ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ultibro Breezhaler 85 micrograms/43 micrograms inhalation powder hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

4.2 Posology and method of administration

Posology

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

Elderly population
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).

Paediatric population
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 6.6). The inhaler provided with each new prescription should be used.

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

For instructions on use of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 the active substances of Ultibro Breezhaler. If signs suggesting allergic reactions occur, in particular, angioedema (difficulties in breathing or swallowing, swelling of the tongue, lips and face) urticaria or skin rash, treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

Administration of Ultibro Breezhaler may result in paradoxical bronchospasm which 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 combination products such as Ultibro Breezhaler should be used with caution in patients with known or suspected prolongation of the QT interval or treated with medicinal products affecting the QT interval.

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%) at the recommended dose than on placebo (2.7%). Ultibro Breezhaler has not been investigated in patients for whom diabetes mellitus is not well controlled, therefore caution and appropriate monitoring are advised in such patients.

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 active substances, did not affect the pharmacokinetics of either active substance.

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 active substances.

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).

Sympathomimetics
Concomitant administration of other sympathomimetics (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 data from the use of Ultibro Breezhaler in pregnant women available. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3).

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. Available pharmacokinetic/toxicological data have shown excretion of indacaterol, glycopyrronium and their metabolites in the milk of lactating rats. 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 active substances.

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 is characterised by typical anticholinergic and beta-adrenergic symptoms related to the individual components of the combination. Other most common adverse reactions related to the medicinal product (at least 3% of patients for Ultibro Breezhaler and also greater than placebo) were cough, nasopharyngitis and headache.

Tabulated summary of adverse reactions

Adverse reactions detected during clinical trials and from post-marketing sources are listed by MedDRA system organ class (Table 1). Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, 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); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse reactions	Frequency category
Infections and infestations	
Upper respiratory tract infection	Very common
Nasopharyngitis	Common
Urinary tract infection	Common
Sinusitis	Common
Rhinitis	Common
Immune system disorders	
Hypersensitivity	Common
Angioedema[2]	Uncommon
Metabolism and nutrition disorders	
Hyperglycaemia and diabetes mellitus	Common
Psychiatric disorders	
Insomnia	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Paraesthesia	Rare
Eye disorders	
Glaucoma[1]	Uncommon

Cardiac disorders	
Ischaemic heart disease	Uncommon
Atrial fibrillation	Uncommon
Tachycardia	Uncommon
Palpitations	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Oropharyngeal pain including throat irritation	Common
Paradoxical bronchospasm	Uncommon
Dysphonia[2]	Uncommon
Epistaxis	Uncommon
Gastrointestinal disorders	
Dyspepsia	Common
Dental caries	Common
Gastroenteritis	Uncommon
Dry mouth	Uncommon
Skin and subcutaneous tissue disorders	
Pruritus/rash	Uncommon
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	Uncommon
Muscle spasm	Uncommon
Myalgia	Uncommon
Pain in extremity	Uncommon
Renal and urinary disorders	
Bladder obstruction and urinary retention	Common
General disorders and administration site conditions	
Pyrexia[1]	Common
Chest pain	Common
Oedema peripheral	Uncommon
Fatigue	Uncommon

[1] Adverse reaction observed with Ultibro Breezhaler, but not with the individual components.
[2] Reports received from post-marketing experience; frequencies calculated, however, on the basis of clinical trial data.

Description of selected adverse reactions

Cough was common, but usually of mild intensity.

Reporting of suspected adverse reactions

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

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

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. 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 micrograms/86 micrograms and 464 micrograms/86 micrograms 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 micrograms/86 micrograms 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 twice daily) study.

In four 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 with a

history of ≥1 moderate or severe COPD exacerbation in the previous year. In the 52-week active-controlled study, patients were enrolled who had moderate to very severe COPD with a history of ≥1 moderate or severe COPD exacerbation in the previous year.

