment, therefore caution should be observed in these patients (see section 5.2).

Pediatric population
There is no relevant use of COSEBLAR in the pediatric population (under 18 years) in the indication COPD. The safety and efficacy of COSEBLAR in children have not been established. No data are available.

Geriatric population
COSEBLAR can be used at the recommended dose in elderly patients (75 years and older).

4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Asthma-related breathing problems associated with long-acting beta-agonist preparations can rarely occur, which can be serious and sometimes fatal.

COSEBLAR is not recommended for the initial treatment of asthma.

Long-acting beta agonists should be used for the shortest period of time that allows controlling asthma symptoms and your doctor will discontinue it, if possible, once asthma control is achieved. Patients should then be maintained with a control treatment.

In pediatric and adolescent patients receiving long-acting beta-agonists in addition to inhaled corticosteroids, it is recommended to use a combination preparation containing both inhaled corticosteroids and long-acting beta-agonists to ensure compliance with both medicines.

Treatment with long-acting beta-agonists should not be initiated if patients are in exacerbation periods or have asthma symptoms that are significantly or acutely worsening.

It should not be used together with medicinal products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, which are pharmacotherapeutic groups to which the components of COSEBLAR belong (see section 4.5).

Asthma
COSEBLAR should not be used to treat asthma due to lack of data in this indication.

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

Not for acute use
COSEBLAR is not indicated for the treatment of acute episodes of bronchospasm.

Hypersensitivity
Sudden hypersensitivity reactions have been reported after administration of indacaterol or glycopyrronium, the active ingredients of COSEBLAR. If symptoms indicating allergic reactions occur, especially angioedema (difficulty breathing or swallowing, swelling of the tongue, lips and face), urticaria, skin rash, treatment should be stopped immediately and an alternative treatment started.

Paradoxical bronchospasm
COSEBLAR administration may result in paradoxical bronchospasm, which may be life threatening. In this case, treatment should be stopped immediately and an alternative treatment started.

Anticholinergic effects related to glycopyrronium
Narrow-angle glaucoma
There are no available data on patients with narrow-angle glaucoma and therefore COSEBLAR should be used with caution in these patients.
Patients should be informed of the signs and symptoms of acute narrow-angle glaucoma and should be instructed to discontinue COSEBLAR if these signs or symptoms occur.

Urinary retention
There are no available data on patients with urinary retention and therefore COSEBLAR should be used with caution in these patients.

Patients with severe renal impairment
There was a moderate mean increase in total system exposure (AUC_{last}) to glycopyrronium of 1.4-fold in volunteers with mild to moderate renal impairment and 2.2-fold in patients with severe renal impairment and end-stage renal disease. In patients with severe renal impairment (estimated glomerular filtration rate less than 30 ml/min/1.73m^2), including those with end-stage renal disease requiring dialysis, COSEBLAR should only be used if the expected benefit exceeds the potential risk (see section 5.2). These patients should be closely monitored for potential adverse reactions.

Cardiovascular events
COSEBLAR should be used with caution in patients with cardiovascular disease (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, high blood pressure).

Beta$_2$-adrenergic agonists may produce a clinically significant cardiovascular effect in some patients, as measured by an increase in pulse rate, blood pressure and/or symptoms. If such effects occur with this medicinal product, it may be necessary to discontinue treatment. Furthermore, beta-adrenergic agonists have been reported to produce electrocardiographic (ECG) changes (flattening of the T wave, prolongation of the QT interval and ST segment depression), but the clinical significance of these findings is unknown. Therefore, long-acting beta$_2$-adrenergic agonists (LABA) or LABA-containing combination products such as COSEBLAR should be used with caution in patients with prolongation of the QT interval or suspected prolongation of the QT interval or in patients treated with medicines that affect the QT interval.

Patients with unstable ischemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (except chronic stable atrial fibrillation), history of long QT syndrome or prolonged QTc interval (>450 ms) (Fridericia method) were not included in clinical studies and therefore there is no experience in these patient groups. COSEBLAR should be used with caution in these patient groups.

Hypokalemia
Beta$_2$-adrenergic agonists may cause significant hypokalemia with the potential for cardiovascular adverse effects in some patients. Decreased serum potassium levels are usually transient and do not require supplementation. In patients with severe COPD, hypokalemia may be increased by hypoxia and concomitant treatments (see section 4.5.), which may increase susceptibility to cardiac arrhythmias.
Clinically significant effects of hypokalemia were not observed in clinical COSEBLAR studies at the recommended therapeutic dose (see section 5.1).

Hyperglycemia
Inhalation of high doses of beta$_2$-adrenergic agonists may lead to increases in plasma glucose. Following initiation of COSEBLAR treatment, plasma glucose should be monitored more closely in diabetic patients.
Clinically significant changes in blood glucose during long-term clinical studies were observed more frequently in the group administered COSEBLAR at recommended doses (4.9%) than in the placebo group (2.7%). COSEBLAR has not been studied in patients with poorly controlled *diabetes mellitus*, therefore caution and appropriate monitoring of these patients is recommended.

General disorders
COSEBLAR should be used with caution in patients with convulsive disorders or thyrotoxicosis or in patients who are unusually sensitive to beta$_2$-adrenergic agonists.

4.5 Interaction with other medicinal products and other forms of interaction
The simultaneous administration of orally inhaled indacaterol and glycopyrronium under steady-state conditions of both active substances did not affect the pharmacokinetics of these two active substances.

Specific interaction studies with indacaterol maleate/glycopyrronium bromide have not been performed. Information on the potential for interaction is based on the potential of the two active substances of this product.

