Drug Regulatory Affairs

ULTIBRO™ BREEZHALER®

(Indacaterol maleate and glycopyrronium bromide fixed dose combination)

110/50 microgram Inhalation powder, hard capsules

International Package Leaflet

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Ultibro™ Breezhaler®

beta₂-adrenergic agonist/anticholinergic

DESCRIPTION AND COMPOSITION

Pharmaceutical form

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

Transparent yellow cap and natural 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 substances

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.

Active moieties

Indacaterol and glycopyrronium

Excipients

Capsule fill: Lactose monohydrate, magnesium stearate.

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

Information might differ in some countries.

INDICATIONS

Ultibro Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD).

DOSAGE AND ADMINISTRATION

General target population

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

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 Ultibro Breezhaler should be used only if the expected benefit outweighs the potential risk. See also sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY.

Hepatic impairment

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

Ultibro Breezhaler should not be used in patients under 18 years of age.

Geriatric patients

Ultibro Breezhaler can be used at the recommended dose in elderly patients 75 years of age and older.

Method of administration

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

Ultibro Breezhaler 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.

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

When prescribing 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

Ultibro Breezhaler is contraindicated in patients with hypersensitivity to indacaterol or glycopyrronium, which are components of Ultibro Breezhaler, or to any of the excipients.
WARNINGS AND PRECAUTIONS

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 of Ultibro Breezhaler belong (see section INTERACTIONS).

Asthma

Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication.

Long-acting beta2-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, Ultibro Breezhaler should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

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

Anticholinergic effects related to glycopyrronium

Like other anticholinergic containing drugs, 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 Ultibro Breezhaler 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 m²) 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 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 Ultibro Breezhaler at the recommended dose, as with other compounds containing a beta₂-adrenergic agonist, Ultibro Breezhaler 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 beta₂-adrenergic agonists.

As with other drugs containing an inhaled beta₂-adrenergic agonist, Ultibro Breezhaler 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, Ultibro Breezhaler 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.

Clinically relevant effects on prolongation of the QTc-interval have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose (see section CLINICAL PHARMACOLOGY).

Hypokalaemia with beta-agonists

Beta₂-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 Ultibro Breezhaler at the recommended therapeutic dose (see section CLINICAL PHARMACOLOGY).

Hyperglycaemia with beta-agonists

Inhalation of high doses of beta₂-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 clinical studies, more patients on Ultibro Breezhaler experienced clinically notable changes in blood glucose (4.1%) at the recommended dose than on placebo (2.3%). Ultibro Breezhaler has not been investigated in patients for whom diabetes mellitus is not well controlled.
ADVERSE DRUG REACTIONS

The presentation of the safety profile of Ultibro Breezhaler is based on the experience with Ultibro Breezhaler and the individual 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 (110/50 microgram).

The Ultibro Breezhaler Phase III clinical development program consisted of 6 key studies and enrolled over 6000 patients with a clinical diagnosis of moderate to very severe COPD. Safety data from 5 of these studies with treatment durations of 12 weeks or longer were pooled from 1805 patients exposed to Ultibro Breezhaler 110/50 microgram once-daily.

The safety profile was characterized by typical anticholinergic and beta-adrenergic symptoms related to the individual components of the combination. Other most common adverse drug reactions related to the drug product (reported ≥3% and greater than placebo) were cough and oropharyngeal pain (including throat irritation).

At the recommended dose, the adverse drug reaction profile of Ultibro Breezhaler in patients with COPD showed clinically insignificant systemic effects of beta2-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 QTcF were not detectable in comparison to placebo. The frequency of notable QTcF intervals \( [i.e., >450 \text{ ms}] \) and reports of hypokalemia were similar to placebo.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions reported during the first 6 months of two pooled pivotal Phase III trials of 6- and 12-months duration are listed by MedDRA system organ class (Table 1) (6-month Core Safety database). Within each system organ class, the adverse drug reactions are ranked by frequency based on the Ultibro Breezhaler treatment arm, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common \((≥1/10)\); common \((≥1/100 \text{ to } <1/10)\); uncommon \((≥1/1,000 \text{ to } <1/100)\); rare \((≥1/10,000, <1/1,000)\); very rare \((<1/10,000)\), including isolated reports.

