

ULTIBRO® BREEZHALER®

(indacaterol maleate and glycopyrronium bromide
fixed-dose combination)

inhalation powder hard capsules

Product Information

(draft v1)

Based on CDS version 3.1 (23-Jun-2020)

Trade name

ULTIBRO[®] BREEZHALER[®] (indacaterol/glycopyrronium) 110/50 microgram, inhalation powder hard capsules

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.

Indications

ULTIBRO BREEZHALER is indicated as once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) who are still symptomatic despite treatment with indacaterol alone or glycopyrronium alone or the combination of salmeterol/fluticasone.

ULTIBRO BREEZHALER is indicated as once-daily maintenance bronchodilator treatment to relieve symptoms in patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are still symptomatic despite treatment with tiotropium alone.

Dosage regimen 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 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 section Clinical pharmacology.

Pediatric patients (below 18 years)

ULTIBRO BREEZHALER should not be used in patients under 18 years of age.

Geriatric patients (75 years or above)

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 section Pharmaceutical information).

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

Serious Warnings and Precautions

WARNING: ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of another LABA (salmeterol) or placebo added to patients' usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol maleate, one of the active ingredients of ULTIBRO BREEZHALER.

ULTIBRO BREEZHALER is only indicated for COPD.

The safety and efficacy of ULTIBRO BREEZHALER in patients with asthma have not been established. ULTIBRO BREEZHALER is not indicated for the treatment of asthma.

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).

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. Therefore, long-acting beta₂-adrenergic agonists (LABA) or LABA containing products such as ULTIBRO BREEZHALER should be used with caution in patients with known or suspected prolongation of the QT interval or patients treated with medicinal products affecting the QT interval.

Hypokalaemia with beta-agonists

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 long-term clinical studies ([ENLIGHTEN] and [RADIATE]), more patients on ULTIBRO BREEZHALER experienced clinical notable changes in blood glucose (4.9%) than on placebo (2.7%). ULTIBRO BREEZHALER has not been investigated in patients for whom diabetes mellitus is not well controlled.

Excipients

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

Adverse drug reactions

The presentation of the safety profile of ULTIBRO BREEZHALER is based on the experience with ULTIBRO BREEZHALER and the individual monotherapy components.

Summary of the safety profile

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

The ULTIBRO BREEZHALER Phase III clinical development program consisted of 11 studies and enrolled over 10,000 patients with a clinical diagnosis of moderate to very severe COPD. Safety data from 9 of these studies with treatment durations of 4 weeks or longer were pooled from 4352 patients exposed to ULTIBRO BREEZHALER 110/50 microgram once-daily.

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

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 QT_cF were not detectable in comparison to placebo. The frequency of notable QT_cF intervals (i.e., > 450 ms) and reports of hypokalemia were similar to placebo.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions are listed by MedDRA system organ class (Table 1). The frequency of adverse drug reactions was based on a pool of 3 Phase III placebo-controlled trials of 6 and 12

months in duration. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); and very rare ($< 1/10,000$).

ULTIBRO BREEZHALER showed similar adverse drug reactions as the individual monotherapy components. As ULTIBRO BREEZHALER contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of the monotherapy components may be expected in the combination.

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

Adverse drug reactions	Indacaterol/ glycopyrronium 110/50 µg once daily N=1106 Rate (95% CI)	Placebo N=748 Rate (95% CI)	Frequency category
Infections and infestations			
Upper respiratory tract infection	16.96 (14.53, 19.74)	19.64 (16.67, 23.06)	Very common
Nasopharyngitis	9.03 (7.26, 11.20)	8.78 (6.77, 11.37)	Common
Urinary tract infection	2.86 (1.91, 4.29)	1.49 (0.80, 2.75)	Common
Sinusitis	1.8 (1.11, 2.93)	1.54 (0.82, 2.88)	Common
Rhinitis	1.86 (1.16, 2.99)	2.98 (1.16, 2.99)	Common
Immune system disorders			
Hypersensitivity	2.06 (1.31, 3.21)	1.90 (1.04, 3.47)	Common
Metabolism and nutrition disorders			
Hyperglycaemia and diabetes mellitus	1.65 (0.92, 2.95)	2.42 (1.46, 4.00)	Common
Psychiatric disorders			
Insomnia	0.81 (0.37, 1.76)	0.98 (0.44, 2.21)	Uncommon
Nervous system disorders			
Dizziness	1.74 (1.05, 2.88)	0.95 (0.42, 2.14)	Common
Headache	3.24 (2.28, 4.60)	2.66 (1.64, 4.29)	Common
Paraesthesia	0.09 (0.01, 0.64)	(0)	Rare
Eye disorders			
Glaucoma*	0.19 (0.05, 0.75)	(0)	Uncommon
Cardiac disorders			
Ischemic heart disease	0.67	0.78	Uncommon

