NOVARTIS

Indacaterol maleate **+**
Glycopyrronium bromide

Ultibro™ Breezhaler®

110 mcg/50 mcg Powder for Inhalation in Hard Capsule

Beta2-Adrenergic Agonist/Anticholinergic

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Indacaterol/glycopyrronium 110/50 microgram, inhalation powder in hard capsules.

Transparent yellow cap and transparent body capsules containing a white to practically white powder, with the product code “IGP110.50” printed in blue under two blue bars on the body and the company logo) printed in black on the cap.

Active substance

Each capsule contains 143 micrograms indacaterol maleate equivalent to 110 micrograms indacaterol and 63 micrograms glycopyrronium bromide equivalent to 50 micrograms glycopyrronium.

The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 85 micrograms indacaterol and 43 micrograms glycopyrronium.

Excipients

Capsule fill: Lactose monohydrate, magnesium stearate.

Capsule shell components: Hypromellose, purified water, carrageenan, potassium chloride, FD&C Yellow5/Tartrazine.

INDICATIONS

Once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in adult patients with chronic obstructive pulmonary disease (COPD).

DOSAGE REGIMEN AND ADMINISTRATION

General target population

The recommended dosage is the once-daily inhalation of the content of one 110/50 microgram capsule using the Breezhaler® inhaler.

Special populations

Renal impairment

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) can be used at the recommended dose in patients with mild to 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 also sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY.

Hepatic impairment

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment. See also section CLINICAL PHARMACOLOGY.

Pediatric patients (below 18 years)

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) should not be used in patients under 18 years of age.

Geriatric patients (75 years or above)

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) can be used at the recommended dose in elderly patients 75 years of age and older.

Method of administration

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) capsules must be administered only by the oral inhalation route and only using the Breezhaler® inhaler. Capsules must not be swallowed (see also section OVERDOSAGE).

It should be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

Capsules must always be stored in the blister to protect from moisture, and only removed IMMEDIATELY BEFORE USE (see also section STORAGE).

When prescribing indacaterol/glycopyrronium (Ultibro™ Breezhaler®) patients should be instructed on correct use of the inhaler. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

CONTRAINDICATIONS

Hypersensitivity to the active substances, or to any of the excipients.

WARNINGS AND PRECAUTIONS

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) should not be administered concomitantly with products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, drug classes to which the components belong (see section INTERACTIONS).

Asthma

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) should not be used for the treatment of asthma due to the absence of data in this indication.

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.

Not for acute use

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) is not indicated for the treatment of acute episodes of bronchospasm.

Hypersensitivity

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

Paradoxical bronchospasm

As with other inhalation therapy, administration of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) should be discontinued immediately and alternative therapy instituted.

Anticholinergic effects related to glycopyrronium

Like other anticholinergic containing drugs, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Patients should be advised about signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using it and to contact their doctor immediately should any of these signs or symptoms develop.

Patients with severe renal impairment

For patients with severe renal impairment (estimated glomerular filtration rate below 30 mL/min/1.73 m^2) including those with end-stage renal disease requiring dialysis, it should be used only if the expected benefit outweighs the potential risk (see section CLINICAL PHARMACOLOGY). These patients should be monitored closely for potential adverse drug reactions.

Systemic effects of beta-agonists

Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) at the recommended dose, as with other compounds containing a $beta_2$-adrenergic agonist, it 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.

As with other drugs containing an inhaled $beta_2$-adrenergic agonist, it should not be used more often or at higher doses than recommended.

Cardiovascular effects of beta-agonists

Like other drugs containing a beta2-adrenergic agonist, it may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, the drug may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of QT interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, long-acting $beta_2$-adrenergic agonists (LABA) or LABA containing products such as ULTIBRO BREEZHALER should be used with caution in patients with known or suspected prolongation of the QT interval or patients treated with medicinal products affecting the QT interval.

Hypokalaemia with beta-agonists

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 INTERACTIONS) which may increase the susceptibility to cardiac arrhythmias.

Clinically relevant effects of hypokalemia have not been observed in clinical studies of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) at the recommended therapeutic dose (see section CLINICAL PHARMACOLOGY).

Hyperglycaemia with beta-agonists

Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with indacaterol/glycopyrronium (Ultibro™ Breezhaler®), plasma glucose should be monitored more closely in diabetic patients. During long-term clinical studies ([ENLIGHTEN] and [RADIATE]), more patients on indacaterol/glycopyrronium (Ultibro™ Breezhaler®) experienced clinically notable changes in blood glucose (4.9%) than on placebo (2.7%). It has not been investigated in patients for whom diabetes mellitus is not well controlled.

ADVERSE EFFECTS

The presentation of the safety profile is based on the experience with indacaterol/glycopyrronium (Ultibro™ Breezhaler®) and the individual monotherapy components.

Summary of the safety profile

The safety experience was comprised of exposure of up to 15 months at the recommended therapeutic dose (110/50 microgram).

The Phase III clinical development program consisted of 11 studies and enrolled over 10000 patients with a clinical diagnosis of moderate to very severe COPD. Safety data from 9 of these studies with treatment durations of 4 weeks or longer were pooled from 4352 patients exposed to indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 110/50 microgram once-daily.

The safety profile was characterized by typical anticholinergic and beta-adrenergic symptoms related to the individual monotherapy components of the combination. Other most common adverse drug reactions related to the drug product (≥3% and greater than placebo) were headache, cough and nasopharyngitis.

At the recommended dose, the adverse drug reaction profile in patients with COPD showed clinically insignificant systemic effects of beta$_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per min, and tachycardia was infrequent and reported at a lower rate than with placebo. Relevant prolongations of QT_cF were not detectable in comparison to placebo. The frequency of notable QT_cF intervals [*i.e.*, >450 ms] and reports of hypokalemia were similar to placebo.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions are listed by MedDRA system organ class (Table 1). The frequency of adverse drug reactions was based on a pool 3 Phase III placebo-controlled trials of 6 and 12 months in duration. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000, <1/1,000); and very rare (<1/10,000).

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) showed similar adverse drug reactions as the individual monotherapy components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of the monotherapy components may be expected in the combination.

Table 1 Kaplan-Meier cumulative incidence (%) of the adverse drug reactions at week 52 (Placebo-controlled COPD Pool)

Adverse drug reactions	Indacaterol/ glycopyrronium 110/50 µg once daily N=1106 Rate (95% CI)	Placebo N=748 Rate (95% CI)	Frequency category
Infections and infestations			
Upper respiratory tract infection	16.96 (14.53, 19.74)	19.64 (16.67, 23.06)	Very common
Nasopharyngitis	9.03 (7.26, 11.20)	8.78 (6.77, 11.37)	Common
Urinary tract infection	2.86 (1.91, 4.29)	1.49 (0.80, 2.75)	Common
Sinusitis	1.8 (1.11, 2.93)	1.54 (0.82, 2.88)	Common
Rhinitis	1.86 (1.16, 2.99)	2.98 (1.16, 2.99)	Common
Immune system disorders			
Hypersensitivity	2.06 (1.31, 3.21)	1.90 (1.04, 3.47)	Common
Metabolism and nutrition disorders			
Hyperglycaemia and diabetes mellitus	1.65 (0.92, 2.95)	2.42 (1.46, 4.00)	Common
Psychiatric disorders			
Insomnia	0.81 (0.37, 1.76)	0.98 (0.44, 2.21)	Uncommon
Nervous system disorders			
Dizziness	1.74 (1.05, 2.88)	0.95 (0.42, 2.14)	Common
Headache	3.24 (2.28, 4.60)	2.66 (1.64, 4.29)	Common
Paraesthesia	0.09 (0.01, 0.64)	(0)	Rare
Eye disorders			
Glaucoma*	0.19 (0.05, 0.75)	(0)	Uncommon
Cardiac disorders			
Ischaemic heart disease	0.67 (0.32, 1.41)	0.78 (0.29, 2.12)	Uncommon
Atrial fibrillation	0.8 (0.33, 1.95)	0.24 (0.03, 1.68)	Uncommon
Tachycardia	0.39 (0.15, 1.04)	0.7 (0.29, 1.66)	Uncommon
Palpitations	0.73 (0.34, 1.56)	1.38 (0.68, 2.80)	Uncommon
Respiratory, thoracic and mediastinal disorders			
Cough	6.84 (5.38, 8.68)	5.94 (4.30, 8.17)	Common
Oropharyngeal pain incl throat irritation	2.95 (2.05, 4.23)	2.71 (1.70, 4.29)	Common
Epistaxis	0.28 (0.09, 0.85)	0.24 (0.03, 1.68)	Uncommon
Paradoxical bronchospasm	0.18 (0.05, 0.73)	0.51 (0.16, 1.64)	Uncommon
Gastrointestinal disorders			
Dyspepsia	2.29 (1.49, 3.51)	2.25 (1.32, 3.81)	Common
Dental caries	1.39 (0.79, 2.44)	0.97 (0.43,	Common