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 (least squares [LS] mean treatment difference 100 ml, p<0.001), at week 52 compared to placebo (LS mean treatment difference 189 ml, p<0.001) and at all visits up to week 64 compared to glycopyrronium (LS mean treatment difference 70-80 ml, p<0.001) and tiotropium (LS mean treatment difference 60-80 ml, p<0.001). In the 52-week active-controlled study, the mean pre-dose FEV_1 was statistically significant in favour of Ultibro Breezhaler at all visits up to week 52 compared to fluticasone/salmeterol (LS mean treatment difference 62-86 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 (LS mean treatment difference 330 ml) (p<0.001).

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

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 (LS mean treatment difference 1.09, p<0.001), tiotropium (LS mean treatment difference 0.51, p=0.007) and fluticasone/salmeterol (LS mean treatment difference 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 (LS mean treatment difference -3.01, p=0.002) and tiotropium (LS mean treatment difference -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 (LS mean treatment difference -2.69, p<0.001). At 52 weeks, the reduction compared to fluticasone/salmeterol was statistically significant (LS mean treatment difference -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, odds ratio: 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 (LS mean treatment difference 8.45%, p<0.001). At week 64, Ultibro Breezhaler showed numerical improvement over glycopyrronium (LS mean treatment difference 1.95%; p=0.175) and statistical improvement over tiotropium (LS mean treatment difference 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 the 52-week study comparing Ultibro Breezhaler (n=1,675) and fluticasone/salmeterol (n=1,679), Ultibro Breezhaler met the primary study objective of non-inferiority in rate of all COPD exacerbations (mild, moderate or severe) compared to fluticasone/salmeterol. The number of all COPD exacerbations/patient-years was 3.59 for Ultibro Breezhaler (4,531 events) and 4.03 for fluticasone/salmeterol (4,969 events). Ultibro Breezhaler further showed superiority in reducing the annualised rate of all exacerbations by 11% versus fluticasone/salmeterol (p=0.003).

Compared to fluticasone/salmeterol, Ultibro Breezhaler reduced the annualised rate of both moderate or severe exacerbations by 17% (p<0.001), and of severe exacerbations (requiring hospitalisation) by 13% (not statistically significant, p=0.231). The number of moderate or severe COPD exacerbations/patient-years was 0.98 for Ultibro Breezhaler (1,265 events) and 1.19 for fluticasone/salmeterol (1,452 events). Ultibro Breezhaler prolonged time to first moderate or severe

exacerbation with a 22% reduction in risk of an exacerbation ($p<0.001$) and prolonged time to first severe exacerbation with a 19% reduction in risk of an exacerbation ($p=0.046$).

The incidence of pneumonia 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 ($p=0.013$).

In another study comparing Ultibro Breezhaler (n=258) and fluticasone/salmeterol (n=264), for 26 weeks, 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 ($p=0.098$).

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 reduced the use of rescue medication by 0.25 puffs per day compared to fluticasone/salmeterol ($p<0.001$).

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ultibro Breezhaler in all subsets of the paediatric population in chronic obstructive pulmonary disease (COPD) (see section 4.2 for information on paediatric use).

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 micrograms and 480 micrograms (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 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 micrograms to 480 micrograms) 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 micrograms.

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.

Patients with 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.

Patients with 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 ≥30 ml/min/1.73 m^2) glycopyrronium bromide can be used at the recommended dose.

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 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. 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.

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

Capsule shell

Hypromellose
Calcium chloride
Tartrazine (E102)

Printing ink, black (cap)

Shellac (E904)
Propylene glycol
Ammonium hydroxide
Potassium hydroxide
Iron oxide, black (E172)

Printing ink, blue (body)

Shellac (E904)
Indigo carmine (E132)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

The inhaler in each pack should be disposed of after all capsules in that pack have been used.

6.4 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.

6.5 Nature and contents of container

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. Each blister contains either 6 or 10 hard capsules.

Single pack containing 6x1, 10x1, 12x1, 30x1 or 90x1 hard capsules, together with 1 inhaler.