Concomitant use not recommended with:
Beta-adrenergic blockers
Beta-adrenergic blockers can weaken or antagonize the effect of beta$_2$-adrenergic agonists. Therefore, COSEBLAR should not be used in combination with beta$_2$-adrenergic blockers (including eye drops) unless their use is mandatory. Cardioselective beta-adrenergic blockers should be preferred when necessary, but they should be administered with caution.

Anticholinergics
The concomitant administration of indacaterol maleate/glycopyrronium bromide with other anticholinergic medicinal products has not been studied and is therefore not recommended (see section 4.4).

Sympathomimetics
Concomitant administration of other sympathomimetic agents (alone or as part of combination treatment) may potentiate the adverse effects of indacaterol (see section 4.4).

Cautions in case of concomitant use:
Hypokalemic treatment
Concomitant treatment with methylxanthine derivatives, steroids or non-potassium-sparing diuretics may potentiate the possible hypokalemic effect of beta$_2$-adrenergic agonists and should therefore be used with caution (see Section 4.4).

Considerations for concomitant use:
Metabolic and transporter-based interactions:
Inhibition of CYP3A4 and P-glycoprotein (P-gp), which play a key role in indacaterol clearance, increases systemic indacaterol exposure up to twofold. Given the safety experience obtained in clinical trials in which indacaterol was used at doses up to 2 times the maximum recommended therapeutic doses for up to 1 year, the increased magnitude of exposure due to drug interactions does not raise any safety concerns.

Cimetidine or other organic cation transport inhibitors
In a clinical study in healthy volunteers, cimetidine, an organic cation transport inhibitor thought to contribute to the renal excretion of glycopyrronium, increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically significant drug interactions are expected when glycopyrronium is coadministered with cimetidine or other organic cation transport inhibitors.

Additional information on special populations
There are no data on special populations.

Pediatric population: There are no data on the pediatric population.

4.6 Pregnancy, lactation, and fertility
General advice
Pregnancy category is C.

Women with childbearing potential / Contraception
There are no special requirements for women with childbearing potential.

Pregnancy
There are no data from the use of COSEBLAR 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).

Animal studies are insufficient in terms of effects on pregnancy /and-or/ embryonic/fetal development /and-or/ parturition /and-or/ postnatal development (see section 5.3.). The potential risk to humans is unknown.

Indacaterol may inhibit labor due to a relaxant effect on uterine smooth muscle. Therefore, COSEBLAR should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

COSEBLAR should not be used during pregnancy unless necessary (the conditions for this should be specified).

Breastfeeding
It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. Available pharmacokinetic/toxicological data have shown excretion of indacaterol, glycopyrronium and their metabolites in the milk of lactating rats. The use of COSEBLAR by breastfeeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant (see section 5.3).

Fertility
Reproduction studies and other data in animals do not indicate a concern regarding fertility in either males or females.

4.7 Effects on ability to drive and use machines
This medicinal product has no or negligible influence on the ability to drive and use machines. However, the occurrence of dizziness may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects
The presentation of the safety profile is based on the experience with indacaterol maleate/glycopyrronium bromide and each active substance.

Summary of the safety profile
Safety experience with indacaterol maleate/glycopyrronium bromide consists of up to 15 months of exposure at the recommended therapeutic dose.

Adverse reactions occurring with indacaterol maleate/glycopyrronium bromide appeared similar to the adverse reactions occurring with each component. Because this product contains glycopyrronium and indacaterol, adverse reactions of the type and severity associated with each of these components can also be expected in combination.

The safety profile is characterized by anticholinergic and beta-2-adrenergic class effects associated with each component of the combination. Common adverse reactions associated with the product (those reported for indacaterol maleate/glycopyrronium bromide in at least 3% of patients and at a higher rate than placebo) are cough, nasopharyngitis and headache.

Tabulated summary of adverse reactions

Adverse reactions identified in clinical studies and from post-marketing sources are listed by MedDRA system organ class (Table 1). Within each system organ class, adverse reactions are ranked according to their frequency and the most common reactions are ranked first. Adverse reactions in each frequency group are presented in order of decreasing severity.

In addition, the corresponding frequency category for each adverse reaction is arranged as follows: 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 available data).

Table 1. Adverse Reactions

System organ class	Adverse reactions
Infections and infestations	
Very common	Upper respiratory tract infection
Common	Nasopharyngitis
Common	Urinary tract infection
Common	Sinusitis
Common	Rhinitis
Immune system disorders	
Common	Hypersensitivity
Uncommon	Angioedema[2]
Metabolism and nutrition disorders	
Common	Hyperglycemia and diabetes mellitus
Psychiatric disorders	
Uncommon	Insomnia
Nervous system disorders	
Common	Dizziness
Common	Headache
Rare	Paresthesia
Eye disorders	
Uncommon	Glaucoma[1]
Cardiac disorders	
Uncommon	Ischemic heart disease
Uncommon	Atrial fibrillation
Uncommon	Tachycardia
Uncommon	Palpitation
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Common	Oropharyngeal pain including laryngeal irritation
Uncommon	Paradoxical bronchospasm
Uncommon	Dysphonia[2]
Uncommon	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Common	Dental caries

Uncommon	Gastroenteritis
Uncommon	Dry mouth
Skin and subcutaneous tissue disorders	
Uncommon	Pruritus/rash
Musculoskeletal, connective tissue and bone disorders	
Uncommon	Musculoskeletal pain
Uncommon	Muscle spasm
Uncommon	Myalgia
Uncommon	Pain in extremity
Renal and urinary disorders	
Common	Bladder obstruction and urinary retention
General disorders and administration site conditions	
Common	Pyrexia[1]
Common	Chest pain
Uncommon	Edema peripheral
Uncommon	Fatigue

[1] Adverse reaction seen with indacaterol maleate/glycopyrronium bromide but not with individual components.
[2] Reports from post-marketing experience; however, frequencies were calculated based on clinical study data.