Adverse drug reactions	Indacaterol/ glycopyrronium 110/50 µg once daily N=1106 Rate (95% CI)	Placebo N=748 Rate (95% CI)	Frequency category
		2.19)	
Dry mouth	0.64 (0.31, 1.34)	0.45 (0.14, 1.39)	Uncommon
Gastroenteritis	0.28 (0.06, 1.18)	0.97 (0.43, 2.18)	Uncommon
Skin and subcutaneous tissue disorders			
Pruritus/rash	0.56 (0.25, 1.25)	0.91 (0.37, 2.24)	Uncommon
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	0.92 (0.47, 1.81)	1.3 (0.60, 2.78)	Uncommon
Muscle spasm	0.85 (0.41, 1.73)	0.44 (0.14, 1.37)	Uncommon
Pain in extremity	0.74 (0.37, 1.47)	0.14 (0.02, 0.98)	Uncommon
Myalgia	0.57 (0.25, 1.26)	0.53 (0.17, 1.70)	Uncommon
Renal and urinary disorders			
Bladder obstruction and urinary retention	1.03 (0.52, 2.03)	(0)	Common
General disorders and administration site conditions			
Pyrexia*	1.96 (1.26, 3.05)	1.47 (0.79, 2.72)	Common
Chest pain	1.85 (1.13, 3.02)	1.5 (0.77, 2.92)	Common
Peripheral edema	0.65 (0.28, 1.48)	1.09 (0.51, 2.33)	Uncommon
Fatigue	0.83 (0.41, 1.68)	0.54 (0.20, 1.43)	Uncommon

Of the 1106 patients on indacaterol/glycopyrronium (Ultibro™ Breezhaler®), 946 (86%) were exposed for at least 26 weeks, and 447 (40%) were exposed for at least 52 weeks. Of the 748 patients on placebo, 588 (79%) were exposed for at least 26 weeks, and 339 (45%) were exposed for at least 52 weeks.

*adverse drug reaction observed with the combination indacaterol/glycopyrronium (Ultibro™ Breezhaler®) but not with the monotherapy components.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been reported with indacaterol/glycopyrronium (Ultibro™ Breezhaler®) in post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

Immune system disorders
Angioedema
Respiratory, thoracic and mediastinal disorders
Dysphonia

Description of selected adverse drug reactions

The most common anticholinergic adverse event was dry mouth (0.64% versus 0.45% for placebo); however, this adverse event was reported at a lower frequency with indacaterol/glycopyrronium (Ultibro™ Breezhaler®) than with glycopyrronium monotherapy. The majority of the reports of dry mouth were suspected to be drug related and of mild degree, none was severe. Cough was common, but usually of mild intensity.

Some serious adverse events, including hypersensitivity and ischemic heart disease, have been reported as ADRs for indacaterol administered as monotherapy. The reported frequencies for indacaterol/glycopyrronium (Ultibro™ Breezhaler®) for hypersensitivity and ischemic heart disease were 2.06% versus 1.9% for placebo and 0.67% versus 0.78% for placebo, respectively.

INTERACTIONS

Interactions linked to the Indacaterol/glycopyrronium (Ultibro™ Breezhaler®)

Concomitant administration of orally inhaled indacaterol and glycopyrronium under steady-state conditions of both drugs did not affect the pharmacokinetics (PK) of either drug.

No specific drug-drug interaction studies were conducted. Information on the potential for interactions is based on the potential for each of its two monotherapy components.

Interactions linked to indacaterol

In vitro investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medications at the systemic exposure levels achieved in clinical practice (see section CLINICAL PHARMACOLOGY – Biotransformation/metabolism and elimination).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-adrenergic agonists.

Therefore it 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.

Drugs known to prolong QTc interval

As other $beta_2$-adrenergic agonist containing drugs, it should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see section WARNINGS AND PRECAUTIONS).

Sympathomimetic agents

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of indacaterol (see section WARNINGS AND PRECAUTIONS).

Hypokalemia

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists (see section WARNINGS AND PRECAUTIONS).

Metabolic and transporter based drug interaction

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of indacaterol. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (*i.e.*, ketoconazole, erythromycin verapamil and ritonavir). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5- fold increase in C_{max}. Co-administration of erythromycin with indacaterol resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for C_{max}. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and C_{max}, respectively. Concomitant treatment with ritonavir, another dual inhibitor of CYP3A4 and P-gp, resulted in a 1.6- to 1.8-fold increase in AUC whereas C_{max} was unaffected. Taken together, the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. The magnitude of exposure increases due to drug interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical trials of up to one year at doses of 600 microgram.

Interactions linked to glycopyrronium

In vitro studies showed that glycopyrronium is not likely to inhibit or induce the metabolism of other drugs, nor processes involving drug transporters. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see section CLINICAL PHARMACOLOGY – Biotransformation/metabolism and elimination). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

Anticholinergics

The co-administration of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) with inhaled anticholinergic-containing drugs has not been studied and is therefore, like for other anticholinergic-containing drugs, not recommended.

Cimetidine or other inhibitors of organic cation transport

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is 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 relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There are no adequate and well-controlled studies n pregnant women to inform a product-associated risk. Likewise there are no data from the use of either indacaterol or glycopyrronium in pregnant women.

No effects on the embryo or fetus were seen at any dose level of indacaterol/glycopyrronium **(**Ultibro™ Breezhaler) during an inhalation embryo-fetal development study in rats. Indacaterol and glycopyrronium were not teratogenic in rats or rabbits following subcutaneous and inhalation administration respectively.

The potential risk for humans is unknown. Therefore as there is no adequate experience in pregnant women, it should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Clinical Considerations

Labor and delivery

Information related to indacaterol

Like other beta$_2$-adrenergic agonist containing drugs, Indacaterol may inhibit labor due to a relaxant effect on uterine smooth muscle.

Information related to glycopyrronium

In pregnant women undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide, the concentration of glycopyrronium in the umbilical venous (0.28 (0.25) ng/mL) and in the umbilical arterial (0.18 (0.11) ng/mL) plasma were low (clinically insignificant).

Data

Animal data

Indacaterol: Adverse effects with respect to pregnancy and embryonal/foetal development in rabbits after subcutaneous administration, was only be demonstrated at doses more than 500-fold than achieved following the daily inhalation of 150 microgram in humans (based on AUC0-24h).

Glycopyrronium: Glycopyrronium was not teratogenic in rats or rabbits following inhalation. Reproduction studies in rats and other data in animals did not indicate a concern regarding pre- and post-natal development. Glycopyrronium and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Published data for glycopyrronium in animals do not indicate any reproductive toxicity issues.

Lactation

It is not known whether indacaterol and/or glycopyrronium passes into human breast milk. There are no data on the effects of indacaterol and/or glycopyrronium on the breastfed child or on milk production. Indacaterol and glycopyrronium (including its metabolites) have been detected in the milk of lactating rats after subcutaneous and intravenous administration. Glycopyrronium reached up to 10- fold higher concentrations in the milk than in the blood of the dam after intravenous administration.Therefore the use of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) by breastfeeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Females and males of reproductive potential

There are no special recommendations.

Infertility

Information related to indacaterol and glycopyrronium

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

OVERDOSAGE

Information related to indacaterol/glycopyrronium (Ultibro™ Breezhaler®)

In a single dose study in healthy volunteers the 4-fold of the therapeutic dose of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) (four dose steps of 110/50 microgram separated by

one hour, each) was well tolerated with no relevant effects on heart rate, QTc-interval, serum potassium or blood glucose.

In COPD patients, doses of up to 600/100 microgram were inhaled over two weeks and there were no relevant effects on heart rate, QTc-interval, blood glucose or serum potassium. There was an increase in ventricular ectopies after 14 days of dosing with 300/100 and 600/100 microgram indacaterol/glycopyrronium, but low prevalence and small patient numbers (N=49 and N=51 for 600/100 microgram and 300/100 microgram indacaterol/glycopyrronium, respectively) did preclude accurate analysis. In a total of four patients non-sustained ventricular tachycardia was recorded with the longest episode recorded being 9 beats (4 seconds).