Ultibro Breezhaler showed similar adverse drug reactions as the individual components. As Ultibro Breezhaler contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of the components may be expected in the combination.
### Table 1  Adverse drug reactions observed with Ultibro Breezhaler in two placebo-controlled clinical trials

<table>
<thead>
<tr>
<th>Adverse drug reactions</th>
<th>Indacaterol/glycopyrronium 110/50 μg once daily N=699 n (%)</th>
<th>Placebo N=345 n (%)</th>
<th>Frequency category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>81 (11.6)</td>
<td>56 (16.2)</td>
<td>Very common</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>37 (5.3)</td>
<td>24 (7.0)</td>
<td>Common</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13 (1.9)</td>
<td>3 (0.9)</td>
<td>Common</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11 (1.6)</td>
<td>2 (0.6)</td>
<td>Common</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>8 (1.1)</td>
<td>3 (0.9)</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (0.1)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus and hyperglycemia</td>
<td>3 (0.4)</td>
<td>5 (1.4)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (0.6)</td>
<td>2 (0.6)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (1.7)</td>
<td>3 (0.9)</td>
<td>Common</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (3.0)</td>
<td>5 (1.4)</td>
<td>Common</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>1 (0.1)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma*</td>
<td>1 (0.1)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3 (0.4)</td>
<td>1 (0.3)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (0.1)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (0.1)</td>
<td>3 (0.9)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Palpitations</td>
<td>6 (0.9)</td>
<td>4 (1.2)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>40 (5.7)</td>
<td>11 (3.2)</td>
<td>Common</td>
</tr>
<tr>
<td>Oropharyngeal pain incl throat irritation</td>
<td>23 (3.3)</td>
<td>9 (2.6)</td>
<td>Common</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (0.4)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>15 (2.1)</td>
<td>4 (1.2)</td>
<td>Common</td>
</tr>
<tr>
<td>Dental caries</td>
<td>8 (1.1)</td>
<td>2 (0.6)</td>
<td>Common</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4 (0.6)</td>
<td>1 (0.3)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus/rash</td>
<td>5 (0.7)</td>
<td>2 (0.6)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>7 (1.0)</td>
<td>1 (0.3)</td>
<td>Common</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>5 (0.7)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (0.7)</td>
<td>1 (0.3)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder obstruction and urinary retention</td>
<td>4 (0.6)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>15 (2.1)</td>
<td>5 (1.4)</td>
<td>Common</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11 (1.6)</td>
<td>2 (0.6)</td>
<td>Common</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>2 (0.3)</td>
<td>3 (0.9)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (0.7)</td>
<td>1 (0.3)</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

*new adverse drug reaction observed with the combination Ultibro Breezhaler but not with the monotherapy components.
Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reaction has been reported in post-marketing experience: angioedema (frequency not known).

Additional information on individual components

Gastroenteritis, pain in extremity and paradoxical bronchospasm have been observed previously with the individual components but not with Ultibro Breezhaler in the two placebo-controlled trials and are therefore not listed in Table 1 above.

Description of selected adverse drug reactions

The most common anticholinergic adverse event was dry mouth (0.6% versus 0.3% for placebo); however, this adverse event was reported at a lower frequency with 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 Ultibro Breezhaler for hypersensitivity and ischemic heart disease were 0.1% versus 0.0% for placebo and 0.4% versus 0.3% for placebo, respectively.

Special populations

In elderly patients above 75 years of age the frequencies of urinary tract infection were higher on Ultibro Breezhaler than on placebo, with 3.5 versus 2.8%, respectively.

INTERACTIONS

Interactions linked to the 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 with Ultibro Breezhaler. Information on the potential for interactions for Ultibro Breezhaler is based on the potential for each of its two components.

Interactions linked to indacaterol

Indacaterol has not been shown to cause drug interactions with co-medications. In vitro investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medications at the systemic exposure levels achieved in clinical practice (see section CLINICAL PHARMACOLOGY – Biotransformation/metabolism and elimination).
Anticipated interactions resulting in concomitant use not being recommended

**Beta-adrenergic blockers**

Beta-adrenergic blockers may weaken or antagonize 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.

**Drugs known to prolong QTc interval**

Ultibro Breezhaler, as other beta$_2$-adrenergic agonist containing drugs, 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 hypokalemic effect of beta$_2$-adrenergic agonists (see section WARNINGS AND PRECAUTIONS).

**Observed interactions to be considered**

**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$_{\text{max}}$. 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$_{\text{max}}$. 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$_{\text{max}}$, 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$_{\text{max}}$ 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.

Anticipated interactions resulting in concomitant use not being recommended

Anticholinergics

The co-administration of Ultibro Breezhaler with inhaled anticholinergic-containing drugs has not been studied and is therefore, like for other anticholinergic-containing drugs, not recommended.

