NOVARTIS

1. NAME OF THE MEDICINAL PRODUCT

Ultibro™ Breezhaler® 110 micrograms/50 micrograms, inhalation powder hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium.

Excipient(s) with known effect:
Each capsule contains 23.5 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Capsules with transparent yellow cap and natural transparent body containing a white to almost 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ultibro Breezhaler isindicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD) and for the reduction of exacerbations of COPD in patients with a history of exacerbations.

4.2 Posology and method of administration

Posology
The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler.

Ultibro Breezhaler 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.

Special populations
Geriatric patients (75 years or above)
Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older).

Renal impairment
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 sections 4.4 and 5.2).

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

Pediatric patients (below 18 years)
There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available.
Method of administration
For inhalation use only. The capsules must not be swallowed.

The capsules must be administered only using the Ultibro Breezhaler inhaler (see section 6.5).

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

For instructions on use of the medicinal product before administration, see section 6.5.

4.3 Contraindications

Hypersensitivity to indacaterol or glycopyrronium, which are components of Ultibro Breezhaler, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong (see section 4.5).

Asthma
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
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, which are components of Ultibro Breezhaler. 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, treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm
In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be

life-threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted.

Anticholinergic effects related to glycopyrronium

Narrow-angle glaucoma

No data are available in patients with narrow-angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients.

Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop.

Urinary retention

No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients.

Patients with severe renal impairment

A moderate mean increase in total system exposure (AUC_{last}) to glycopyrronium 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. In 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, Ultibro Breezhaler should be used only if the expected benefit outweighs the potential risk (see section 5.2). These patients should be monitored closely for potential adverse reactions.

Cardiovascular effects

Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension).

$Beta_2$-adrenergic agonists 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 with this medicinal product, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiographic (ECG) changes, such as flattening of the T wave, prolongation of QT interval and ST segment depression, although the clinical significance of these observations is unknown. Therefore, long-acting $beta_2$-adrenergic agonists (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.

Patients with unstable ischaemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or whose QTc (Fridericia method) was prolonged (>450 ms) were excluded from the clinical trials, and therefore there is no experience in these patient groups. Ultibro Breezhaler should be used with caution in these patient groups.

Hypokalaemia

$Beta_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias (see section 4.5).

Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose (see section 5.1).

Hyperglycaemia

Inhalation of high doses of $beta_2$-adrenergic agonists may produce increases in plasma glucose. Upon

initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients.

During long-term clinical studies, more patients on Ultibro Breezhaler experienced clinically notable changes in blood glucose (4.9%) than on placebo (2.7%). Ultibro Breezhaler has not been investigated in patients for whom diabetes mellitus is not well controlled.

General disorders
Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to $beta_2$-adrenergic agonists.

Excipients
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of orally inhaled indacaterol and glycopyrronium, under steady-state conditions of both components, did not affect the pharmacokinetics of either component.

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

Concomitant use not recommended
Beta-adrenergic blockers
Beta-adrenergic blockers may weaken or antagonise the effect of $beta_2$-adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Anticholinergics
The co-administration of Ultibro Breezhaler with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended (see section 4.4).

Sympathomimetic agents
Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol (see section 4.4).

Caution required with concomitant use
Hypokalaemic treatment
Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists, therefore use with caution (see section 4.4).

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3).

Like other $beta_2$–adrenergic agonist containing drugs, Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding
It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. There are no data on the effects of indacaterol and/or glycopyrronium on the breastfed child or on milk production. Available pharmacokinetic/toxicological data have shown excretion of indacaterol, glycopyrronium and their metabolites in the milk of lactating rats after subcutaneous and intravenous administration. The use of Ultibro Breezhaler by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant (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 Ultibro Breezhaler and the individual monotherapy components.

Summary of the safety profile
The safety experience with Ultibro Breezhaler was comprised of exposure of up to 15 months at the recommended therapeutic dose.

Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination.

The safety profile was characterised 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 product (>3% of patients for Ultibro Breezhaler and also greater than placebo) were headache, cough and nasopharyngitis.

Tabulated summary of adverse reactions
Adverse drug reactions are listed by MedDRA system organ class. The frequency of adverse drug reactions was based on a pool of 3 III placebo-controlled trials of 6 and 12 months in duration. The corresponding frequency category for each adverse reaction is based on the following convention: 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); not known (cannot be estimated from the available data).