An overdose could lead to exaggerated effects typical of beta2-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia, and hyperglycemia or could induce anticholinergic effects, i.e. 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 beta2- adrenergic effects, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

Information related to indacaterol

In COPD patients single doses of 3000 microgram were associated with a moderate increase in pulse rate, systolic blood pressure increase and QTc interval.

Information related to glycopyrronium

In COPD patients, repeated orally inhaled administration of glycopyrronium at total doses of 100 and 200 microgram once-daily for 28 days were well tolerated.

Acute intoxication by inadvertent oral ingestion of glycopyrronium capsules is unlikely due to the low oral bioavailability (about 5%).

Peak plasma levels and total systemic exposure following i.v. administration of 150 microgram glycopyrronium bromide (equivalent to 120 microgram glycopyrronium) in healthy volunteers were respectively about 50-fold and 6-fold higher than the peak and total systemic exposure at steady-state achieved with the recommended dose (50 microgram once-daily) of glycopyrronium and were well tolerated.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®)

When indacaterol and glycopyrronium are administered together, they provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve small muscle relaxation. Due to the differential density of $beta_2$-adrenoceptors and M_3-receptors in central versus smaller airways, $beta_2$-agonists should be more effective in relaxing small airways whilst an anti-cholinergic compound may be more effective in large airways. Thus for optimal bronchodilation in all regions of the human lung, a combination of a $beta_2$-adrenergic agonist and a muscarinic antagonist may be beneficial.

Indacaterol

Indacaterol is an 'ultra' long-acting $beta_2$-adrenergic agonist for once-daily administration. The pharmacological effects of $beta_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol 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. This selectivity profile is similar to formoterol.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full 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 $beta_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenergic receptors are the predominant receptors in the human heart, there are also $beta_2$-adrenergic receptors in the human heart comprising 10% to 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.

Glycopyrronium

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic) for once-daily maintenance bronchodilator treatment of COPD. Parasympathetic nerves are the major bronchoconstrictive neural pathway in airways, and cholinergic tone is the key reversible component of airflow obstruction in COPD. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

Of the five known muscarinic receptor subtypes (M_{1-5}), only subtypes M_{1-3} have a defined physiological function in the human lung. Glycopyrronium bromide is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M_3 and M_1 receptors over the human M_2 receptor in competition binding studies. It has a rapid onset of action as evidenced by observed receptor association/dissociation kinetic parameters and the onset of action after inhalation in clinical studies.

The long duration of action can be partly attributed to sustained drug concentrations in the lungs as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the glycopyrronium inhaler in contrast to the half-life after i.v. administration (see section CLINICAL PHARMACOLOGY – Elimination). Lung pharmacokinetic data in rats following inhalation of glycopyrronium bromide provides further evidence for this.

Pharmacodynamics (PD)

Primary pharmacodynamic effects

The combination of indacaterol and glycopyrronium showed a rapid onset of action within 5 minutes after dosing (see section CLINICAL STUDIES, Table 3). The effect remains constant over the whole 24 h dosing interval (see section CLINICAL STUDIES, Figures 1 and 2).

The mean bronchodilator effect derived from serial FEV_1 measurements over 24 h was 0.32 L after 26 weeks of treatment when compared to placebo. The effect was significantly greater for indacaterol/glycopyrronium (Ultibro™ Breezhaler®), when compared to indacaterol, glycopyrronium or tiotropium alone (difference 0.11 L, for each comparison), (serial spirometry subset).

There was no evidence for tachyphylaxis to the effect of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) over time when compared to placebo or its monotherapy components.

Secondary pharmacodynamic effects

The systemic side effects of inhaled $beta_2$-adrenergic agonists and inhaled muscarinic receptor antagonists are the result of activation of systemic $beta_2$-adrenergic receptors and blockade of muscarinic receptors after systemic absorption of the drugs. The side effect profile of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) was explored in healthy subjects) and in COPD patients.

Effects on heart rate

Heart rate effects in healthy volunteers were investigated after a single dose of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 440/200 microgram administered in four dose steps separated by one hour and compared to the effects of placebo, 600 microgram indacaterol, 200 microgram glycopyrronium and 200 microgram salmeterol.

The largest time matched heart rate increase compared to placebo was +5.69 bpm, the largest decrease was -2.51 bpm. Overall the effect on heart rate over time did not show a consistent PD- effect.

Whilst there were no significant effects when indacaterol/glycopyrronium (Ultibro™ Breezhaler®) was compared with indacaterol and glycopyrronium alone, heart rate seemed to be slightly higher (the largest difference being around 11 bpm) after inhalation of 200 microgram salmeterol.

Heart rate in COPD patients at supratherapeutic dose levels was investigated in indacaterol/glycopyrronium (Ultibro™ Breezhaler®) up to doses of 150/100, 300/100 and 600/100 microgram. There were no relevant effects of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) on mean heart rate over 24 h and heart rate assessed after 30 min, 4 h and 24 h.

QT-interval

A thorough QT (TQT) -study in healthy volunteers with doses of inhaled indacaterol up to 600 micrograms did not demonstrate a clinically relevant effect on the QT-interval. Also for glycopyrronium, no QT-prolongation has been observed in a TQT study after an inhaled dose of 400 microgram.

The effects on QTc-interval were investigated in healthy volunteers after inhalation of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 440/200 microgram in four dose steps separated by one hour. The largest time matched difference versus placebo was 4.62 ms (90% CI 0.40, 8.85 ms), the largest time matched decrease was -2.71 ms (90% CI -6.97, 1.54 ms), indicating that it had no relevant impact on the QT-interval as was expected by the properties of its components.

In COPD patients, doses up to 600/100 microgram of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) also had no apparent influence on the QTc-interval in repeated ECG assessments executed between 15 min and 24 h after dosing. A slightly higher proportion of patients had QTc-prolongations above 450 ms at the indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 600/100 microgram group. The number of notable QTcF changes versus baseline (>30 ms) was similar across all active treatment groups (600/100 microgram, 300/100 microgram, 150/100 microgram and indacaterol 300 microgram), but was lower with placebo.

Serum potassium and blood glucose

In healthy volunteers, after administration of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 440/200 microgram, the effect on serum potassium was very small (maximal difference −0.14 mmol/L when compared to placebo). The maximal effect on blood glucose was 0.67 mmol/L. When indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 440/200 microgram was compared with 200 microgram salmeterol, the effect on serum potassium (maximum difference 0.21 mmol/L) and blood glucose was smaller (maximum difference 0.21 and 1.19 mmol/L, respectively).

Pharmacokinetics (PK)

Absorption

Following inhalation, the median time to reach peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 minutes and 5 minutes, respectively.

Based on the *in vitro* performance data, the dose of indacaterol delivered to the lung is expected to be similar for indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 110/50 microgram and indacaterol 150 microgram monotherapy product. The steady-state exposure to indacaterol after indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 110/50 microgram inhalation was either similar or

slightly lower than systemic exposure after indacaterol 150 microgram monotherapy product inhalation.

Absolute bioavailability of indacaterol after indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 110/50 microgram inhalation ranged from 47% to 66% whereas that of glycopyrronium was about 40%.

The steady-state exposure to glycopyrronium after indacaterol/glycopyrronium (Ultibro™ Breezhaler®) 110/50 microgram inhalation was similar to systemic exposure after glycopyrronium 50 microgram monotherapy product inhalation.

Indacaterol

The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e., AUC over the 24-h dosing interval on Day 14 or Day 15 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 microgram and 600 microgram.

Glycopyrronium

Following oral inhalation using the glycopyrronium inhaler, glycopyrronium was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption. The absolute bioavailability of orally administered glycopyrronium was estimated to be about 5%.

Following repeated once-daily inhalation in patients with COPD, PK steady-state of glycopyrronium was reached within one week of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium for a 50 microgram once-daily dosing regimen were 166 pg/mL and 8 pg/mL, respectively. With once-daily doses of 100 and 200 microgram, steady-state exposure to glycopyrronium (AUC over the dosing interval) was about 1.4-to 1.7-fold higher than after the first dose. Urinary excretion data at steady-state compared to the first dose suggest that systemic accumulation is independent of dose in the dose range of 25 to 200 microgram.