Multipacks containing 96 (4 packs of 24x1) hard capsules and 4 inhalers.
Multipacks containing 150 (15 packs of 10x1) hard capsules and 15 inhalers.
Multipacks containing 150 (25 packs of 6x1) hard capsules and 25 inhalers.

Not all pack sizes may be marketed.

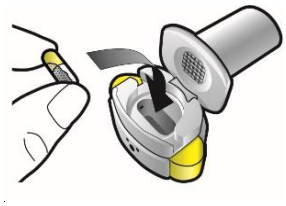
6.6 Special precautions for disposal and other handling

The inhaler provided with each new prescription should be used. The inhaler in each pack should be disposed of after all capsules in that pack have been used.

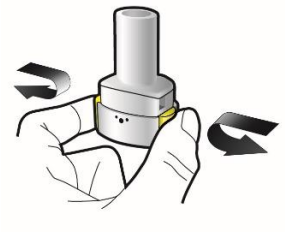
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for handling and use

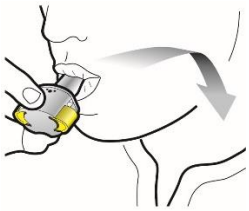
Please read the full **Instructions for Use** before using the Ultibro Breezhaler.



Insert



Pierce and release

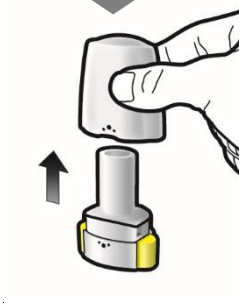


Inhale deeply

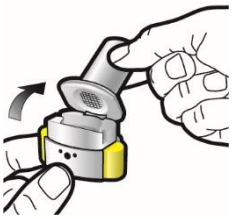


Check capsule is empty

1

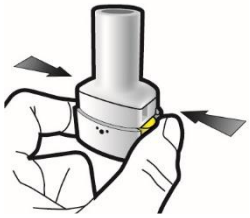


Step 1a:
Pull off cap

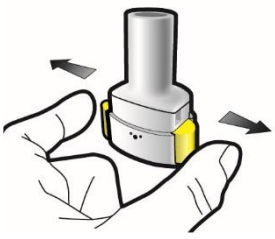


Step 1b:
Open inhaler

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.

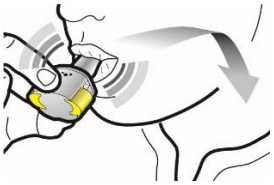


Step 2b:
Release side buttons

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.
Do not press the side buttons.

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.

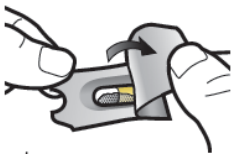


Powder remaining



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

Breathe in quickly and as deeply as you can.
During inhalation you will hear a whirring noise.
You may taste the medicine as you inhale.



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



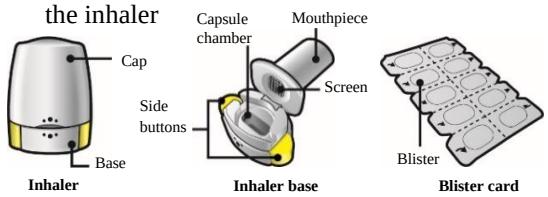
Remove empty capsule
Put the empty capsule in your household waste.
Close the inhaler and replace the cap.

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



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.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/862/001-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2013
Date of latest renewal: 22 May 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Ultibro Breezhaler 85 micrograms/43 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 110 microgram indacaterol and 50 microgram glycopyrronium. The amount of indacaterol and glycopyrronium inhaled is 85 micrograms (equivalent to 110 micrograms of indacaterol maleate) and 43 micrograms (equivalent to 54 micrograms of glycopyrronium bromide), respectively.