Observed interactions to be considered

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.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential

There are no special recommendations for women of child-bearing potential.

Pregnancy

There are no data from the use of Ultibro Breezhaler in pregnant women. 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 Ultibro Breezhaler during an embryo-fetal development study in rats. Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration. Reproductive toxicity was seen for indacaterol as an increased incidence of one skeletal variation following administration to rabbits (see section NON-CLINICAL SAFETY DATA). Glycopyrronium was not teratogenic in rats or rabbits following inhalational administration (see section NON-CLINICAL SAFETY DATA). In human parturients undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide, umbilical plasma concentrations were low.
The potential risk for humans is unknown. Therefore as there is no adequate experience in pregnant women, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

**Breast-feeding**

It is not known whether indacaterol and/or glycopyrronium passes into human breast milk. Indacaterol and glycopyrronium (including its metabolites) have been detected in the milk of lactating rats. Therefore the use of 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 (see section NON-CLINICAL SAFETY DATA).

**Fertility**

**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 (see section NON-CLINICAL SAFETY DATA).

**Labor and delivery**

**Information related to indacaterol**

Like other beta2-adrenergic agonist containing drugs, Ultibro Breezhaler may inhibit labor due to a relaxant effect on uterine smooth muscle.

**OVERDOSAGE**

**Information related to Ultibro Breezhaler**

In a single dose study in healthy volunteers the 4-fold of the therapeutic dose of 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 Ultibro Breezhaler 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 Ultibro Breezhaler, but low prevalence and small patient numbers (N=49 and N=51 for 600/100 microgram and 300/100 microgram Ultibro Breezhaler, 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**

**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 small muscle relaxation. Due to the differential density of beta2-adrenoceptors and M3-receptors in central versus smaller airways, beta2-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 beta2-adrenergic agonist and a muscarinic antagonist may be beneficial.

**Indacaterol**
Indacaterol is an ‘ultra’ long-acting beta2-adrenergic agonist for once-daily administration. The pharmacological effects of beta2-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 beta2-receptors compared to beta1-receptors and 20-fold greater agonist activity compared to beta3-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 beta2-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although beta2-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenergic receptors are the predominant receptors in the human heart, there are also beta2-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of beta2-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective beta2-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 (M1-5), only subtypes M1, M3 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 M3 and M1 receptors over the human M2 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 in Ultibro Breezhaler 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 FEV₁ measurements over 24 h was 0.32 L after 26 weeks of treatment when compared to placebo. The effect was significantly greater for 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 Ultibro Breezhaler over time when compared to placebo or its monotherapy components.

Secondary pharmacodynamic effects

The systemic side effects of inhaled beta₂-adrenergic agonists and inhaled muscarinic receptor antagonists are the result of activation of systemic beta₂-adrenergic receptors and blockade of muscarinic receptors after systemic absorption of the drugs. The side effect profile of 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 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 for Ultibro Breezhaler 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 of Ultibro Breezhaler.

Whilst there were no significant effects when 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 Ultibro Breezhaler up to doses of 150/100, 300/100 and 600/100 microgram. There were no relevant effects of Ultibro Breezhaler on mean heart rate over 24 h and heart rate assessed after 30 min, 4 h and 24 h.

QT-interval

The components of Ultibro Breezhaler (indacaterol and glycopyrronium) are not known to have a QT-prolongation potential at clinical dose levels. 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 of Ultibro Breezhaler on QTc-interval were investigated in healthy volunteers after inhalation of 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 Ultibro Breezhaler 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 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 Ultibro Breezhaler 600/100 microgram group. The number of notable QTcF changes versus baseline (>30 ms) was similar across all active treatment groups (Ultibro Breezhaler 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 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 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 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 110/50 microgram and indacaterol 150 microgram monotherapy product. The steady-state exposure to indacaterol after 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 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 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 (Vz) 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 $C_{\text{max}}$ 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. $\leq 0.5\%$ 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 [3H]-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**

**Ultibro Breezhaler**

A population PK analysis 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 FEV₁ had no apparent effect on systemic exposure to indacaterol and glycopyrronium after inhalation of 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 Cₘₐₓ 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 FEV₁ had no apparent effect on systemic exposure.

**Patients with hepatic impairment**

Based on the clinical PK 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.

Patients with mild and moderate hepatic impairment showed no relevant changes in Cₘₐₓ 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.

Patients with renal impairment

Based on the clinical PK 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, 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 m²) glycopyrronium can be used at the recommended dose.