Distribution

Indacaterol

After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,361 to 2,557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Glycopyrronium

After i.v. dosing, the steady-state volume of distribution (Vss) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (Vz) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7310 L, which reflects the much slower elimination after inhalation. The *in vitro* human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/mL. These concentrations were at least 6-fold higher than the steady state mean peaks levels achieved in plasma for a 50 micrograms once-daily dosing regimen.

Biotransformation/metabolism

Indacaterol

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. 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.

Glycopyrronium

In vitro metabolism studies showed consistent metabolic pathways for glycopyrronium bromide between animals and humans. No human specific metabolites were found. Hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen.

In vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. The hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family.

After inhalation, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. Since *in vitro* studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4% of parent drug C_{max} and AUC) after i.v. administration, it is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium bromide by pre-systemic hydrolysis and/or via first pass metabolism. After inhalation as well as i.v. administration, only minimal amounts of M9 were found in the urine (i.e. ≤ 0.5% of dose). Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

In vitro inhibition studies demonstrated that glycopyrronium bromide has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. In vitro enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium bromide for any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2.

Elimination

Indacaterol

In clinical studies which included urine collection, the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 L/h. When compared with the serum clearance of indacaterol of 18.8 to 23.3 L/h, it is evident that renal clearance plays a minor role (about 2 to 6% 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 drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 56 hours which is consistent with the observed time to steady state of approximately 12 to 15 days.

Glycopyrronium

After i.v. administration of [^{3}H]-labelled glycopyrronium bromide to humans, the mean urinary excretion of radioactivity in 48 h amounted to 85% of the dose. A further 5% of the dose was found in the bile. Thus, mass balance was almost complete.

Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium whereas non-renal clearance processes account for about 30 to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 50 and 200 microgram glycopyrronium by healthy volunteers and patients with COPD mean renal clearance of glycopyrronium was in the range of 17.4 and 24.4 L/h. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20% of the dose was found in urine as parent drug.

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 57 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. The elimination pattern suggests a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 h after inhalation.

Linearity/non-linearity

Indacaterol

Systemic exposure to indacaterol increased with increasing dose (150 microgram to 600 microgram) in a dose proportional manner. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Glycopyrronium

In COPD patients' systemic exposure as well as total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about dose-proportionally over the dose range of 50 microgram to 200 microgram.

Special populations

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®)

A population PK analysis in COPD patients after inhalation of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) indicated no significant effect of age, gender and (lean body) weight on the systemic exposure to indacaterol and glycopyrronium. Lean body weight (which is a function of weight and height) was identified as a covariate. A negative correlation between systemic exposure and lean body-weight (or body weight) was observed; however, no dose adjustment is recommended due to the magnitude of the change or the predictive precision of lean body weight.

Smoking status and baseline FEV_1 had no apparent effect on systemic exposure to indacaterol and glycopyrronium after inhalation of indacaterol/glycopyrronium (Ultibro™ Breezhaler®).

Indacaterol

A population analysis of the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated that indacaterol can be used at the recommended dose in all age and weight groups and regardless of gender.

The pharmacokinetics of indacaterol was investigated in two different UGT1A1 genotypes – the fully functional [$(TA)_6$, $(TA)_6$] genotype and the low activity [$(TA)_7$, $(TA)_7$] genotype (Gilbert's syndrome genotype). The study demonstrated that steady-state AUC and C_{max} of indacaterol were 1.2-fold higher in the [$(TA)_7$, $(TA)_7$] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

Glycopyrronium

A population PK analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. Glycopyrronium 50 microgram once-daily can be used at the recommended dose in all age and body weight groups.

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

Hepatic impairment

Based on the clinical PK characteristics of its monotherapy components, it can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe 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.

Clinical studies in patients with hepatic impairment have not been conducted. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion (see section CLINICAL PHARMACOLOGY – Elimination). Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase of systemic exposure.

Renal impairment

Based on the clinical PK characteristics of its monotherapy components, it can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis indacaterol/glycopyrronium (Ultibro™ Breezhaler®) should be used only if the expected benefit outweighs the potential risk.

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

Glycopyrronium: Renal impairment has an impact on the systemic exposure to glycopyrronium. A moderate mean increase in total systemic exposure (AUC last) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease. Using a population PK analysis, it was concluded that in COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate eGFR ≥30 mL/min/1.73 m^2) glycopyrronium can be used at the recommended dose.

Race/Ethnicity

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®): When corrected by lean body weight, no statistically significant effect of ethnicity (Japanese versus non-Japanese) on exposure for both compounds was found.

Indacaterol: No difference between ethnic subgroups was identified. Limited treatment experience is available for the black population.

Glycopyrronium: There were no major differences in total systemic exposure (AUC) between Japanese and Caucasian subjects. Insufficient PK data is available for other ethnicities or races.

CLINICAL STUDIES

The Phase III clinical development program [IGNITE] included six studies in which over 8,000 patients were enrolled: one 26-week placebo- and active-controlled (indacaterol 150 microgram once daily, glycopyrronium 50 microgram once daily, open-label tiotropium 18 microgram once daily) study [SHINE]; one 26-week active-controlled (fluticasone/salmeterol 500/50 microgram twice daily) study [ILLUMINATE]; a 64-week active-controlled (glycopyrronium 50 microgram once daily, open-label tiotropium 18 microgram once daily) study [SPARK]; a 52-week placebo-controlled study [ENLIGHTEN]; a 3-week placebo- and active-controlled (tiotropium once daily) exercise tolerance study [BRIGHT]; and a 52-week active-controlled (fluticasone/salmeterol 500/50 microgram twice daily) study [FLAME].

These studies enrolled patients with a clinical diagnosis of moderate to very severe COPD, who were 40 years old or older, and had a smoking history of at least 10 pack years. Of these 5 studies, the [SHINE] and [ENLIGHTEN] studies had a post-bronchodilator FEV_1 <80% and ≥30% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio of less than 70%. The 26-week active-

controlled study, [ILLUMINATE], enrolled patients with a post-bronchodilator FEV_1 of <80% and ≥40% of the predicted normal value. In comparison, the 64-week [SPARK] study enrolled patients with severe to very severe COPD, with a history of ≥1 moderate or severe COPD exacerbation in the previous year, and a post-bronchodilator FEV_1 <50% of the predicted normal value. The 52-week active-controlled study, [FLAME], enrolled moderate to very severe COPD patients with a history of ≥1 moderate or severe COPD exacerbation in the previous year, and a post-bronchodilator FEV1 of ≥25 and < 60% of the predicted normal value.

Effects on lung function

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) administered at 110/50 microgram once daily showed clinically meaningful improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1), in a number of clinical studies. In Phase III studies, bronchodilator effects were seen within 5 minutes after the first dose and were maintained over the 24-hour dosing interval from the first dose. Within the 26-week [SHINE] and 52-week [ENLIGHTEN] studies, there was no attenuation of the bronchodilator effect over time.

Trough FEV_1

In the [SHINE] study, it increased post-dose trough FEV_1 by 200 mL compared to placebo at the 26-week primary endpoint (p<0.001) and showed significant increases compared to each monotherapy component treatment arm (indacaterol and glycopyrronium) as well as the tiotropium treatment arm (see Table 2).

Table 3 Post-dose trough FEV_1 (least squares mean) at Day 1 and Week 26 (primary endpoint)

Treatment difference	Day 1	Week 26
Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) - placebo	190 mL (p<0.001)	200 mL (p<0.001)
Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) - indacaterol	80 mL (p<0.001)	70 mL (p<0.001)
Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) - glycopyrronium	80 mL (p<0.001)	90 mL (p<0.001)
Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) - tiotropium	80 mL (p<0.001)	80 mL (p<0.001)

The mean pre-dose FEV_1 (average of the values taken at -45 and -15 min prior to the morning dose of study drug) was clinically meaningful and statistically significant in favor of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) at Week 26 compared to fluticasone/salmeterol (100 mL, p<0.001) [ILLUMINATE], at Week 52 compared to placebo (189 mL, p<0.001) [ENLIGHTEN] and at all visits up to Week 64 compared to glycopyrronium (70-80 mL, p-value <0.001) and tiotropium (60-80 mL, p- value <0.001) [SPARK]. In the [FLAME] study, the mean pre-dose FEV_1 was clinically meaningful and statistically significant in favor of indacaterol/glycopyrronium (Ultibro™ Breezhaler®) at all visits up to Week 52 compared to fluticasone/salmeterol (62 86 ml, p<0.001).