Table 1 Adverse reactions reported in the placebo-controlled COPD pool

Adverse reactions	Frequency category
Infections and infestations	
Upper respiratory tract infection[2]	Very common
Nasopharyngitis[2]	Common
Urinary tract infection[2]	Common
Sinusitis[2]	Common
Rhinitis[2]	Common
Immune system disorders	
Hypersensitivity[2]	Common
Metabolism and nutrition disorders	
Hyperglycaemia and diabetes mellitus[2]	Common
Psychiatric disorders	
Insomnia[2]	Uncommon
Nervous system disorders	
Dizziness[2]	Common
Headache[2]	Common
Paraesthesia[2]	Rare
Eye disorders	
Glaucoma[1]	Uncommon
Cardiac disorders	
Ischaemic heart disease[2]	Uncommon
Atrial fibrillation[2]	Uncommon
Tachycardia[2]	Uncommon
Palpitations[2]	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough[2]	Common
Oropharyngeal pain including throat irritation[2]	Common
Paradoxical bronchospasm[3]	Uncommon
Epistaxis[2]	Uncommon
Paradoxical bronchospasm	Uncommon
Gastrointestinal disorders	
Dyspepsia[2]	Common
Dental caries[2]	Common
Gastroenteritis[3]	Uncommon
Dry mouth[2]	Uncommon
Skin and subcutaneous tissue disorders	
Pruritus/rash[2]	Uncommon
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain[2]	Uncommon
Muscle spasm[2]	Uncommon
Myalgia[2]	Uncommon
Pain in extremity[3]	Uncommon
Renal and urinary disorders	
Bladder obstruction and urinary retention[2]	Common

General disorders and administration site conditions	
Pyrexia[1]	Common
Chest pain[2]	Common
Peripheral oedema[2]	Uncommon
Fatigue[2]	Uncommon

[1] Adverse reaction observed with Ultibro Breezhaler, but not with the individual components.
[2] Adverse reaction observed with Ultibro Breezhaler and at least one of the individual components.
[3] Adverse reaction observed with at least one of the individual components, but not with Ultibro Breezhaler; frequency category according to section 4.8 of Summary of Product Characteristics of the individual components.

Description of selected adverse reactions
Cough was common, but usually of mild intensity.

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

The following adverse drug reactions have been reported with 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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

There is no information on clinically relevant overdosing with Ultibro Breezhaler.

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, hypokalaemia and hyperglycaemia 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 hospitalised. 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 (MOA)

Ultibro Breezhaler

When indacaterol and glycopyrronium are administered together in Ultibro Breezhaler, they provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve smooth muscle relaxation. Due to the differential density of $beta_2$-adrenoceptors and M3-receptors in central versus peripheral airways, $beta_2$-agonists should be more effective in relaxing peripheral airways, whilst an anticholinergic compound may be more effective in central airways. Thus for bronchodilation in both peripheral and central airways of the human lung a combination of a $beta_2$-adrenergic agonist and a muscarinic antagonist may be beneficial.

Indacaterol

Indacaterol is a 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 catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol has multi-fold greater agonist activity at $beta_2$-receptors compared to $beta_1$ and $beta_3$-receptors.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial agonist at the human $beta_2$-adrenergic receptor with nanomolar potency.

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. Their presence in the heart 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 (anticholinergic) 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.

Glycopyrronium bromide is a high affinity muscarinic receptor antagonist. A greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor has been demonstrated using radioligand binding studies.

Pharmacodynamic effects

The combination of indacaterol and glycopyrronium in Ultibro Breezhaler showed a rapid onset of action within 5 minutes after dosing. The effect remains constant over the whole 24-h dosing interval.

The mean bronchodilator effect derived from serial FEV_1 measurements over 24 h was 320 ml after 26 weeks of treatment. The effect was significantly greater for Ultibro Breezhaler, when compared to indacaterol, glycopyrronium or tiotropium alone (difference 110 ml, for each comparison).

There was no evidence for tachyphylaxis to the effect of Ultibro Breezhaler over time when compared to placebo or its monotherapy components.

Effects on heart rate

Heart rate effects in healthy volunteers were investigated after a single dose of 4 times the recommended therapeutic dose of Ultibro Breezhaler administered in four dose steps each separated by one hour and compared to the effects of placebo, indacaterol, glycopyrronium and salmeterol.

The largest time-matched heart rate increase compared to placebo was +5.69 bpm (90% CI [2.71, 8.66]), the largest decrease was -2.51 bpm (90% CI [-5.48, 0.47]). Overall the effect on heart rate over

time did not show a consistent pharmacodynamic effect of Ultibro Breezhaler.

Heart rate in COPD patients at supratherapeutic dose levels was investigated. There were no relevant effects of Ultibro Breezhaler on mean heart rate over 24 h and heart rate assessed after 30 minutes, 4 h and 24 h.

QT interval
A thorough QT (TQT) study in healthy volunteers with high doses of inhaled indacaterol (up to twice the maximum recommended therapeutic dose) did not demonstrate a clinically relevant effect on the QT interval. Similarly, for glycopyrronium no QT prolongation was observed in a TQT study after an inhaled dose of 8 times the recommended therapeutic dose.

The effects of Ultibro Breezhaler on QTc interval were investigated in healthy volunteers after inhalation of Ultibro Breezhaler up to 4 times the recommended therapeutic dose in four dose steps each 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 Ultibro Breezhaler had no relevant impact on the QT interval, as was expected by the properties of its components.