Description of selected adverse medicine reactions
Cough is common but usually mild in severity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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
There are no clinically relevant data available regarding overdose with the combination of indacaterol maleate/glycopyrronium bromide.
An overdose could 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 or could induce anticholinergic effects such as increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalized. Use of cardioselective beta-blockers may be considered for treating beta$_2$-adrenergic effects, 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 airway diseases; adrenergics in combination with anticholinergics
ATC code **:** R03AL04

Mechanism of action

Indacaterol maleate/glycopyrronium bromide

When administered together in an inhaler, indacaterol and glycopyrronium provide additional efficacy through different mechanisms of action targeting different receptors and pathways for smooth muscle relaxation. As a result of the different density of M3 receptors and beta$_2$-adrenoceptors in the central and peripheral airways of the lungs, beta$_2$-agonists may be more effective in relaxing the peripheral airways, while an anticholinergic compound may be more effective in relaxing the central airways. Therefore, the combination of a beta$_2$-adrenergic agonist and a muscarinic antagonist may be useful for bronchodilation in both the peripheral and central airways of the human lung.

Indacaterol

Indacaterol is a long-acting beta$_2$-adrenergic agonist for once-daily administration. The pharmacological effects of beta$_2$-adrenoceptor agonists such as indacaterol may be attributed, at least in part, to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). High cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that the agonist activity of a long-acting indacaterol at beta$_2$-receptors is much greater than at beta1 and beta$_3$-receptors.

When inhaled, indacaterol exerts a bronchodilator effect locally in the lungs. Indacaterol is a partial agonist with nanomolar potency at the human beta$_2$-adrenergic receptor level.

Although beta$_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenergic receptors in the human heart, beta$_2$-adrenergic receptors account for 10-50% of the total adrenergic receptors in the human heart. The presence of beta$_2$-adrenergics in the heart increases the likelihood of cardiac effects of even highly selective beta$_2$-adrenergic agonists.

Glycopyrronium

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) for once-daily bronchodilator maintenance treatment of COPD. Parasympathetic nerves are the major bronchoconstrictive neural pathway in the airways and cholinergic tone is a critical reversible component of airway obstruction in COPD. Glycopyrronium acts by blocking the bronchoconstrictor effect of acetylcholine on airway smooth muscle cells and thus dilating the airways.

Glycopyrronium is a high-affinity muscarinic receptor antagonist. In radioligand binding studies, its selectivity for human M3 receptors was 4-fold higher compared to human M2 receptors.

Pharmacodynamic effects

Combination of indacaterol and glycopyrronium in the inhaler showed a rapid onset of action within 5 minutes of dosing. The effect remained constant over the 24-hour dosing interval.
The mean bronchodilator effect obtained from serial FEV_1 measurements at 24 hours was 320 ml after 26 weeks of treatment. This effect was significantly higher for indacaterol maleate/glycopyrronium bromide compared with indacaterol, glycopyrronium or tiotropium alone (difference of 110 ml for each comparison).

There was no evidence of tachyphylaxis in the effect of indacaterol maleate/glycopyrronium bromide compared with placebo or monotherapy components.

Effects on heart rate
Effects on heart rate in healthy volunteers were investigated after administration of 4 times the recommended therapeutic dose of indacaterol maleate/glycopyrronium bromide in four doses one hour apart and compared with placebo, indacaterol, glycopyrronium and salmeterol.

Compared with placebo, the largest time-matched heart rate increase was +5.69 beats/min (90% CI [2.71, 8.66]) and the largest decrease was -2.51 beats/min (90% CI [-5.48, 0.47]). Overall, the effect on heart rate did not indicate a stable pharmacodynamic effect of indacaterol maleate/glycopyrronium bromide.

Heart rate of COPD patients at supratherapeutic doses was studied. Indacaterol maleate/glycopyrronium bromide had no significant effect on 24-hour mean heart rate or on heart rates assessed after 30 minutes, 4 hours and 24 hours.

QT interval
A comprehensive QT (TQT) study in healthy volunteers with high doses of inhaled indacaterol (above the maximum recommended therapeutic dose) showed no clinically significant effect on QT interval. In a TQT study for glycopyrronium, no QT prolongation was observed after 8 times the recommended therapeutic dose was administered by inhalation.

Effects of indacaterol maleate/glycopyrronium bromide on the QTc interval were studied in healthy volunteers after inhalation of up to four times the recommended therapeutic dose, up to four times, one hour apart. Compared to placebo, the highest time-matched difference was 4.62 ms (90% CI 0.4, 8.85 ms) and the highest time-matched decrease was -2.71 ms (90% CI -6.97, 1.54 ms), indicating that, as expected based on the properties of its components, Indacaterol maleate/glycopyrronium bromide had no significant effect on QT interval.

In patients with COPD, supratherapeutic doses of Indacaterol maleate/glycopyrronium bromide ranging from 116 mcg/86 mcg to 464 mcg/86 mcg resulted in a higher proportion of patients with QTcF prolongation of 30 ms and 60 ms in terms of baseline values compared to placebo (16.0% to 21.6%; 1.9% for placebo), but no QTcF prolongation of >60 ms compared to baseline. The highest dose level of 464 mcg/86 mcg of Indacaterol maleate/ glycopyrronium bromide resulted in a higher proportion of patients with absolute QTcF values >450 ms (12.2%; 5.7% for placebo).