Ethnicity

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 Ultibro Breezhaler Phase III clinical development program [IGNITE] included five studies (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]; and a 3-week placebo- and active-controlled (tiotropium once daily) exercise tolerance study [BRIGHT] which enrolled over 5,000 patients.
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 4 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 post-bronchodilator FEV$_1$ <50% of the predicted normal value.

**Effects on lung function**

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, 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 significant increases compared to each monotherapy component treatment arm (indacaterol and glycopyrronium) as well as the tiotropium treatment arm (see Table 2).

**Table 2** Post-dose trough FEV$_1$ (least squares mean) at Day 1 and Week 26 (primary endpoint)

<table>
<thead>
<tr>
<th>Treatment difference</th>
<th>Day 1</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultibro Breezhaler - placebo</td>
<td>190 mL (p&lt;0.001)</td>
<td>200 mL (p&lt;0.001)</td>
</tr>
<tr>
<td>Ultibro Breezhaler - indacaterol</td>
<td>80 mL (p&lt;0.001)</td>
<td>70 mL (p&lt;0.001)</td>
</tr>
<tr>
<td>Ultibro Breezhaler - glycopyrronium</td>
<td>80 mL (p&lt;0.001)</td>
<td>90 mL (p&lt;0.001)</td>
</tr>
<tr>
<td>Ultibro Breezhaler - tiotropium</td>
<td>80 mL (p&lt;0.001)</td>
<td>80 mL (p&lt;0.001)</td>
</tr>
</tbody>
</table>

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 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].

**Peak FEV$_1$**

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].
**FEV₁AUC**

Ultibro Breezhaler increased post-dose FEV₁ AUC₀-₁₂ (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, 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

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>versus placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>130 mL*</td>
<td>290 mL*</td>
</tr>
<tr>
<td>30 minutes</td>
<td>200 mL*</td>
<td>320 mL*</td>
</tr>
<tr>
<td><strong>versus tiotropium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>70 mL*</td>
<td>120 mL*</td>
</tr>
<tr>
<td>30 minutes</td>
<td>90 mL*</td>
<td>140 mL*</td>
</tr>
<tr>
<td><strong>versus fluticasone/salmeterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>80 mL*</td>
<td>150 mL*</td>
</tr>
<tr>
<td>30 minutes</td>
<td>80 mL*</td>
<td>160 mL*</td>
</tr>
</tbody>
</table>

* 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 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 FEV$_1$ (L) at Day 1 (FAS, serial spirometry subset)

![Graph showing the 24 hour profile of least squares means of FEV$_1$ (L) at Day 1. The graph compares Ultibro Breezhaler, Indacaterol, Glycopyrronium, and Tiotropium to Placebo.]
In the [SHINE] serial spirometry subset, Ultibro Breezhaler demonstrated a statistically significant improvement in FEV₁ 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 FEV₁ 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).
In the [ILLUMINATE] study, 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.

**Symptomatic outcomes**

**Breathlessness**

Ultibro Breezhaler significantly reduced breathlessness as evaluated by the Transitional Dyspnoea Index (TDI). 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 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 vs. 59.2% tiotropium, p=0.016) [SHINE] and fluticasone/salmeterol (65.1% Ultibro Breezhaler vs. 55.5% fluticasone/salmeterol, p=0.088) [ILLUMINATE].
Health related quality of life

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] and at 64 weeks compared to tiotropium (-2.69, p<0.001) [SPARK]. 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 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) [SHINE], and at Week 64 compared to glycopyrronium and tiotropium (57.3% Ultibro Breezhaler vs. 51.8% glycopyrronium, p=0.055; vs. 50.8% tiotropium, p=0.051, respectively) [SPARK].

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) [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, 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, Ultibro Breezhaler 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 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, Ultibro Breezhaler demonstrated a 7% risk reduction compared to glycopyrronium (p=0.319).

Glycopyrronium and tiotropium showed no difference in risk reduction.

Use of rescue medication

Over 26 weeks, 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, 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.

Exercise tolerance
In a 3-week study [BRIGHT] where exercise tolerance was tested via cycle ergometry at submaximal (75%) workload (submaximal exercise tolerance test), 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 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, 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 Ultibro Breezhaler**

A bridging toxicology program was performed for 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 Ultibro Breezhaler during cardiovascular safety pharmacology or repeated-dose toxicity studies in dogs. 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. The highest doses of indacaterol administered alone or in the Ultibro Breezhaler 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 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 beta2-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.