In COPD patients, supratherapeutic doses between 116 µg/86 µg and 464 µg/86 µg of Ultibro Breezhaler showed a higher proportion of patients with QTcF increases vs. baseline between 30 ms and 60 ms (ranging from 16.0% to 21.6% vs. 1.9% for placebo), but there were no QTcF increases >60 ms from baseline. The highest dose level of 464 µg/86 µg Ultibro Breezhaler also showed a higher proportion of absolute QTcF values >450 ms (12.2% vs. 5.7% for placebo).

Serum potassium and blood glucose
In healthy volunteers, after the administration of 4 times the recommended therapeutic dose of Ultibro Breezhaler, 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.

Clinical efficacy and safety
The Ultibro Breezhaler clinical Phase III development programme included six studies in which over 8,000 patients were enrolled: 1) a 26-week placebo- and active-controlled (indacaterol once daily, glycopyrronium once daily, open-label tiotropium once daily) study; 2) a 26-week active-controlled (fluticasone/salmeterol twice daily) study; 3) a 64-week active-controlled (glycopyrronium once daily, open-label tiotropium once daily) study; 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 (fluticasone/salmeterol 500/50 microgram twice daily) study.

In five of these studies patients were enrolled who had a clinical diagnosis of moderate to severe COPD. In the 64-week study patients were enrolled who had severe to very severe COPD.

Effects on lung function
Ultibro Breezhaler 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. There was no attenuation of the bronchodilator effect over time.

The magnitude of the effect was dependent on the degree of reversibility of airflow limitation at baseline (tested by administration of a short-acting muscarinic antagonist bronchodilator and a short-acting $beta_2$-agonist bronchodilator): Patients with the lowest degree of reversibility at baseline (<5%) generally exhibited a lower bronchodilator response than patients with a higher degree of reversibility at baseline (≥5%). At 26 weeks (primary endpoint), Ultibro Breezhaler increased trough FEV_1 by 80 ml in patients (Ultibro Breezhaler n=82; placebo n=42) with the lowest degree of reversibility (<5%) (p=0.053) and by 220 ml in those patients (Ultibro Breezhaler n=392, placebo n=190) with a higher degree of reversibility at baseline (≥5%) compared to placebo (p<0.001).

Trough and peak FEV_1:
Ultibro Breezhaler increased post-dose trough FEV_1 by 200 ml compared to placebo at the 26-week primary endpoint ($p<0.001$) and showed statistically significant increases compared to each monotherapy component treatment arm (indacaterol and glycopyrronium) as well as the tiotropium treatment arm, as shown in the below table.

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

Treatment difference	Day 1	Week 26
Ultibro Breezhaler – placebo	190 ml ($p<0.001$)	200 ml ($p<0.001$)
Ultibro Breezhaler – indacaterol	80 ml ($p<0.001$)	70 ml ($p<0.001$)
Ultibro Breezhaler – glycopyrronium	80 ml ($p<0.001$)	90 ml ($p<0.001$)
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 minutes prior to the morning dose of study medication) was statistically significant in favour of Ultibro Breezhaler at week 26 compared to fluticasone/salmeterol (100 ml, $p<0.001$), at week 52 compared to placebo (189 ml, $p<0.001$) and at all visits up to week 64 compared to glycopyrronium (70-80 ml, $p<0.001$) and tiotropium (60-70 ml, $p<0.001$). At week 26, Ultibro Breezhaler produced statistically significant improvement in peak FEV_1 compared to placebo in the first 4 hours post dose (330 ml) ($p<0.001$). In the 52-week study, the mean pre-dose FEV_1 was clinically meaningful and statistically significant in favor of Ultibro Breezhaler at all visits up to Week 52 compared to fluticasone/salmeterol (62-86 ml, $p<0.001$)

FEV_1 AUC:
Ultibro Breezhaler increased post-dose FEV_1 AUC_{0-12} (primary endpoint) by 140 ml at 26 weeks ($p<0.001$) compared to fluticasone/salmeterol.

Onset of action

In the studies, Ultibro Breezhaler demonstrated a statistically significant rapid onset of bronchodilator effect on Day 1 and at Week 26.

Table 3 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 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 FEV1 values over 12 hours at Day 1 and trough FEV1 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 FEV1 (L) at Day 1 (FAS, serial spirometry subset)**