Serum potassium and blood sugar
In healthy volunteers, the effect on serum potassium after administration of 4 times the recommended therapeutic dose of indacaterol maleate/glycopyrronium bromide was very small (maximum difference is -0.14 mmol/L compared with placebo). The maximum effect on blood glucose is 0.67 mmol/L.

Clinical efficacy and safety
The Phase III clinical development program of indacaterol maleate/glycopyrronium bromide included six studies involving more than 8,000 patients:
1) A 26-week placebo and active-controlled study (indacaterol once daily, glycopyrronium once daily, open-label tiotropium once daily);

2) A 26-week active controlled study (fluticasone/salmeterol twice daily);
3) A 64-week active controlled study (glycopyrronium once daily, open-label tiotropium once daily);
4) A 52-week placebo-controlled study;
5) A 3-week placebo and active-controlled (tiotropium once daily) exercise tolerance study; and
6) A 52-week active controlled study (fluticasone/salmeterol twice daily).

Four of these studies included patients with moderate to severe COPD. The 64-week study included patients with severe to very severe COPD with ≥1 moderate or severe COPD exacerbation in the previous year. Patients with moderate to very severe COPD with ≥1 moderate or severe COPD exacerbation in the previous year were enrolled to 52-week active controlled study.

Effects on lung function
Indacaterol maleate/glycopyrronium bromide has led to clinically significant improvements in lung function (measured by forced expiratory volume in one second, FEV_1) in a number of clinical trials. In Phase III studies, bronchodilator effects were seen within 5 minutes of the first dose and were sustained over a 24-hour dosing interval from the first dose. There was no reduction in bronchodilator effect over time.

The magnitude of the effect depended on the degree of reversibility of the initial airway restriction (tested by administering a short-acting muscarinic antagonist and a short-acting $beta_2$-agonist): Patients with the lowest (<5%) reversibility at baseline generally exhibited a lower bronchodilator response than patients with higher (≥5%) reversibility. At week 26 (primary endpoint), Indacaterol maleate/glycopyrronium bromide increased trough FEV1 by 80 ml (Indacaterol maleate/glycopyrronium bromide n=82, placebo n=42; p=0.053) in patients with the lowest reversibility (<5%) and by 220 ml (Indacaterol maleate/glycopyrronium bromide n=392, placebo n=190; p<0.001) in patients with higher reversibility (≥5%) compared to placebo.

Trough and peak FEV_1:
In the primary endpoint, indacaterol maleate/glycopyrronium bromide increased the post-dose trough FEV_1 at week 26 by 200 mL compared to placebo (p<0.001) and resulted in significant increases compared to both the monotherapy component (indacaterol and glycopyrronium) treatment arm and the tiotropium treatment arm as shown in the table below.

Post-dose trough FEV_1 at day 1 and week 26 (primary endpoint) (least squares mean)

Treatment difference	Day 1	Week 26
Indacaterol maleate / glycopyrronium bromide – placebo	190 ml (p < 0.001)	200 ml (p < 0.001)
Indacaterol maleate / glycopyrronium bromide – indacaterol	80 ml (p < 0.001)	70 ml (p < 0.001)
Indacaterol maleate / glycopyrronium bromide – glycopyrronium	80 ml (p < 0.001)	90 ml (p < 0.001)
Indacaterol maleate / glycopyrronium bromide – tiotropium	80 ml (p < 0.001)	80 ml (p < 0.001)

The mean pre-dose FEV1 value mean of values taken 45 and 15 minutes before the morning dose of the study medicine) was statistically significant in favor of Indacaterol maleate/ glycopyrronium bromide compared with fluticasone/salmeterol at week 26 (least squares mean treatment difference 100 mL, p<0.001) [compared with placebo at week 52 (least squares [LS] mean treatment difference 189 mL, p<0.001)] and compared with glycopyrronium (least squares mean treatment difference 70-80 mL, p<0.001) and tiotropium (least squares mean treatment difference 60-80 mL, p<0.001) at all visits up to week 64. In the 52-week active controlled study, the mean pre-dose FEV_1 value was statistically significant in favor of Indacaterol maleate/glycopyrronium bromide at all visits up to week 52 compared with fluticasone/salmeterol (least squares mean treatment difference 62-86 ml, p<0.001). At week 26, indacaterol maleate/glycopyrronium bromide resulted in a statistically significant improvement in peak FEV_1 compared with placebo in the first 4 hours after dosing (least squares mean treatment difference 330 ml) (p<0.001).
FEV_1 AUC:
In the active controlled study, indacaterol maleate/glycopyrronium bromide increased the post-dose FEV_1 AUC0-12 (primary endpoint) by 140 mL more than fluticasone/salmeterol at week 26 (p<0.001).

Symptomatic outcomes
Dyspnea:
Indacaterol maleate/glycopyrronium bromide significantly reduced dyspnea as assessed by the Transitional Dyspnea Index (TDI). Indacaterol maleate/glycopyrronium bromide provided clinically and statistically significant improvement in TDI focal score at week 26 compared to placebo, tiotropium and fluticasone/salmeterol (least squares mean treatment difference 1.09, p<0.001; 0.51, p=0.007 and 0.76, p=0.003, respectively). The improvements compared to indacaterol and glycopyrronium were 0.26 and 0.21, respectively.