Adverse effects with respect to fertility, pregnancy, embryonal/foetal development, pre- and postnatal development could only be demonstrated at doses more than 500-fold the daily inhalation dose of 150 microgram in humans (based on AUC0-24h). The effects, namely an increased incidence of one skeletal variation, were observed in rabbits. Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration. 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 beta2-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.

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

**STORAGE**

See folding box.

Ultibro Breezhaler should not be used after the date marked “EXP” on the pack.

Ultibro Breezhaler must be kept out of the reach and sight of children.

**INSTRUCTIONS FOR USE AND HANDLING**

**Your Ultibro Breezhaler pack**

One Ultibro Breezhaler pack contains:

- one Ultibro Breezhaler inhaler
- one or more blisters containing Ultibro Breezhaler capsules to be used in the inhaler

![Inhaler, Blister card, Inhaler base](image)

Only use the Ultibro Breezhaler inhaler contained in this pack. Do not use Ultibro Breezhaler capsules with any other inhaler, do not use Ultibro Breezhaler inhaler to take any
other capsule medicine.

Do not push the capsule through the foil to remove it from the blister.

Dispose each inhaler after 30 days of use. Ask your pharmacist how to dispose of medicines and inhalers no longer required.

**Do not swallow Ultibro Breezhaler capsules.** The powder in the capsules is for you to inhale.

**How to use your inhaler**

1. **Pull off cap.**

2. **Open inhaler:**
   Hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler.

3. **Prepare capsule:**
   Separate one of the blisters from the blister card by tearing along the perforation.
   Take one blister and peel away the protective backing to expose the capsule.
   Do not push capsule through the foil.
Remove one Ultibro Breezhaler capsule:
Capsules should always be stored in the blister and only removed immediately before use.
With dry hands, remove one capsule from the blister.
Do not swallow the Ultibro Breezhaler capsule.

Insert capsule:
Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

Close the inhaler:
Close the inhaler fully. You should hear a ‘click’ as it fully closes.

Pierce the capsule:
Hold the inhaler upright with the mouthpiece pointing up.
Press both buttons together firmly at the same time. You should hear a ‘click’ as the capsule is being pierced.

Do not press the piercing buttons more than once.
Release the buttons fully.

Breathe out:
Before placing the mouthpiece in your mouth, breathe out fully.

Never blow into the mouthpiece.

Inhale the medicine:
Before breathing in:
- Hold the inhaler as shown in the picture with the buttons to the left and right (not up and down).
- Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece.
- Breathe in rapidly but steadily, as deeply as you can. **Do not press the piercing buttons.**

Note:
As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavor as the medicine goes into your lungs.

If you do not hear a whirring noise, the capsule may be stuck in the capsule chamber. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. **Do not press the piercing buttons to loosen the capsule.** Repeat steps 9 and 10 if necessary.
Hold breath:

Continue to hold your breath for at least 5-10 seconds or as long as comfortably possible while removing the inhaler from your mouth. Then breathe out.

Open the inhaler to see if any powder is left in the capsule. If there is powder left in the capsule, close the inhaler and repeat steps 9 to 12. Most people are able to empty the capsule with one or two inhalations.

Some people occasionally cough briefly soon after inhaling the medicine. If you do, don’t worry, as long as the capsule is empty, you have received the full dose.

Remove capsule:

After you have finished taking your daily dose of Ultibro Breezhaler, open the mouthpiece again, remove the empty capsule by tipping it out of the capsule chamber, and discard it. Close the inhaler and replace the cap.

Do not store the capsules in the Ultibro Breezhaler inhaler.

REMEMBER:

- Do not swallow Ultibro Breezhaler capsules.
- Only use the Ultibro Breezhaler inhaler contained in this pack.
- Ultibro Breezhaler capsules must always be stored in the blister, and only removed immediately before use.
- Never place a Ultibro Breezhaler capsule directly into the mouthpiece of the Ultibro Breezhaler inhaler.
- Do not press the piercing buttons more than once.
- Never blow into the mouthpiece of the Ultibro Breezhaler inhaler.
- Always release the push buttons before inhalation.
- Never wash the Ultibro Breezhaler inhaler with water. Keep it dry. See below “How to clean your inhaler”.
- Never take the Ultibro Breezhaler inhaler apart.
- Always use the new Ultibro Breezhaler inhaler that comes with your new Ultibro Breezhaler medication pack.
- Do not store the capsules in the Ultibro Breezhaler inhaler.
- Always keep the Ultibro Breezhaler inhaler and Ultibro Breezhaler capsules in a dry place.
Additional information

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is pierced more than once (step 7).

How to clean your inhaler

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

Manufacturer:

See folding box.

International Package Leaflet

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