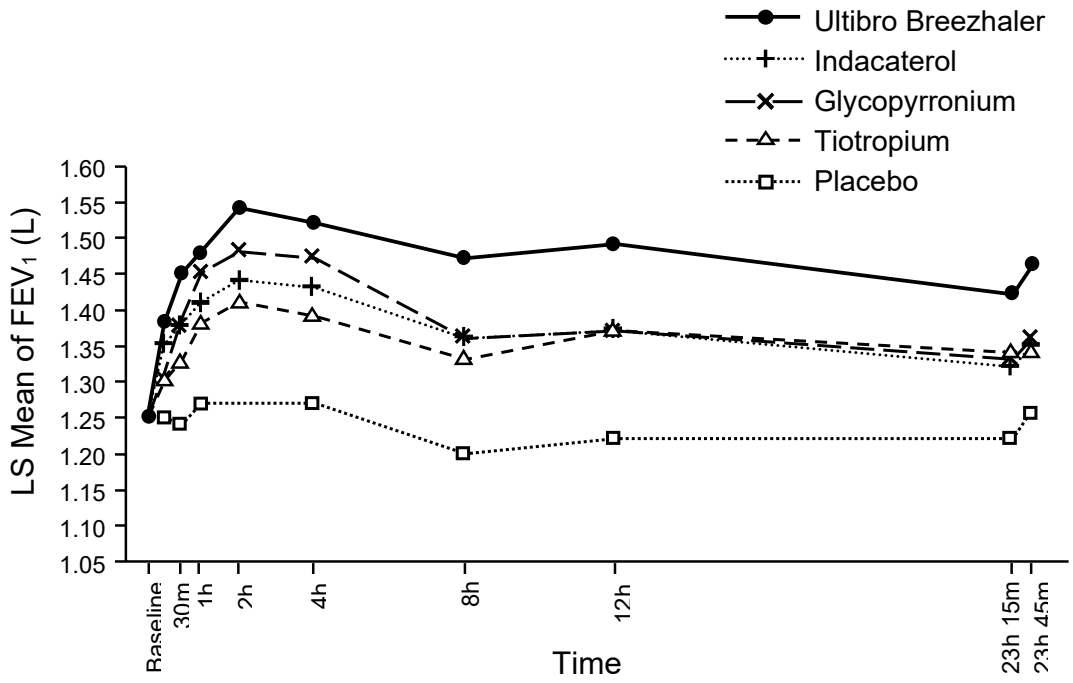
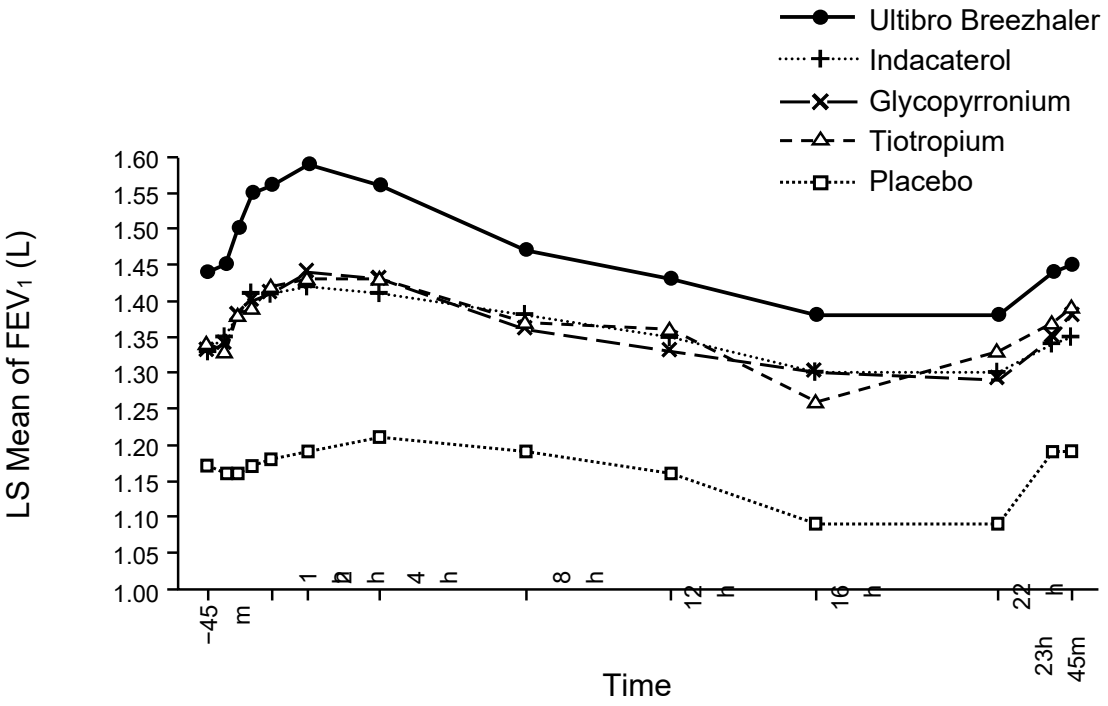