A greater percentage of patients receiving indacaterol maleate/glycopyrronium bromide compared to placebo achieved an improvement of 1 point or more in the TDI focal score at Week 26 (57.5% and 68.1%, respectively, p=0.004). At Week 26, a higher proportion of patients receiving indacaterol maleate/glycopyrronium bromide had a clinically significant response compared to those receiving tiotropium and fluticasone/salmeterol: 68.1% with indacaterol maleate/glycopyrronium bromide and 59.2% with tiotropium (p=0.016); 65.1% with indacaterol maleate/glycopyrronium bromide and 55.5% with fluticasone/salmeterol (p=0.088).

Health-related quality of life:
Indacaterol maleate/glycopyrronium bromide also resulted in a statistically significant improvement (reduction in total score) at week 26 in health-related quality of life as assessed by the St. George Respiratory Questionnaire (SGRQ): difference compared to placebo (least squares mean treatment difference -3.01, p=0.002) and difference compared to tiotropium (least squares mean treatment difference -2.13, p=0.009); the reductions compared to indacaterol and glycopyrronium were -1.09 and -1.18, respectively. At week 64, the reduction compared with tiotropium was statistically significant (least squares mean treatment difference -2.69, p<0.001). At week 52, the reduction compared with fluticasone/salmeterol was statistically significant (least squares mean treatment difference -1.3, p=0.003).

A higher percentage of patients receiving indacaterol maleate/glycopyrronium bromide achieved clinically meaningful improvement in SGRQ score (at least a 4-unit decrease from

baseline): 63.7% with indacaterol maleate/glycopyrronium bromide at week 26 (56.6% with placebo [p=0.088 for difference] and 56.4% with tiotropium [p=0.047 for difference]) and 57.3% with indacaterol maleate/glycopyrronium bromide at week 64 (51.8% with glycopyrronium [p=0.055] and 50.8% with tiotropium [p=0.051]); At week 52, 49.2% with indacaterol maleate/glycopyrronium bromide (49.2% with fluticasone/salmeterol (compared to 43.7% with indacaterol maleate/glycopyrronium bromide, risk ratio: 1,3, p<0,001).

Daily activities
Indacaterol maleate/glycopyrronium bromide showed a greater improvement than tiotropium in the percentage of 'days in which it was possible to perform normal daily activities' at week 26 (least squares mean treatment difference 8.45%, p<0.001). At week 64, indacaterol maleate/glycopyrronium bromide showed a numerically significant improvement compared to glycopyrronium (least squares mean treatment difference 1.95%; p=0.175) and a statistically significant improvement compared to tiotropium (least squares mean treatment difference 4.96%; p=0.001).

COPD exacerbations
In a 64-week study comparing indacaterol maleate/glycopyrronium bromide (n=729), glycopyrronium (n=739) and tiotropium (n=737), once-daily indacaterol maleate/glycopyrronium bromide reduced the annual rate of moderate or severe COPD exacerbations by 12% (p=0.038) compared to glycopyrronium and 10% (p=0.096) compared to tiotropium. The number of moderate or severe COPD exacerbations per patient-year was 0.94 (812 events) for indacaterol maleate/glycopyrronium bromide, 1.07 (900 events) for glycopyrronium and 1.06 (898 events) for tiotropium. Furthermore, indacaterol maleate/glycopyrronium bromide reduced the annual exacerbation (mild, moderate, severe) rate by 15% (p=0.001) compared to glycopyrronium and 14% (p=0.002) compared to tiotropium. The number of all exacerbations per patient year was 3.34 (2,893 events) for indacaterol maleate/glycopyrronium bromide, 3.92 (3,294 events) for glycopyrronium and 3.89 (3,301 events) for tiotropium.

In the 52-week study comparing indacaterol maleate/glycopyrronium bromide (n=1,675) and fluticasone/salmeterol (n=1,679), the primary study objective of equal efficacy compared to fluticasone/salmeterol was achieved in terms of the rate of COPD exacerbations (mild, moderate or severe). The number of all COPD exacerbations per patient year was 3.59 (4,531 events) for indacaterol maleate/glycopyrronium bromide and 4.03 (4,969 events) for fluticasone/salmeterol. Indacaterol maleate/glycopyrronium bromide was additionally superior (11%; p=0.003) to fluticasone/salmeterol in reducing the annual exacerbation rate.

Compared with fluticasone/salmeterol, indacaterol maleate/glycopyrronium bromide reduced the rate of moderate or severe exacerbations by 17% (p<0.001) and severe exacerbations (requiring hospitalization) by 13% (not statistically significant, p=0.231). The number of moderate or severe exacerbations per patient-year was 0.98 (1,265 events) for indacaterol maleate/glycopyrronium bromide and 1.19 (1,452 events) for fluticasone/salmeterol. Indacaterol maleate/glycopyrronium bromide prolonged the time to first moderate or severe exacerbation by reducing the risk of exacerbation by 22% (p<0.001) and the time to first severe exacerbation by by reducing the risk of exacerbation by 19% (p=0.046).

The incidence of pneumonia was 3.2% in the indacaterol maleate/glycopyrronium bromide arm and 4.8% in the fluticasone/salmeterol arm (p=0.017). The time to first pneumonia was

longer in the indacaterol maleate/glycopyrronium bromide arm compared to fluticasone/salmeterol (p=0.013).

In another study comparing indacaterol maleate/glycopyrronium bromide (n=258) with fluticasone/salmeterol (n=264), the number of moderate or severe COPD exacerbations/patient year at 26 weeks was 0.15 and 0.18 (18 events versus 22 events), respectively (p=0.512), and the number of all COPD exacerbations/patient year (mild, moderate or severe) was 0.72 and 0.94 (86 events versus 113 events), respectively (p=0.098).