3. LIST OF EXCIPIENTS

Also contains: lactose and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

6 x 1 capsules + 1 inhaler
10 x 1 capsules + 1 inhaler
12 x 1 capsules + 1 inhaler
30 x 1 capsules + 1 inhaler
90 x 1 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Read the package leaflet before use.
Inhalation use
Treatment for 90 days [90 x 1 capsules + 1 inhaler only].

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store the capsules in the original blister in order to protect from moisture and do not remove until immediately before use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/862/001	6 capsules + 1 inhaler
EU/1/13/862/007	10 capsules + 1 inhaler
EU/1/13/862/002	12 capsules + 1 inhaler
EU/1/13/862/003	30 capsules + 1 inhaler
EU/1/13/862/004	90 capsules + 1 inhaler

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ultibro Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ultibro Breezhaler 85 micrograms/43 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 110 microgram indacaterol and 50 microgram glycopyrronium. The amount of indacaterol and glycopyrronium inhaled is 85 micrograms (equivalent to 110 micrograms of indacaterol maleate) and 43 micrograms (equivalent to 54 micrograms of glycopyrronium bromide), respectively.

3. LIST OF EXCIPIENTS

Also contains: lactose and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

Multipack: 96 (4 packs of 24 x 1) capsules + 4 inhalers.
Multipack: 150 (15 packs of 10 x 1) capsules + 15 inhalers.
Multipack: 150 (25 packs of 6 x 1) capsules + 25 inhalers.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Read the package leaflet before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store the capsules in the original blister in order to protect from moisture and do not remove until immediately before use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/862/005	Multipack comprising 4 packs (24 capsules + 1 inhaler)
EU/1/13/862/008	Multipack comprising 15 packs (10 capsules + 1 inhaler)
EU/1/13/862/006	Multipack comprising 25 packs (6 capsules + 1 inhaler)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ultibro Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ultibro Breezhaler 85 micrograms/43 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 110 microgram indacaterol and 50 microgram glycopyrronium. The amount of indacaterol and glycopyrronium inhaled is 85 micrograms (equivalent to 110 micrograms of indacaterol maleate) and 43 micrograms (equivalent to 54 micrograms of glycopyrronium bromide), respectively.

3. LIST OF EXCIPIENTS

Also contains: lactose and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

24 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.
10 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.
6 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Read the package leaflet before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store the capsules in the original blister in order to protect from moisture and do not remove until immediately before use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/862/005	Multipack comprising 4 packs (24 capsules + 1 inhaler)
EU/1/13/862/008	Multipack comprising 15 packs (10 capsules + 1 inhaler)
EU/1/13/862/006	Multipack comprising 25 packs (6 capsules + 1 inhaler)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ultibro Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF OUTER CARTON OF UNIT PACK AND OF INTERMEDIATE CARTON OF MULTIPACK

1. OTHER

1	Insert
2	Pierce and release
3	Inhale deeply
Check	Check capsule is empty

Read the leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Ultibro Breezhaler 85 mcg/43 mcg inhalation powder
indacaterol/glycopyrronium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use only

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ultibro Breezhaler 85 micrograms/43 micrograms inhalation powder, hard capsules
indacaterol/glycopyrronium

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultibro Breezhaler is and what it is used for
2. What you need to know before you use Ultibro Breezhaler
3. How to use Ultibro Breezhaler
4. Possible side effects
5. How to store Ultibro Breezhaler
6. Contents of the pack and other information

Instructions for use of Ultibro Breezhaler inhaler

1. What Ultibro Breezhaler is and what it is used for

What Ultibro Breezhaler is
This medicine contains two active substances called indacaterol and glycopyrronium. These belong to a group of medicines called bronchodilators.

What Ultibro Breezhaler is used for
This medicine is used to make breathing easier for adult patients who have breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD). In COPD the muscles around the airways tighten. This makes breathing difficult. This medicine blocks the tightening of these muscles in the lungs, making it easier for air to get in and out of the lungs.

If you use this medicine once a day, it will help to reduce the effects of COPD on your everyday life.