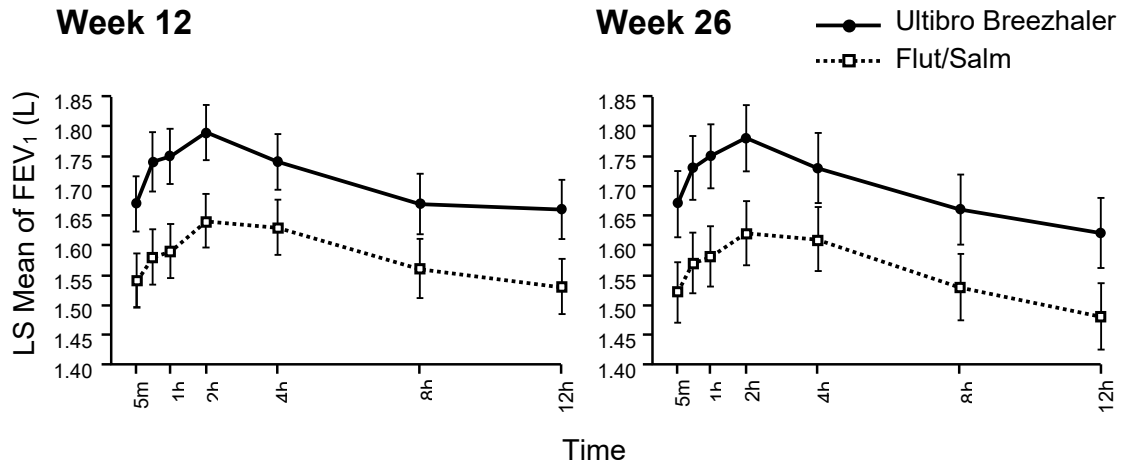
Figure 2 **23 h 45 min profile of least squares means of FEV1 (L) after 26 weeks of treatment (FAS, serial spirometry subset)**



In the serial spirometry subset, 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.

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)



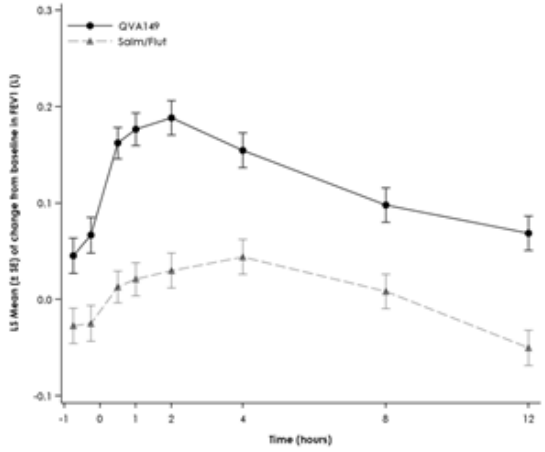
In the study, Ultibro Breezhaler demonstrated significant overall improvements in lung function compared with fluticasone/salmeterol, across all key subgroups, including age, gender, smoking history and disease severity.

In the 52-week (serial spirometry subset), Ultibro Breezhaler demonstrated clinically meaningful and statistically significant improvements in FEV1 AUC0-12h at 52 weeks of treatment. The Ultibro

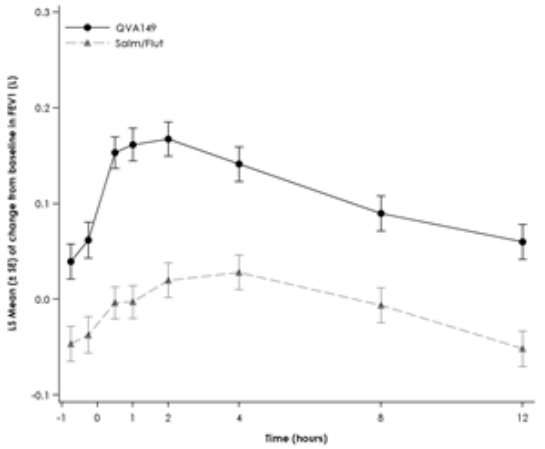
Breezhaler group was statistically superior to the fluticasone/salmeterol group from Day 1 onwards (all $p<0.05$).

Figure 4 Profile of least squares mean change from baseline in FEV1 (L) -45 min to 12 h at Week 12, Week 26, and Week 52 (Serial spirometry set)

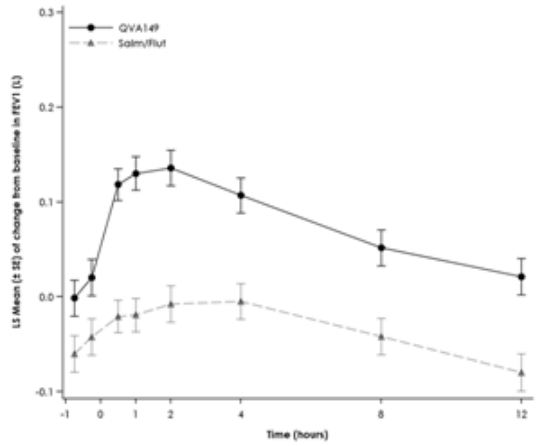
Week 12



Week 26



Week 52



Symptomatic outcomes
Breathlessness:
Ultibro Breezhaler statistically significantly reduced breathlessness as evaluated by the Transitional Dyspnoea Index (TDI); it demonstrated a statistically significant improvement in the TDI focal score at week 26 compared to placebo (1.09, p<0.001), tiotropium (0.51, p=0.007) and fluticasone/salmeterol (0.76, p=0.003). Improvements versus indacaterol and glycopyrronium were 0.26 and 0.21, respectively.