Peak FEV_1

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) produced statistically significant improvement in peak FEV_1 compared to placebo in the first 4 hours post-dose on Day 1 (210 mL, p<0.001), at Week 26 (330 mL, p<0.001), and compared to indacaterol (120 mL), glycopyrronium (130 mL), tiotropium (130 mL) at Week 26 (p<0.001 for all comparisons) [SHINE], and compared to fluticasone/salmeterol on Day 1 (70 mL, p<0.001) and Week 26 (150 mL, p<0.001) [ILLUMINATE].

FEV_1 AUC

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) increased post-dose FEV_1 AUC_{0-12} (primary endpoint) by 140 mL at 26 weeks (p<0.001) in the active-controlled [ILLUMINATE] study compared to fluticasone/salmeterol.

Onset of action

In the [SHINE and ILLUMINATE] studies, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated a statistically significant rapid onset of bronchodilator effect on Day 1 and at Week 26.

Table 4 **Onset of action versus placebo, tiotropium and fluticasone/salmeterol at 5 and 30 minutes on Day 1 and Week 26**

	Day 1	Week 26
versus placebo		
5 minutes	130 mL*	290 mL*
30 minutes	200 mL*	320 mL*
versus tiotropium		
5 minutes	70 mL*	120 mL*
30 minutes	90 mL*	140 mL*
versus fluticasone/salmeterol		
5 minutes	80 mL*	150 mL*
30 minutes	80 mL*	160 mL*

* $p < 0.001$ for all treatment comparisons

Serial spirometry subset

In the 26-week, placebo-controlled [SHINE] study, 12-hour serial spirometry was performed on Day 1 (Figure 1) and 24-hour serial spirometry at Week 26 (Figure 2) in a subset of 294 patients. Serial FEV_1 values over 12 hours at Day 1 and trough FEV_1 values at Day 2 are shown in Figure 1, and at Week 26 in Figure 2. Improvement of lung function was maintained for 24 hours after the first dose and consistently maintained over the 26-week treatment period with no evidence of tolerance.

Figure 1 **24 hour profile of least squares means of FEV_1 (L) at Day 1 (FAS, serial spirometry subset)**

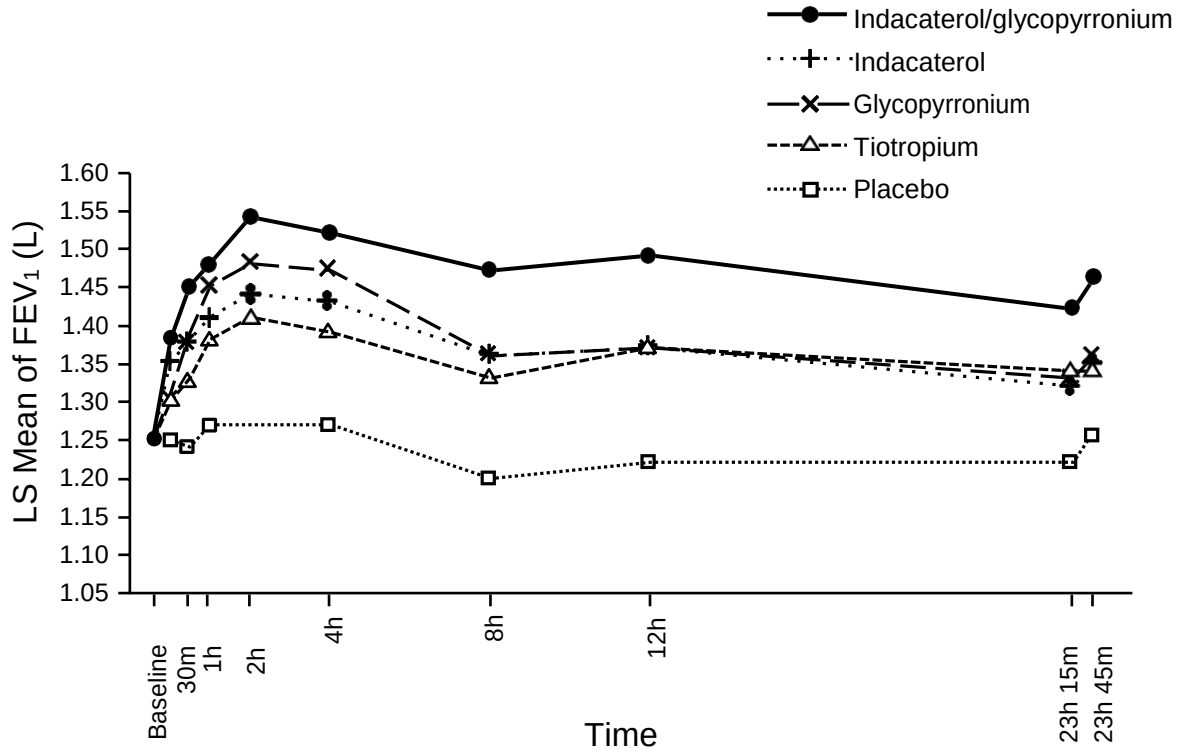
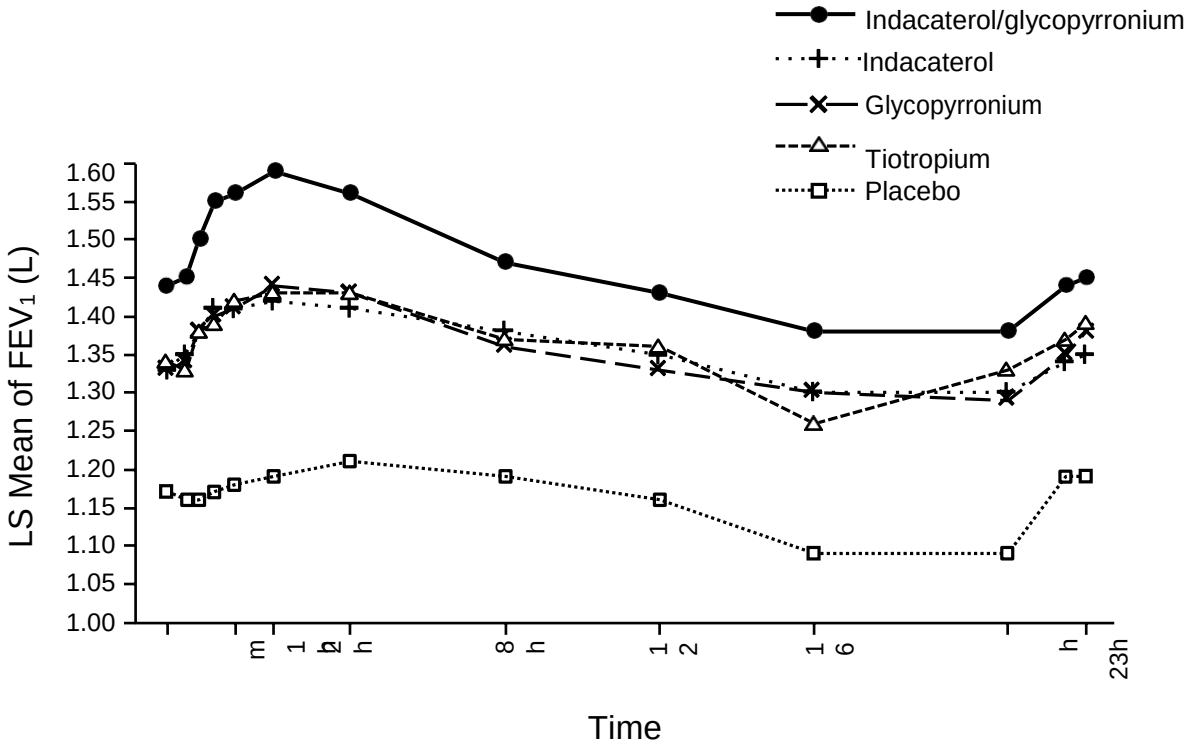