2. What you need to know before you use Ultibro Breezhaler

Do not use Ultibro Breezhaler
- if you are allergic to indacaterol or glycopyrronium or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Ultibro Breezhaler if any of the following applies to you:
- you have asthma - this medicine should not be used as a treatment for asthma.
- you have heart problems.
- you have seizure or fits.
- you have thyroid gland problems (thyrotoxicosis).
- you have diabetes.
- you are using any medicines for your lung disease which contain active substances similar (same class) to those in Ultibro Breezhaler (see section “Other medicines and Ultibro Breezhaler”).

- you have kidney problems.
- you have severe liver problems.
- you have an eye problem called narrow-angle glaucoma.
- you have difficulty passing urine.

If any of the above applies to you (or you are not sure), **talk to your doctor, pharmacist or nurse before using this medicine.**

During treatment with Ultibro Breezhaler

- **Stop using this medicine and seek medical help immediately** if you experience any of the following:
  - eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes – these may be signs of an acute attack of narrow-angle glaucoma.
  - difficulty breathing or swallowing, swelling of the tongue, lips or face, skin rash, itching and hives (signs of an allergic reaction).
  - tightness of the chest, coughing, wheezing or breathlessness immediately after using this medicine – these may be signs of a condition called paradoxical bronchospasm.
- **Tell your doctor immediately** if your COPD symptoms such as breathlessness, wheezing or cough do not improve or get worse.

Ultibro Breezhaler is used as an ongoing treatment for your COPD. Do not use this medicine to treat a sudden attack of breathlessness or wheezing.

Children and adolescents

Do not give this medicine to children or adolescents below the age of 18 years. This is because it has not been studied in this age group.

Other medicines and Ultibro Breezhaler

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular, please tell your doctor or pharmacist if you are using:

- any medicines that may be similar to Ultibro Breezhaler (contain similar active substances).
- medicines called beta blockers that may be used for high blood pressure or other heart problems (such as propranolol), or for an eye problem called glaucoma (such as timolol).
- medicines that lower the amount of potassium in your blood. These include:
  - steroids (such as prednisolone),
  - diuretics (water tablets) used for high blood pressure (such as hydrochlorothiazide),
  - medicines for breathing problems (such as theophylline).

Pregnancy and breast-feeding

There are no data on the use of this medicine in pregnant women and it is not known whether the active substances of this medicine pass into human milk. Indacaterol, one of the active substances in Ultibro Breezhaler, may prevent labour due to its effect on the uterus.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. You should not use Ultibro Breezhaler unless your doctor tells you to do so.

Driving and using machines

It is unlikely that this medicine will affect your ability to drive and use machines. However, this medicine may cause dizziness (see section 4). If you feel dizzy while taking this medicine, do not drive or use machines.

Ultibro Breezhaler contains lactose
This medicine contains lactose (23.5 mg per capsule). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicine.

Ask your doctor or pharmacist for advice before using any medicine.

3. How to use Ultibro Breezhaler

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Ultibro Breezhaler to use
The usual dose is to inhale the content of one capsule each day.
You only need to inhale once a day because the effect of this medicine lasts for 24 hours. Do not use more than your doctor tells you to use.

Elderly (age 75 years and over)
You can use this medicine if you are aged 75 years and over at the same dose as for other adults.

When to inhale Ultibro Breezhaler
Use this medicine at the same time each day. This will also help you to remember to use it.
You can inhale Ultibro Breezhaler any time before or after food or drink.

How to inhale Ultibro Breezhaler
- Ultibro Breezhaler is for inhalation use.
- In this pack, you will find an inhaler and capsules (in blisters) that contain the medicine as inhalation powder. Only use the capsules with the inhaler provided in this pack (Ultibro Breezhaler inhaler). The capsules should remain in the blister until you need to use them.
- Peel the backing away from the blister to open it - do not push the capsule through the foil.
- When you start a new pack, use the new Ultibro Breezhaler inhaler that is supplied in the pack.
- Dispose of the inhaler in each pack after all capsules in that pack have been used.
- Do not swallow the capsules.
- Please read the instructions at the end of this leaflet for more information on how to use the inhaler.