Use of rescue medication
During the 26-week period, once-daily indacaterol maleate/glycopyrronium bromide significantly reduced the use of rescue medication (salbutamol) by 0.96 puff/day compared to placebo (p<0.001), 0.54 puff/day compared to tiotropium (p<0.001) and 0.39 puff/day compared to fluticasone/salmeterol (p=0.019). In a 64-week study, this reduction was 0.76 puff/day (p<0.001) compared to tiotropium. In a 52-week study, indacaterol maleate/glycopyrronium bromide reduced rescue medication use by 0.25 puff/day compared to fluticasone/salmeterol (p<0.001).

Exercise tolerance
Morning administration of indacaterol maleate/glycopyrronium bromide reduced dynamic hyperinflation and prolonged exercise duration from the first dose. On the first day of treatment, inspiratory capacity during exercise improved significantly compared to placebo (least squares mean treatment difference 250 ml, p<0.001). After three weeks of treatment, the improvement in inspiratory capacity was greater with indacaterol maleate/glycopyrronium bromide (least squares mean treatment difference 320 ml, p<0.001) and the duration of exercise endurance increased compared to placebo (least squares mean treatment difference 59.5 seconds, p=0.006).

Pediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with indacaterol maleate/glycopyrronium bromide in all subsets of the pediatric population in chronic obstructive pulmonary disease (COPD) (see section 4.2 for "Pediatric population").

5.2 Pharmacokinetic properties
General properties:
Absorption
Indacaterol maleate/glycopyrronium bromide
After inhalation of indacaterol maleate/glycopyrronium bromide, the median time to peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 and 5 minutes, respectively.

Based on *in vitro* performance data, the dose of indacaterol reaching the lung is expected to be similar for indacaterol maleate/glycopyrronium bromide and the indacaterol monotherapy product. The steady-state exposure of indacaterol after inhalation of indacaterol maleate/glycopyrronium bromide was similar to or slightly lower than the systemic exposure after inhalation of indacaterol monotherapy product.

The absolute bioavailability of indacaterol after inhalation of indacaterol maleate/glycopyrronium bromide is estimated to be in the range of 61-85% of the

administered dose; for glycopyrronium, this is estimated to be approximately 47%.

Steady-state exposure to glycopyrronium following inhalation of indacaterol maleate/glycopyrronium bromide was similar to systemic exposure following inhalation of a monotherapy product containing glycopyrronium.

Indacaterol
Steady-state concentrations of indacaterol were reached within 12 to 15 days of once-daily administration. The mean accumulation rate of indacaterol, i.e. the AUC over the 24-hour dosing interval on day 14 or 15 compared with day 1, was in the range 2.9-3.8 for once-daily inhalation doses between 60 mcg and 480 mcg (administered dose).

Glycopyrronium
Following repeated once-daily inhalation in patients with COPD, steady-state pharmacokinetics of glycopyrronium were reached within one week of treatment. The steady-state mean peak and trough concentrations of glycopyrronium in the recommended once-daily dosing regimen were 166 picogram/ml and 8 picogram/ml, respectively. Steady-state exposure (AUC over a 24-hour dosing interval) was approximately 1.4 to 1.7 times higher than after the first dose.

Distribution
Indacaterol
The volume of distribution of indacaterol after intravenous infusion was 2557 liters in the terminal phase, indicating a widespread distribution. Binding to human serum and plasma proteins under *in vitro* conditions was approximately 95%.

Glycopyrronium
After intravenous administration, the steady-state volume of distribution of glycopyrronium is 83 L and the volume of distribution in the terminal phase is 376 L. The apparent volume of distribution in the terminal phase after inhalation is approximately 20 times higher, reflecting the much slower elimination after inhalation. The in vitro human plasma protein binding of glycopyrronium is 38% to 41% at concentrations of 1 to 10 nanograms/mL.

Biotransformation
Indacaterol
In a human ADME (absorption, distribution, metabolism, excretion) study, after oral administration of radioactive element-labeled indacaterol, unchanged indacaterol was found to be the major component in serum, accounting for approximately one-third of the total 24-hour AUC. A hydroxylated derivative is the most prominent metabolite in serum. Hydroxylated indacaterol and phenolic O-glucuronides of indacaterol are other prominent metabolites. The diastereomer of the hydroxylated derivative, an N-glucuronate of indacaterol and C- and N-dealkylated products were the other metabolites identified.

In vitro studies have shown that UGT1A1 is the only UGT isoform that metabolizes indacaterol to phenolic O-glucuronate. However, systemic exposure to indacaterol is not significantly affected by UGT1A1 genotype, as shown in a clinical study conducted in populations with different UGT1A1 genotypes.

Oxidative metabolites were detected in co-incubation with recombinant CYP1A1, CYP2D6

and CYP3A4. It is concluded that CYP3A4 is the major isoenzyme responsible for the hydroxylation of indacaterol. *In vitro* studies have shown that indacaterol is a low affinity substrate for the beating pump P-gp.

Glycopyrronium
In vitro metabolism studies have shown that the metabolic pathways for glycopyrronium bromide are similar in animals and humans. Hydroxylation resulting in various mono- and bi-hydroxylated metabolites and direct hydrolysis resulting in the formation of carboxylic acid derivative (M9) were observed. *Under in vivo* conditions, M9 consists of the ingested portion of an inhaled dose of glycopyrronium bromide. After repeated doses in humans, glucoronide and/or sulfate conjugates of glycopyrronium corresponding to 3% of the administered dose were found in urine.