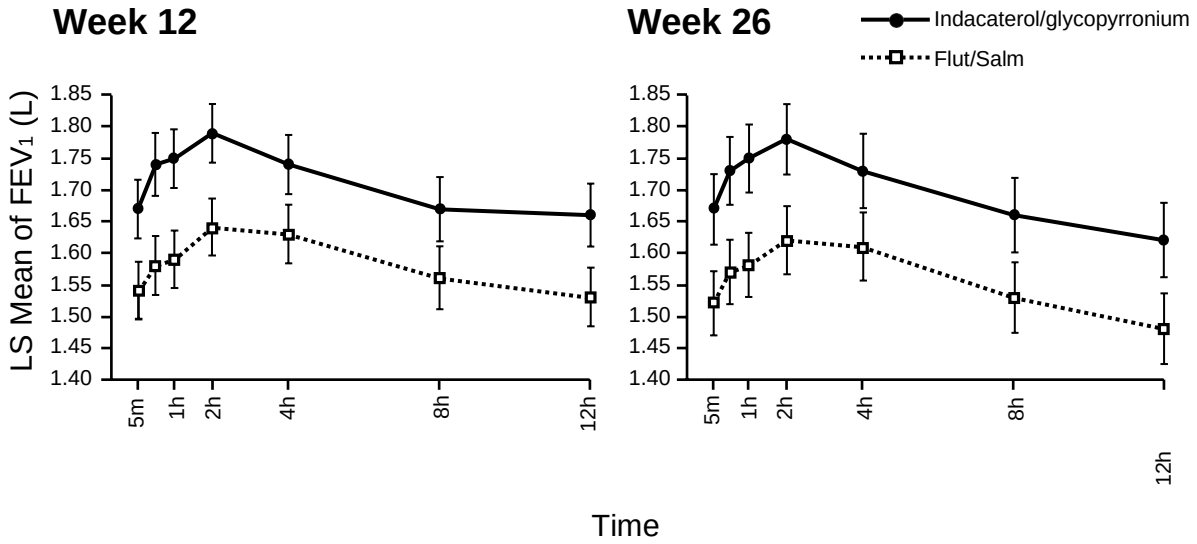
Figure 2 **23 h 45 min profile of least squares means of FEV_1 (L) after 26 weeks of treatment (FAS, serial spirometry subset)**



In the [SHINE] serial spirometry subset, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated a statistically significant improvement in FEV_1 compared to placebo (400 mL, p<0.001) and tiotropium (160 mL, p<0.001) at 2 hours post-dose at Week 26.

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) also had clinically meaningful and statistically significant improvements in FEV_1 compared to fluticasone/salmeterol across all time points from 5 minutes post-dose up to 12 hours post-dose at both Week 12 (p<0.001) and Week 26 (p<0.001) [ILLUMINATE] (see Figure 3).

Figure 3 **Profile of LS means of FEV1 (L) from 5 min up to 12 h post-dose at Week 12 and Week 26 (Full analysis set)**

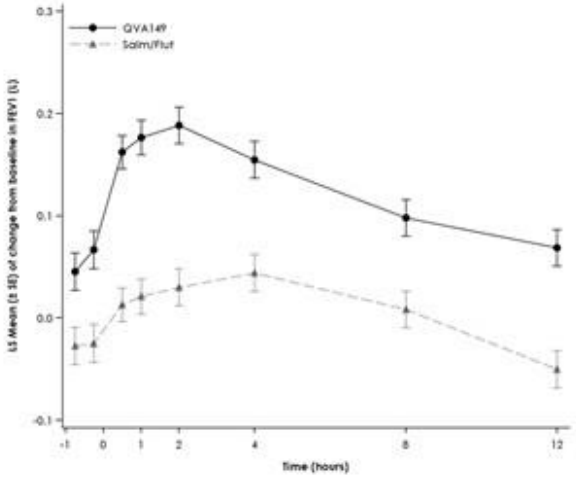


In the [ILLUMINATE] study, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated significant overall improvements in lung function compared with fluticasone/salmeterol, across all key subgroups, including age, gender, smoking history, disease severity, and reversibility.

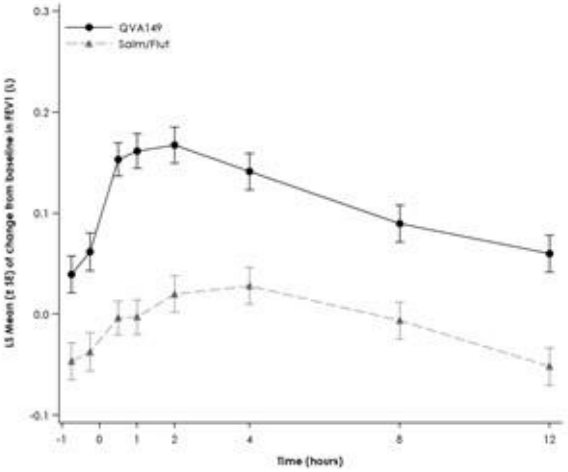
In the [FLAME] serial spirometry subset, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated clinically meaningful and statistically significant improvements in FEV_1 $AUC_{0\text{-}12h}$ at 52 weeks of treatment. The Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) group was statistically superior to the fluticasone/salmeterol group from Day 1 onwards (all p<0.05).

Figure 4 **Profile of least squares mean change from baseline in FEV_1 (L) -45 min to 12 h at Week 12, Week 26, and Week 52 (Sserial spirometry set)**

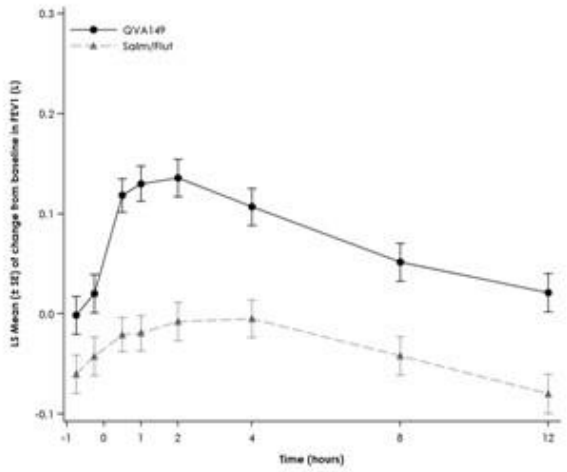
Week 12



Week 26



Week 52



Symptomatic outcomes

Breathlessness

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) significantly reduced breathlessness as evaluated by the Transitional Dyspnoea Index (TDI). Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated a clinically meaningful and statistically significant improvement in the TDI focal score at Week 26 as compared to placebo (1.09, p<0.001), tiotropium (0.51, p=0.007) [SHINE], and fluticasone/salmeterol (0.76, p=0.003) [ILLUMINATE].

A significantly higher percentage of patients receiving indacaterol/glycopyrronium (Ultibro™ Breezhaler®) responded with a 1 point or greater improvement in the TDI focal score at Week 26 compared to placebo (68.1% and 57.5% respectively, p=0.004). A higher proportion of patients demonstrated clinically meaningful response at Week 26 on indacaterol/glycopyrronium (Ultibro™ Breezhaler®) as compared to tiotropium (68.1% indacaterol/glycopyrronium vs. 59.2% tiotropium, p=0.016) [SHINE] and fluticasone/salmeterol (65.1% indacaterol/glycopyrronium vs. 55.5% fluticasone/salmeterol, p=0.088) [ILLUMINATE].

Health related quality of life

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) once daily has also shown a statistically significant effect on health related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ) at 26 weeks as indicated by a reduction in SGRQ total score compared to placebo (-3.01, p=0.002) and tiotropium (-2.13, p=0.009) [SHINE], at 64 weeks compared to tiotropium (-2.69, p<0.001) [SPARK], and at 52 weeks compared to fluticasone/salmeterol (-1.3, p=0.003) [FLAME]. In addition, improvements of the domains of the SGRQ score "symptoms", "activity" and "impact of daily life" were all statistically significant versus tiotropium at Week 64 ("symptoms": -3.06, p=0.003, "activity": -3.14, p < 0.001, "impact of daily life": -2.24, p=0.008) [SPARK].

A higher percentage of patients receiving indacaterol/glycopyrronium (Ultibro™ Breezhaler®) responded with a clinically meaningful improvement in SGRQ score (defined as a decrease of at least 4 units from baseline) at Week 26 compared to placebo (63.7% and 56.6% respectively, p=0.088) and tiotropium (63.7% indacaterol/glycopyrronium vs. 56.4% tiotropium, p=0.047) [SHINE],at Week 64 compared to glycopyrronium and tiotropium (57.3% indacaterol/glycopyrronium vs. 51.8% glycopyrronium, p=0.055; vs. 50.8% tiotropium, p=0.051, respectively) [SPARK] , and at Week 52 compared to fluticasone/salmeterol (49.2% indacaterol/glycopyrronium (Ultibro™ Breezhaler®) vs. 43.7% fluticasone/salmeterol, OR: 1.30, p<0.001) [FLAME].