If you use more Ultibro Breezhaler than you should
If you have inhaled too much of this medicine or if someone else accidentally uses your capsules, you must immediately either tell your doctor or go to the nearest emergency unit. Show the pack of Ultibro Breezhaler. Medical attention may be needed. You may notice that your heart is beating faster than usual, or you may have a headache, feel drowsy, feel nauseous or have to vomit, or you may notice visual disturbances, feel constipated or have difficulty when passing urine.

If you forget to use Ultibro Breezhaler
If you forget to inhale a dose at the usual time, inhale one as soon as possible that day. Then, inhale the next dose as usual the next day. Do not inhale more than one dose on the same day.

How long to continue your treatment with Ultibro Breezhaler
– Keep using Ultibro Breezhaler for as long as your doctor tells you.
– COPD is a long-term disease and you should use Ultibro Breezhaler **every day** and not only when you have breathing problems or other symptoms of COPD.

If you have questions about how long to continue your treatment with this medicine, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious:

Common (may affect up to 1 in 10 people)
- difficulty breathing or swallowing, swelling of tongue, lips or face, urticaria, skin rash – these may be signs of an allergic reaction.
- feeling tired or very thirsty, having an increased appetite without gaining weight and passing more urine than usual – these may be signs of high level of sugar in the blood (hyperglycaemia).

Uncommon (may affect up to 1 in 100 people)
- crushing chest pain with increased sweating – this may be a serious heart problem (ischaemic heart disease).
- swelling mainly of the tongue, lips, face or throat (possible signs of angioedema).
- difficulty breathing with wheezing or coughing.
- eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes – these may be signs of glaucoma.
- irregular heartbeat.

If you get any of these serious side effects, **seek medical help immediately.**

Other side effects may include:

Very common (may affect more than 1 in 10 people)
- blocked nose, sneezing, cough, headache with or without fever - these may be signs of an upper respiratory tract infection.

Common
- combination of sore throat and runny nose - these may be signs of nasopharyngitis.
- painful and frequent urination – these may be signs of a urinary tract infection called cystitis.
- feeling of pressure or pain in the cheeks and forehead – these may be signs of inflammation of the sinuses called sinusitis.
- runny or stuffy nose.
- dizziness.
- headache.
- cough.
- sore throat.
- upset stomach, indigestion.
- dental caries.
- difficulty and pain when passing urine – these may be signs of a bladder obstruction or urinary retention.
- fever.
- chest pain.

Uncommon
- difficulty sleeping.
- fast heart beat.
- palpitations – signs of abnormal heart beat.
- voice alteration (hoarseness).
- nose bleeds.
- diarrhoea or stomach ache.
- dry mouth.
- itching or rash.

- pain that affects the muscles, ligaments, tendons, joints and bones.
- muscle spasm.
- muscle pain, aches or tenderness.
- pain in arms or legs.
- swollen hands, ankles and feet.
- tiredness.

Rare (may affect up to 1 in 1000 people)
- tingling or numbness.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ultibro Breezhaler

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

Do not store above 25°C.

Store the capsules in the original blister in order to protect from moisture and do not remove until immediately before use.

The inhaler in each pack should be disposed of after all capsules in that pack have been used.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultibro Breezhaler contains
- The active substances are indacaterol (as maleate) and glycopyrronium bromide. Each capsule contains 143 micrograms of indacaterol maleate equivalent to 110 micrograms of indacaterol and 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 85 micrograms of indacaterol (equivalent to 110 micrograms of indacaterol maleate) and 43 micrograms of glycopyrronium (equivalent to 54 micrograms of glycopyrronium bromide).
- The other ingredients of the inhalation powder are lactose monohydrate and magnesium stearate (see section 2 under "Ultibro Breezhaler contains lactose").
- The ingredients of the capsule shell are hypromellose, calcium chloride, tartrazine (E102) and black (cap) and blue (body) printing ink.
    - The ingredients of the black printing ink (cap) are shellac (E904), propylene glycol, ammonium hydroxide, potassium hydroxide and iron oxide, black (E172).
    - The ingredients of the blue (body) printing ink are shellac (E904), indigo carmine (E132) and titanium dioxide (E171).