Many CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. Inhibition or induction of glycopyrronium metabolism is not expected to significantly alter systemic exposure to the active substance.

In vitro inhibition studies have shown that glycopyrronium bromide has no capacity to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR and the uptake transporters OCT1 or OCT2. In *in vitro* enzyme induction studies, glycopyrronium bromide did not cause clinically relevant induction of any tested cytochrome P450 isoenzyme, UGT1A1 and MDR1 and MRP2 transporters.

Elimination
Indacaterol
In clinical studies in which urine samples were also collected, the amount of indacaterol excreted unchanged in the urine was usually less than 2.5% of the administered dose. The mean renal clearance of indacaterol is between 0.46 and 1.2 L/hour. Compared with the serum clearance of indacaterol of 23.3 liters/hour, it is clear that renal clearance plays an insignificant role in the systemic excretion of available indacaterol (approximately 2 to 5% of systemic clearance).

In a human ADME study, orally administered indacaterol was excreted in human feces mainly as the unchanged parent component (54% of the dose) and to a lesser extent as hydroxylated indacaterol metabolites (23% of the dose).

Serum concentrations of indacaterol decrease multiphasically, with a mean terminal half-life of 45.5 to 126 hours. The effective half-life calculated from the accumulation of indacaterol after repeated doses ranges from 40 to 52 hours and is approximately consistent with the time to steady state of 12-15 days.

Glycopyrronium
After intravenous administration of[^{3H}]-labeled glycopyrronium bromide to humans, the average urinary excretion of radioactivity at 48 hours was 85% of the dose. In addition, 5% of the dose was detected in bile.

Renal elimination of the parent drug accounts for approximately 60 to 70% of the total clearance of systemically available glycopyrronium, while non-renal clearance processes

account for approximately 30 to 40%. Biliary clearance contributes to non-renal clearance, but non-renal clearance is thought to be largely due to metabolism.

The mean renal clearance of glycopyrronium is between 17.4 and 24.4 L/s. Active tubular secretion contributes to renal elimination of glycopyrronium. Up to 23% of the administered dose was detected as the parent drug in urine.

Glycopyrronium plasma concentrations decreased multiphasically. The mean terminal elimination half-life was much longer after inhalation (33 to 57 hours) compared to after intravenous (6.2 hours) and oral (2.8 hours) administration. Elimination pattern suggests continuous pulmonary absorption and/or glycopyrronium passage into systemic circulation at 24 hours and beyond after inhalation.

Linearity/Non-linearity
Indacaterol
Systemic exposure to indacaterol increased in proportion to the (administered) dose at increasing (120 mcg to 480 micrograms) doses.

Glycopyrronium
In the pharmacokinetic steady state of glycopyrronium in COPD patients, both systemic exposure and total urinary excretion increased approximately in proportion to the dose in the dose range of 44 to 176 micrograms (administered).

Special populations
Indacaterol maleate/glycopyrronium bromide
A population pharmacokinetic (PK) analysis in patients with COPD did not show a significant effect of age, gender and weight (lean body weight) on systemic exposure to indacaterol and glycopyrronium following indacaterol maleate/glycopyrronium bromide inhalation. Lean body weight (a function of weight and height) is defined as a covariate. A negative correlation between systemic exposure and lean body weight (or body weight) was observed, but no dose adjustment is recommended based on the magnitude of change or the predictive accuracy of lean body weight.

Smoking and baseline FEV_1 had no significant effect on systemic exposure to indacaterol and glycopyrronium after indacaterol maleate/glycopyrronium bromide inhalation.

Indacaterol
A population pharmacokinetic analysis showed that age (in adults up to 88 years of age), gender, weight (32 - 168 kg) or race had no clinically relevant effect on the pharmacokinetics of indacaterol. The findings do not indicate any difference between ethnic subgroups.

Glycopyrronium
In a population PK analysis of data on COPD patients, body weight and age were identified as factors implicated in inter-patient variability in systemic exposure. Glycopyrronium can be used at the recommended dose in all age and body weight groups.

Gender, smoking status and baseline FEV_1 had no significant effect on systemic exposure.

Patients with hepatic impairment
Indacaterol maleate/glycopyrronium bromide:
Based on the clinical pharmacokinetic properties of the monotherapy components; indacaterol maleate/glycopyrronium bromide may be used at the recommended dose in patients with mild to moderate hepatic impairment. No data is available on patients with severe hepatic impairment.

Indacaterol:
Patients with mild to moderate hepatic failure did not show significant differences in the C_{max} or AUC of indacaterol, nor did volunteers with mild to moderate hepatic failure and healthy controls differ in protein binding. No studies have been performed in patients with severe hepatic failure.

Glycopyrronium:
Clinical studies have not been performed in patients with hepatic failure. Glycopyrronium is cleared from the systemic circulation predominantly by renal excretion. Impaired hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase in systemic exposure.

Patients with renal failure
Indacaterol maleate/glycopyrronium bromide:
Based on the clinical pharmacokinetic properties of the monotherapy components; indacaterol maleate/glycopyrronium bromide may be used at the recommended dose in patients with mild to moderate renal failure. In patients with severe renal failure or end-stage renal disease requiring dialysis, indacaterol maleate/glycopyrronium bromide should only be used if the expected benefit outweighs the potential risk.

Indacaterol:
Since the urinary tract has a very low contribution to total body elimination, no studies have been conducted in patients with renal failure.