Daily activities

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated a statistically superior improvement versus tiotropium in the percentage of 'days able to perform usual daily activities' over 26 weeks (8.45%, p<0.001) [SHINE] and showed numerical improvement over glycopyrronium (1.87; p=0.195) and statistical improvement over tiotropium (4.95; p=0.001) [SPARK].

COPD exacerbations

At 64 weeks in the [SPARK] study, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) once daily reduced the rate of moderate or severe COPD exacerbations by 12% compared to glycopyrronium (p=0.038) and by 10% compared to tiotropium (p=0.096).

In addition, it was shown to be clinically and statistically superior to glycopyrronium and tiotropium in reducing the rate of all COPD exacerbations (mild, moderate, and severe), with a rate reduction of 15% for indacaterol/glycopyrronium (Ultibro™ Breezhaler®) as compared to glycopyrronium (p=0.001) and 14% as compared to tiotropium (p=0.002).

For time to first moderate or severe COPD exacerbation, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) demonstrated a 7% risk reduction compared to glycopyrronium (p=0.319).

Glycopyrronium and tiotropium showed no difference in risk reduction.

In the 52-week active-controlled [FLAME] study, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) once daily met the primary study objective of non-inferiority in rate of all COPD exacerbations (mild, moderate, or severe) compared to fluticasone/salmeterol. Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) further showed superiority in reducing the annualized rate of all exacerbations by 11% versus fluticasone/salmeterol (3.59 vs. 4.03, p=0.003) and prolonged time-to-first exacerbation with a 16% reduction in risk of an exacerbation (median time: 71 days for indacaterol/glycopyrronium (Ultibro™ Breezhaler®) vs. 51 days for fluticasone/salmeterol, p<0.001).

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) reduced the annualized rate of moderate or severe exacerbations by 17% versus fluticasone/salmeterol (0.98 vs. 1.19, p<0.001) and prolonged time-to-first moderate or severe exacerbation with a 22% reduction in risk of an exacerbation (25th percentile: 127 days for indacaterol/glycopyrronium (Ultibro™ Breezhaler®) vs. 87 days for fluticasone/salmeterol, p<0.001). Less than 50% of patients in the indacaterol/glycopyrronium (Ultibro™ Breezhaler®) group had an exacerbation, therefore the time to the first moderate or severe exacerbation in the first quartile of patients was calculated instead.

Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) numerically reduced the annualized rate of severe exacerbations by 13% versus fluticasone/salmeterol (0.15 vs. 0.17, p=0.231). Indacaterol/glycopyrronium (Ultibro™ Breezhaler®) prolonged time-to-first severe exacerbation with a 19% reduction in risk of an exacerbation (p=0.046).

The incidence of pneumonia (as confirmed by radiographic imaging i.e. chest x-ray or CT scan) was 3.2% in the indacaterol/glycopyrronium (Ultibro™ Breezhaler®) arm compared to 4.8% in the fluticasone/salmeterol arm (p=0.017). Time to first pneumonia was prolonged with indacaterol/glycopyrronium (Ultibro™ Breezhaler®) compared to fluticasone/salmeterol (p=0.013).

Use of rescue medication

Over 26 weeks, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) once daily significantly reduced the use of rescue medication (salbutamol) by 0.96 puffs per day (p<0.001) compared to placebo and 0.54 puffs/day (p <0.001) compared to tiotropium in the [SHINE] study, as well as 0.39 puffs per day (p=0.019) compared to fluticasone/salmeterol in the [ILLUMINATE] study.

Over 64 weeks, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) reduced the use of rescue medication (salbutamol) by 0.76 puffs per day (p<0.001) compared to tiotropium in the [SPARK] study.

Over 52 weeks, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) once daily reduced the use of rescue medication by 1.01 puffs per day from baseline and fluticasone/salmeterol had a reduction of 0.76 puffs per day from baseline. The difference of 0.25 puffs per day was statistically significant (p<0.001).

Exercise tolerance

In a 3-week study [BRIGHT] where exercise tolerance was tested via cycle ergometry at submaximal (75%) workload (submaximal exercise tolerance test), indacaterol/glycopyrronium (Ultibro™ Breezhaler®), dosed in the morning, reduced dynamic hyperinflation and improved the length of time exercise could be maintained from the first dose onwards. On the first day of treatment, inspiratory capacity under exercise was significant improved (250 mL, p<0.001) compared to placebo. After three weeks of treatment, the improvement in inspiratory capacity with indacaterol/glycopyrronium (Ultibro™ Breezhaler®) was greater (320 mL, p<0.001) and exercise endurance time increased (59.5 seconds, p=0.006) compared to placebo. Similar findings were seen with tiotropium.

Whole-Body Plethysmography measurements of Residual volume (RV) and Functional Residual Capacity (FRC) give insights on airway closure and reflects the presence of gas trapping, considered a hallmark of COPD. On the first day of treatment, 60 min post-dose, indacaterol/glycopyrronium (Ultibro™ Breezhaler®) reduced RV by 380 mL (p<0.001) compared to placebo and FRC by 350 mL p< 0.001) compared to placebo. On day 21, 60 min post-dose, further reductions were seen with RV by 520 mL (p< 0.001) and FRC by 520 mL (p< 0.001).

NON-CLINICAL SAFETY DATA

Information related to indacaterol/glycopyrronium (Ultibro™ Breezhaler®)

A bridging toxicology program was performed for indacaterol/glycopyrronium (Ultibro™ Breezhaler®) that included *in vitro* and *in vivo* safety pharmacology assessments, 2-week inhalation toxicity studies in rats and dogs, a 13-week inhalation toxicity study in dogs and an inhalation embryo-fetal development study in rats. Increased heart rates were apparent after the administration of each individual monotherapy and indacaterol/glycopyrronium (Ultibro™ Breezhaler®) during cardiovascular safety pharmacology or repeated-dose toxicity studies in dogs. The effects on heart rate increased in magnitude and duration when compared with the changes observed for each component alone consistent with an additive response. The highest doses of indacaterol administered alone or in combination were associated with a similar incidence and severity of papillary muscle lesions in the heart of a few individuals during the 2-week toxicity study in dogs. Shortening of PR, P width, QT that reflected increased heart rate and decreased systolic and diastolic blood pressure were also apparent following treatment with indacaterol/glycopyrronium (Ultibro™ Breezhaler®) during the cardiovascular safety pharmacology study in dogs. An estimation of the safety margin is based on papillary muscle lesions in the heart of dogs as the most sensitive species. The NOAEL of 0.386/0.125 mg/kg/day (indacaterol/glycopyrronium) in the 13-week toxicity study was devoid of heart lesions and corresponds with systemic exposures based on mean AUC0-24h values of approximately 64 and 59- fold higher than seen in humans at a dose of 110/50 micrograms (indacaterol/glycopyrronium), for each component respectively.

Information related to indacaterol

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction. The effects of indacaterol seen in toxicity studies in dogs were mainly on the cardiovascular system and consisted of tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological effects and could be explained by the beta$_2$-agonistic properties of indacaterol. Other relevant effects noted in repeated-dose toxicity studies were mild irritancy of the upper respiratory tract in rats consisting of rhinitis and epithelial changes of the nasal cavity and larynx. All these findings were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Studies on genotoxicity did not reveal any mutagenic or clastogenic potential. The carcinogenic potential of indacaterol has been evaluated in a 2-year inhalation study in rats and a 26-week oral transgenic mouse study. Lifetime treatment of rats resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle at doses approximately 30-times the dose of 150 microgram once-daily for humans (based on AUC0-24h). Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other beta$_2$-adrenergic agonist drugs. A 26- week oral study in CB6F1/TgrasH2 hemizygous mice with indacaterol did not show any evidence of tumorigenicity at doses of at least 103-times the dose of 150 microgram once-daily for humans (based on AUC0-24h).

Information related to glycopyrronium

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

The effects seen during repeated-dose inhalation toxicity studies were attributable to exacerbations of the expected pharmacological action of glycopyrronium or mild local irritation. These included mild to moderate increases in heart rate in dogs and a number of reversible changes in rat and dogs associated with reduced secretions from the salivary, lacrimal and Harderian glands and pharynx. Lens opacities observed during chronic studies in rats have been described for other muscarinic antagonists and are considered to be species-specific changes with limited relevance for therapeutic use in patients. Findings in the respiratory tract of rats included degenerative/regenerative changes

and inflammation in the nasal cavity and larynx that are consistent with mild local irritation. Minimal epithelial changes in the lung at the bronchioloalveolar junction were also observed in rats and are regarded as a mild adaptive response. All these findings were observed at exposures considered to be sufficiently in excess of the maximum human exposure and therefore indicate limited relevance during clinical use.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium. Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity at systemic exposures (AUC0-24h) of approximately 53-fold higher in mice and 75-fold higher in rats than the dose of 50 microgram once-daily for humans.