A statistically significantly higher percentage of patients receiving 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 Ultibro Breezhaler as compared to tiotropium (68.1% Ultibro Breezhaler versus 59.2% tiotropium, p=0.016) and fluticasone/salmeterol (65.1% Ultibro Breezhaler versus 55.5% fluticasone/salmeterol, p=0.088).

Health-related quality of life:
Ultibro Breezhaler has also shown a statistically significant effect on health-related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ) as indicated by a reduction in SGRQ total score at 26 weeks compared to placebo (-3.01, p=0.002) and tiotropium (-2.13, p=0.009) and reductions versus indacaterol and glycopyrronium were -1.09 and -1.18, respectively. At 64 weeks, the reduction compared to tiotropium was statistically significant (least squares mean difference -2.69, p<0.001), and at 52 weeks compared to fluticasone/salmeterol (-1.3, p=0.003).

A higher percentage of patients receiving 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% Ultibro Breezhaler vs. 56.4% tiotropium, p=0.047), at week 64 compared to glycopyrronium and tiotropium (57.3% Ultibro Breezhaler versus 51.8% glycopyrronium, p=0.055; versus 50.8% tiotropium, p=0.051, respectively) , and at Week 52 compared to fluticasone/salmeterol (49.2% Ultibro Breezhaler vs. 43.7% fluticasone/salmeterol, OR: 1.30, p<0.001)

Daily activities
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). At week 64, Ultibro Breezhaler showed numerical improvement over glycopyrronium (1.95%; p=0.175) and statistical improvement over tiotropium (4.96%; p=0.001).

COPD exacerbations
In a 64-week study comparing Ultibro Breezhaler (n=729), glycopyrronium (n=739) and tiotropium (n=737), Ultibro Breezhaler reduced the annualised rate of moderate or severe COPD exacerbations by 12% compared to glycopyrronium (p=0.038) and by 10% compared to tiotropium (p=0.096). The number of moderate or severe COPD exacerbations/patient-years was 0.94 for Ultibro Breezhaler (812 events), 1.07 for glycopyrronium (900 events) and 1.06 for tiotropium (898 events). Ultibro Breezhaler also statistically significantly reduced the annualised rate of all COPD exacerbations (mild, moderate or severe) by 15% as compared to glycopyrronium (p=0.001) and 14% as compared to tiotropium (p=0.002). The number of all COPD exacerbations/patient-years was 3.34 for Ultibro Breezhaler (2,893 events), 3.92 for glycopyrronium (3,294 events) and 3.89 for tiotropium (3,301 events).

In a 26-week study comparing Ultibro Breezhaler (n=258) and fluticasone/salmeterol (n=264), the number of moderate or severe COPD exacerbations/patient-years was 0.15 versus 0.18 (18 events versus 22 events), respectively (p=0.512), and the number of all COPD exacerbations/patients-years (mild, moderate or severe) was 0.72 versus 0.94 (86 events versus 113 events), respectively (p=0.098).

In the 52-week active-controlled study, 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. 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 Ultibro Breezhaler vs. 51 days for fluticasone/salmeterol, p<0.001).

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 Ultibro Breezhaler vs. 87 days for fluticasone/salmeterol, p<0.001). Less than 50% of patients in the 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].

Ultibro Breezhaler numerically reduced the annualized rate of severe exacerbations by 13% versus fluticasone/salmeterol (0.15 vs. 0.17, p=0.231). 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 Ultibro Breezhaler arm compared to 4.8% in the fluticasone/salmeterol arm (p=0.017). Time to first pneumonia was prolonged with Ultibro Breezhaler compared to fluticasone/salmeterol (p=0.013)

Use of rescue medication
Over 26 weeks, Ultibro Breezhaler statistically significantly reduced the use of rescue medication (salbutamol) by 0.96 puffs per day (p<0.001) compared to placebo, 0.54 puffs per day (p<0.001) compared to tiotropium and 0.39 puffs per day (p=0.019) compared to fluticasone/salmeterol. Over 64 weeks, this reduction was 0.76 puffs per day (p<0.001) compared to tiotropium.

Over 52 weeks, 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
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 significantly improved (250 ml, p<0.001) compared to placebo. After three weeks of treatment, the improvement in inspiratory capacity with Ultibro Breezhaler was greater (320 ml, p<0.001) and exercise endurance time increased (59.5 seconds, p=0.006) compared to placebo.

5.2 Pharmacokinetic properties

Absorption
Ultibro Breezhaler
Following inhalation of Ultibro Breezhaler, 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 Ultibro Breezhaler and indacaterol monotherapy product. Steady-state exposure to indacaterol after Ultibro Breezhaler inhalation was either similar or slightly lower than systemic exposure after indacaterol monotherapy product inhalation.