Glycopyrronium:
Renal failure affects total exposure to glycopyrronium bromide. A moderate increase in total systemic exposure (AUC_{end}) of up to 1.4-fold in patients with mild to moderate renal failure and up to 2.2-fold in patients with severe renal failure and end-stage renal disease were observed. It was concluded that glycopyrronium bromide could be used at the recommended dose, in COPD patients with mild to moderate renal failure (estimated glomerular filtration rate eGFR ≥30 mL/min/1.73 m^2).

Ethnic origin
Indacaterol maleate/glycopyrronium bromide:
There were no significant differences in the total systemic exposure (AUC) of both compounds between Japanese and Caucasian volunteers. Pharmacokinetic data for other ethnicities or races are insufficient.

Indacaterol:
No difference was found between ethnic subgroups. There is limited treatment experience in the black population.

Glycopyrronium:
There were no significant differences in total systemic exposure (AUC) between Japanese and Caucasian volunteers. Pharmacokinetic data for other ethnicities or races are insufficient.

5.3 Preclinical safety data

Indacaterol maleate/glycopyrronium bromide

Preclinical trials included *in vitro* and *in vivo* safety pharmacology assessments, repeated dose inhalation toxicity trials in rats and dogs and inhalation embryo-fetal development trial in rats.

In dogs, there was a marked increase in heart rate at all doses of indacaterol maleate/glycopyrronium bromide and each monotherapy component. The magnitude and duration of the effect on heart rate was increased with indacaterol maleate/glycopyrronium bromide and the duration of the effect compared with each component alone is consistent with an additive response. Shortened electrocardiogram intervals and decreased systolic and diastolic blood pressure were also observed. Indacaterol administered to dogs alone or in indacaterol maleate/glycopyrronium bromide was associated with a similar incidence and severity of myocardial lesions. Systemic exposures (AUC) at the no-adverse-effect-observed level (NOAEL) for myocardial lesions were 64 and 59 times higher than humans for each component, respectively.

During an embryofetal study in the rat, indacaterol maleate/glycopyrronium bromide had no effect on the embryo or fetus at any dose level. Systemic exposures (AUC) at the no-observed-adverse-effect level (NOAEL) were 79 and 126 times higher than the ones determined in humans for indacaterol and glycopyrronium, respectively.

Indacaterol

Effects on the cardiovascular system attributable to the $beta_2$-agonistic properties of indacaterol caused tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritation of the nasal cavity and larynx was observed in rodents. All these findings occurred at exposures sufficiently above those predicted in humans.

Although indacaterol did not affect overall reproductive performance in a rat fertility study, a reduction in the number of pregnant F_1 pups was observed in a peri- and post-developmental rat study conducted at exposures 14 times higher than in humans treated with indacaterol. Indacaterol and its metabolites were rapidly excreted in the milk of lactating rats. Indacaterol is not embryotoxic or teratogenic in rats or rabbits.

Genotoxicity studies have not revealed any mutagenic or clastogenic potential. Carcinogenicity was evaluated in a two-year rat study and a six-month transgenic mouse study. Increases in the incidences of benign ovarian leiomyomas and focal hyperplasia in the rat were similar to those reported for other $beta_2$-adrenergic agonists. No evidence of carcinogenicity was found in mice. Systemic exposures (AUC) at the level at which no adverse effects were observed in these studies were at least 7 and 49 times, respectively, the values in humans treated with indacaterol once daily at the maximum recommended therapeutic dose.

Glycopyrronium

Based on non-clinical data, safety pharmacology, repeated dose toxicity, genotoxicity, cardiogenic potential and conventional studies of reproductive and developmental toxicity, it does not pose a particular hazard to humans.

Effects associated with glycopyrronium bromide as a muscarinic receptor antagonist include mild to moderate increases in heart rate in the dog, lens opacities in the rat and reversible changes associated with decreased glandular secretions in the rat and dog. Mild irritation and adaptive changes in the respiratory tract were observed in the rat. All these findings occurred at exposures sufficiently above those predicted in humans.

Glycopyrronium did not show teratogenic effects in the rat or rabbit after inhaled administration. Fertility and prenatal and postnatal development were not affected in the rat. Glycopyrronium bromide and its metabolites did not significantly cross the placental barrier in mice, rabbits and dogs. Glycopyrronium bromide (including its metabolites) was excreted in the milk of lactating rats and reached concentrations in milk up to 10 times higher than in maternal blood.

Genotoxicity studies have not revealed any mutagenic or clastogenic potential for glycopyrronium bromide. Carcinogenicity studies with oral administration in transgenic mice and inhalation administration in rats revealed no evidence of carcinogenicity at systemic exposures (AUC) approximately 53 times higher than the maximum recommended dose for humans in mice and 75 times higher in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

HPMC Capsules (No:3)
Hypromellose
Tartrazine- FD&C Yellow 5

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.
An inhaler in each box must be discarded after all capsules in that package have been used.

6.4 Special storage precautions

Store at a temperature below 25°C. In order to protect the capsules from moisture, keep them in blister packs and remove only immediately before use.

6.5 Nature and contents of container

The product is packaged in blisters made of OPA-Alu-PVC and Aluminum foil. The blisters are supplied in a cardboard box including a monodose dry powder inhaler device in a plastic separator, along with a package leaflet. The product is available in two different commercial presentations. In initial form of presentation, a cardboard box includes 30 capsules, 1 device (a monodose dry powder inhaler) in a plastic separator and a package leaflet. In the second form of presentation, a cardboard box includes 90 capsules, 1 device (a monodose dry powder inhaler) in a plastic separator and a package leaflet.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2021/509

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization : 13.12.2021
Renewal of the authorization :

10. DATE OF REVISION OF THE TEXT