INCOMPATIBILITIES

Not applicable.

AVAILABILITY

PA/AL/PVC Blister Pack of 6 capsules (Box of 6's) and 1 inhaler device
PA/AL/PVC Blister Pack of 6 capsules (Box of 30's) and 1 inhaler device

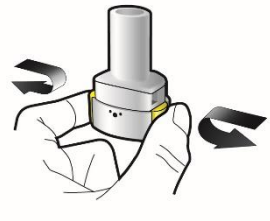
STORAGE

Store at temperatures not exceeding 30ºC.
Protect from moisture.
Do not use after the date marked "EXP" on the pack.
Drugs must be kept out of the reach and sight of children.

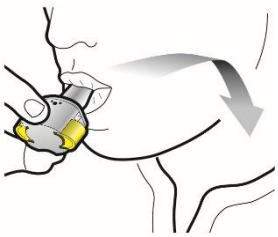
INSTRUCTIONS FOR USE AND HANDLING

Please read the full **Instructions for Use** before using the indacaterol/glycopyrronium (Ultibro™ Breezhaler).

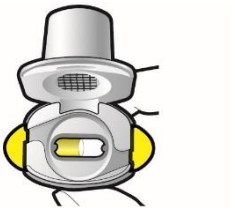
Insert



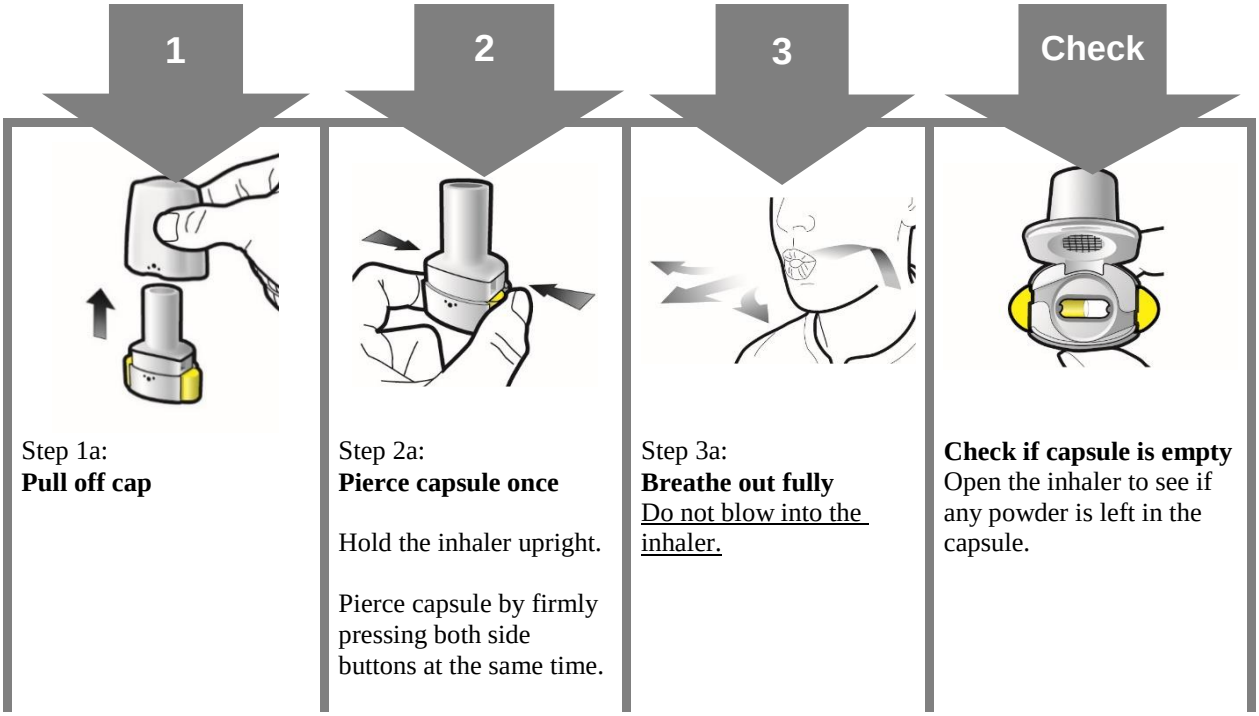
Pierce and release



Inhale deeply



Check if capsule is empty



Step 1a:
Pull off cap

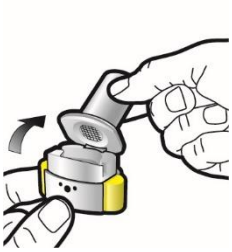
Step 2a:
Pierce capsule once

Hold the inhaler upright.

Pierce capsule by firmly pressing both side buttons at the same time.

Step 3a:
Breathe out fully
Do not blow into the inhaler.

Check if capsule is empty
Open the inhaler to see if any powder is left in the capsule.



Step 1b:
Open inhaler

Step 1c:
Remove capsule

Separate one of the blisters from the blister card.

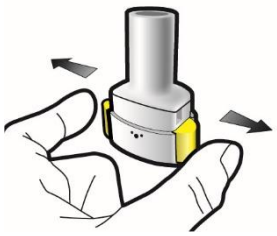
Peel open the blister and remove the capsule.

Do not push the capsule through the foil.

Do not swallow the capsule.

You should hear a noise as the capsule is pierced.

Only pierce the capsule once.



Step 2b:
Release side buttons

Step 3b:
Inhale medicine deeply

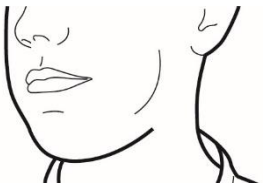
Hold the inhaler as shown in the picture.

Place the mouthpiece in your mouth and close your lips firmly around it.

Do not press the side buttons.
Breathe in quickly and as deeply as you can.

During inhalation you will hear a whirring noise.

You may taste the medicine as you inhale.

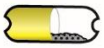


Step 3c:
Hold breath

Hold your breath for up to 5 seconds.

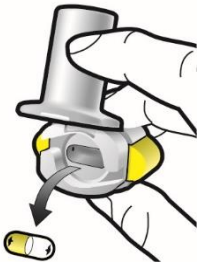
If there is powder left in the capsule:

- Close the inhaler.
- Repeat steps 3a to 3c.



Powder remaining

Empty



Remove empty capsule

Put the empty capsule in your household waste.

Close the inhaler and replace the cap.

Step 1d:
Insert capsule
Never place a capsule directly into the mouthpiece.

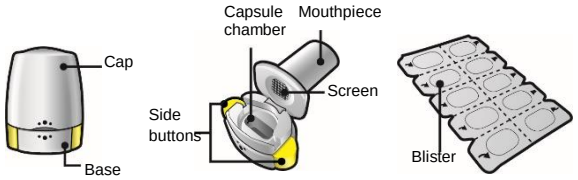
Step 1e:
Close inhaler

Important Information

- Ultibro Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the Ultibro Breezhaler capsules with any other inhaler.
- Do not use the Ultibro Breezhaler inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Do not blow into the mouthpiece.
- Do not press the side buttons while inhaling through the mouthpiece.
- Do not handle capsules with wet hands.
- Never wash your inhaler with water.

Your Ultibro Breezhaler Inhaler pack contains:

- One Ultibro Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Ultibro Breezhaler capsules to be used in the inhaler



Inhaler **Inhaler base** **Blister card**

Frequently Asked Questions

Why didn't the inhaler make a noise when I inhaled?

Cleaning the inhaler
Wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue.
Keep the inhaler dry.
Never wash your inhaler with water.

	The capsule may be stuck in the capsule chamber. If this happens, carefully loosen the capsule by tapping the base of the inhaler. Inhale the medicine again by repeating steps 3a to 3c. **What should I do if there is powder left inside the capsule?** You have not received enough of your medicine. Close the inhaler and repeat steps 3a to 3c. **I coughed after inhaling – does this matter?** This may happen. As long as the capsule is empty you have received enough of your medicine. **I felt small pieces of the capsule on my tongue – does this matter?** This can happen. It is not harmful. The chances of the capsule breaking into small pieces will be increased if the capsule is pierced more than once.	**Disposing of the inhaler after use** Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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