Following inhalation of Ultibro Breezhaler, the absolute bioavailability of indacaterol has been estimated to range from 61 to 85% of the delivered dose, and that of glycopyrronium was about 47% of the delivered dose.

Steady-state exposure to glycopyrronium after Ultibro Breezhaler inhalation was similar to systemic exposure after glycopyrronium monotherapy product inhalation.

Indacaterol
Steady state concentrations of indacaterol were achieved within 12 to 15 days following once-daily

administration. 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 60 µg and 480 µg (delivered dose).

Glycopyrronium
In patients with COPD, pharmacokinetic steady-state of glycopyrronium was reached within one week of the start of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium at the recommended once-daily dosing regimen were 166 picograms/ml and 8 picograms/ml, respectively. Steady-state exposure to glycopyrronium (AUC over the 24-hour dosing interval) was about 1.4- to 1.7-fold higher than after the first dose.

Distribution
Indacaterol
After intravenous infusion the volume of distribution of indacaterol during the terminal elimination phase was 2557 litres indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was about 95%.

Glycopyrronium
After intravenous dosing, the steady-state volume of distribution of glycopyrronium was 83 litres and the volume of distribution in the terminal phase was 376 litres. The apparent volume of distribution in the terminal phase following inhalation was almost 20-fold larger, 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 nanograms/ml.

Biotransformation
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 hours. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro the UGT1A1 isoform is a major contributor to the metabolic clearance of indacaterol. However, as shown in a clinical study in populations with different UGT1A1 genotypes, systemic exposure to indacaterol is not significantly affected by the UGT1A1-genotype.

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. 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 vivo*, M9 is formed from the swallowed dose fraction of inhaled glycopyrronium bromide. Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the delivered dose.

Multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. Inhibition or induction of the metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the active substance.

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 or for UGT1A1 and the transporters MDR1 and MRP2.

Elimination

Indacaterol

In clinical studies, the amount of indacaterol excreted unchanged via urine was generally lower than 2.5% of the delivered dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.2 litres/hour. When compared with the serum clearance of indacaterol of 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study, indacaterol given orally was excreted into human faeces primarily as unchanged parent substance (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose).

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 52 hours which is consistent with the observed time-to-steady state of approximately 12-15 days.

Glycopyrronium

After intravenous administration of [^{3}H]-labelled glycopyrronium bromide, the mean urinary excretion of radioactivity in 48 hours amounted to 85% of the dose. A further 5% of the dose was found in the bile.

Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium whereas non-renal clearance accounts 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.

Mean renal clearance of glycopyrronium following inhalation was in the range of 17.4 and 24.4 litres/h. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 23% of the delivered 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 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 (delivered) dose (120 µg to 480 µg) in a dose proportional manner.

Glycopyrronium

In COPD patients both systemic exposure and total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about dose-proportionally over the (delivered) dose range of 44 to 176 µg.

Special populations

Ultibro Breezhaler

A population pharmacokinetic analysis of data in COPD patients after inhalation of 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 Ultibro Breezhaler.

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

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

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

Hepatic impairment
Ultibro Breezhaler:
Based on the clinical pharmacokinetic characteristics of its monotherapy components, 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.

Indacaterol:
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.

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

Renal impairment
Ultibro Breezhaler:
Based on the clinical pharmacokinetic characteristics of its monotherapy components, 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, 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 maleate, a study in renal impaired subjects was not performed.

Glycopyrronium:
Renal impairment has an impact on the systemic exposure to glycopyrronium bromide. 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. In COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate, eGFR $\geq$30 ml/min/1.73 m^2) glycopyrronium bromide can be used at the recommended dose.

Race/Ethnicity
Ultibro Breezhaler:
There were no major differences in total systemic exposure (AUC) for both compounds between Japanese and Caucasian subjects. Insufficient pharmacokinetic data is available for other ethnicities or races.

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 pharmacokinetic data is available for other ethnicities or races.

5.3 Preclinical safety data

Ultibro Breezhaler
Pre-clinical studies included *in vitro* and *in vivo* safety pharmacology assessments, repeated-dose inhalation toxicity studies in rats and dogs and an inhalation embryo-foetal development study in rats.

Increased heart rates were apparent in dogs at all doses of Ultibro Breezhaler and each monotherapy component. The effects on heart rate for Ultibro Breezhaler increased in magnitude and duration when compared with the changes observed for each component alone consistent with an additive response. Shortening of electrocardiograph intervals and decreased systolic and diastolic blood pressure were also apparent. Indacaterol administered to dogs alone or in Ultibro Breezhaler was associated with a similar incidence and severity of myocardial lesions. Systemic exposures (AUC) at the no-observed-adverse-effect level (NOAEL) for myocardial lesions were 64- and 59-fold higher than in humans, for each component respectively.