What Ultibro Breezhaler looks like and contents of the pack

Ultibro Breezhaler 85 micrograms/43 micrograms inhalation powder, hard capsules are transparent and yellow and contain a white to almost white powder. They have 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.

In this pack, you will find a device called an inhaler together with capsules in blister strips. Each blister contains either 6 or 10 hard capsules.

The following pack sizes are available:
Single pack containing 6x1, 10x1, 12x1, 30x1 or 90x1 hard capsules, together with 1 inhaler.

Multipacks containing 96 (4 packs of 24x1) hard capsules and 4 inhalers.
Multipacks containing 150 (15 packs of 10x1) hard capsules and 15 inhalers.
Multipacks containing 150 (25 packs of 6x1) hard capsules and 25 inhalers.

Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

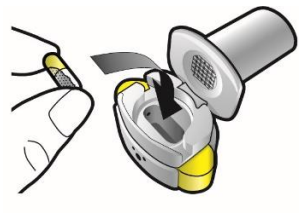
Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

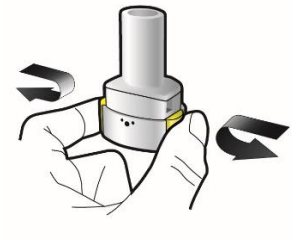
This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

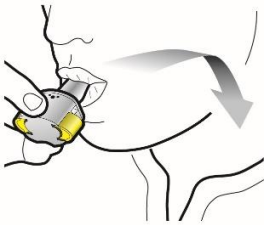
Please read the full **Instructions for Use** before using the Ultibro Breezhaler.



Insert



Pierce and release

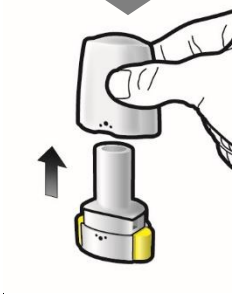


Inhale deeply

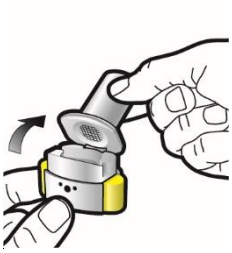


Check capsule is empty

1

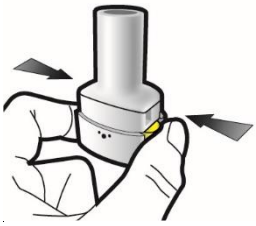


Step 1a:
Pull off cap



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.

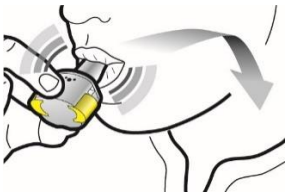


Step 2b:
Release side buttons

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.
Do not press the side buttons.

Check



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

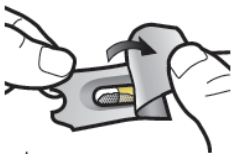
If there is powder left in the capsule:

- 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

Breathe in quickly and as deeply as you can.
During inhalation you will hear a whirring noise.
You may taste the medicine as you inhale.



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



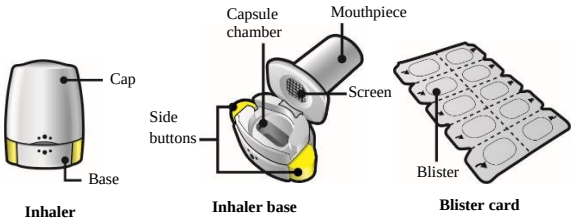
Remove empty capsule
Put the empty capsule in your household waste.
Close the inhaler and replace the cap.

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.