No effects on the embryo or foetus were seen at any dose level of Ultibro Breezhaler during an inhalation embryo-foetal development study in rats. Systemic exposures (AUC) at the no-observed-adverse-effect level (NOAEL) were 79- and 126-fold higher than in humans, for indacaterol and glycopyrronium respectively.

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

Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F_1 offspring was observed in the peri- and post-developmental rat study at an exposure 14-fold higher than in humans treated with indacaterol. Indacaterol and its metabolites transferred rapidly into the milk of lactating rats.Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential. Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent with similar findings reported for other $beta_2$-adrenergic agonists. No evidence of carcinogenicity was seen in mice. Systemic exposures (AUC) in rats and mice at the no-observed-adverse-effect levels in these studies were at least 7- and 49-fold higher, respectively, than in humans treated with indacaterol once a day at the maximum recommended therapeutic dose.

Glycopyrronium
Non-clinical data reveal no special hazard for humans based on conventional studies of safety

pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Effects attributable to the muscarinic receptor antagonist properties of glycopyrronium bromide included mild to moderate increases in heart rate in dogs, lens opacities in rats and, reversible changes associated with reduced glandular secretions in rats and dogs. Mild irritancy or adaptive changes in the respiratory tract were seen in rats. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Fertility and pre- and post-natal development were not affected in rats. Glycopyrronium bromide 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. Glycopyrronium bromide (including its metabolites) was excreted into the milk of lactating rats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam after intravenous administration.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 25°C.

The capsules must always be stored in the original blister to protect from moisture and only removed immediately before use.

6.4 Nature and contents of container

Ultibro Breezhaler is a single-dose inhaler. Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl metacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

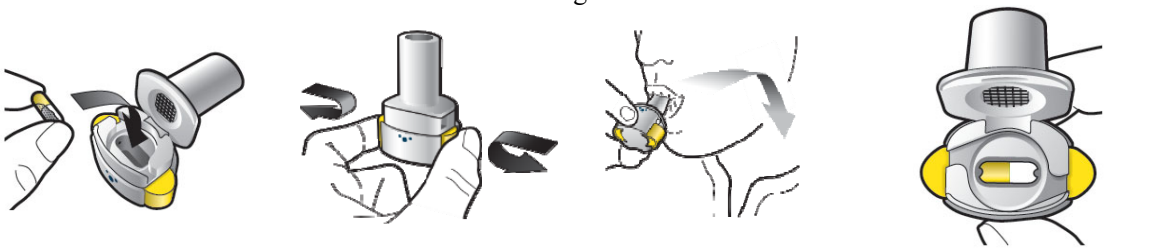
PA/Alu/PVC – Alu perforated unit-dose blister

Single pack 6 capsules (1x6's) or 30 capsules (5 x 6's, 3 x 10's), together with one inhaler.

Not all pack sizes may be marketed.

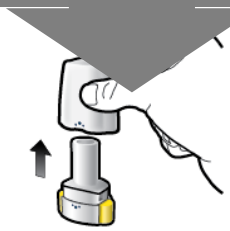
6.5 Special precautions for disposal and other handling

Please read the full **Instructions for Use** before using the Ultibro Breezhaler.

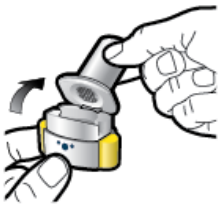


Insert | **Pierce and release** | **Inhale deeply** | **Check capsule is empty**

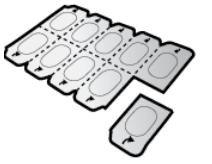
1

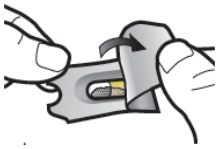


Step 1a:
Pull off cap



Step 1b:
Open inhaler





2

Step 2a:
Pierce capsule once
Hold the inhaler upright.
Pierce capsule by firmly pressing both side buttons at the same time.
You should hear a noise as the capsule is pierced.
Only pierce the capsule once.

Step 2b:
Release side buttons

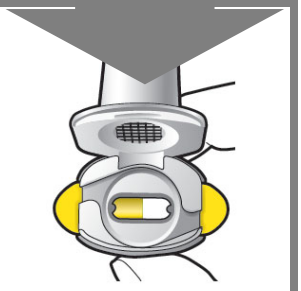
3

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

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.
<u>Do not press the side buttons</u>.

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.

Check



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

If there is powder left in the capsule:
Close the inhaler.
Repeat steps 3a to 3c.

Powder remaining | Empty

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.

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

Step 1e:
Close inhaler

Step 3c:
Hold breath
Hold your breath for up to 5 seconds.

Remove empty capsule
Put the empty capsule in your household waste.

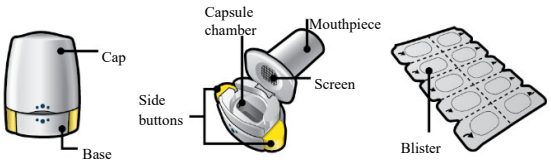
Close the inhaler and replace the cap.

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?
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.

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.

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.

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