Adverse drug reactions	Indacaterol/ glycopyrronium 110/50 µg once daily N=1106 Rate (95% CI)	Placebo N=748 Rate (95% CI)	Frequency category
	(0.32, 1.41)	(0.29, 2.12)	
Atrial fibrillation	0.8 (0.33, 1.95)	0.24 (0.03, 1.68)	Uncommon
Tachycardia	0.39 (0.15, 1.04)	0.7 (0.29, 1.66)	Uncommon
Palpitations	0.73 (0.34, 1.56)	1.38 (0.68, 2.80)	Uncommon
Respiratory, thoracic and mediastinal disorders			
Cough	6.84 (5.38, 8.68)	5.94 (4.30, 8.17)	Common
Oropharyngeal pain including throat irritation	2.95 (2.05, 4.23)	2.71 (1.70, 4.29)	Common
Epistaxis	0.28 (0.09, 0.85)	0.24 (0.03, 1.68)	Uncommon
Paradoxical bronchospasm	0.18 (0.05, 0.73)	0.51 (0.16, 1.64)	Uncommon
Gastrointestinal disorders			
Dyspepsia	2.29 (1.49, 3.51)	2.25 (1.32, 3.81)	Common
Dental caries	1.39 (0.79, 2.44)	0.97 (0.43, 2.19)	Common
Dry mouth	0.64 (0.31, 1.34)	0.45 (0.14, 1.39)	Uncommon
Gastroenteritis	0.28 (0.06, 1.18)	0.97 (0.43, 2.18)	Uncommon
Skin and subcutaneous tissue disorders			
Pruritus/rash	0.56 (0.25, 1.25)	0.91 (0.37, 2.24)	Uncommon
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	0.92 (0.47, 1.81)	1.3 (0.60, 2.78)	Uncommon
Muscle spasm	0.85 (0.41, 1.73)	0.44 (0.14, 1.37)	Uncommon
Pain in extremity	0.74 (0.37, 1.47)	0.14 (0.02, 0.98)	Uncommon
Myalgia	0.57 (0.25, 1.26)	0.53 (0.17, 1.70)	Uncommon
Renal and urinary disorders			
Bladder obstruction and urinary retention	1.03 (0.52, 2.03)	(0)	Common
General disorders and administration site conditions			
Pyrexia*	1.96 (1.26, 3.05)	1.47 (0.79, 2.72)	Common
Chest pain	1.85 (1.13, 3.02)	1.5 (0.77, 2.92)	Common
Peripheral edema	0.65 (0.28, 1.48)	1.09 (0.51, 2.33)	Uncommon

Adverse drug reactions	Indacaterol/ glycopyrronium 110/50 µg once daily N=1106 Rate (95% CI)	Placebo N=748 Rate (95% CI)	Frequency category
Fatigue	0.83 (0.41, 1.68)	0.54 (0.20, 1.43)	Uncommon
Of the 1106 patients on ULTIBRO BREEZHALER, 946 (86%) were exposed for at least 26 weeks, and 447 (40%) were exposed for at least 52 weeks. Of the 748 patients on placebo, 588 (79%) were exposed for at least 26 weeks, and 339 (45%) were exposed for at least 52 weeks.			
*adverse drug reaction observed with the combination ULTIBRO BREEZHALER but not with the monotherapy components.			

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

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

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

Immune system disorders
Angioedema
Respiratory, thoracic and mediastinal disorders
Dysphonia

Description of selected adverse drug reactions

The most common anticholinergic adverse event was dry mouth (0.64% versus 0.45% for placebo); however, this adverse event was reported at a lower frequency with 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 2.06% versus 1.9% for placebo and 0.67% versus 0.78% for placebo, respectively.

Interactions

Interactions linked to 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 monotherapy components.

Interactions linked to indacaterol

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

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonize the effect of beta₂-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 beta₂-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 beta₂-adrenergic agonists (see section Warnings and precautions).

Metabolic and transporter based drug interaction

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of indacaterol. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin verapamil and ritonavir). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in C_{max}. Co-administration of

erythromycin with indacaterol resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for C_{max} . Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and C_{max} , respectively. Concomitant treatment with ritonavir, another dual inhibitor of CYP3A4 and P-gp, resulted in a 1.6- to 1.8-fold increase in AUC whereas C_{max} was unaffected. Taken together, the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. The magnitude of exposure increases due to drug interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical trials of up to one year at doses of 600 microgram.

Interactions linked to glycopyrronium

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

Anticholinergics

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

Cimetidine or other inhibitors of organic cation transport

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

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

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

No effects on the embryo or fetus were seen at any dose level of 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).

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.

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.

Information related to glycopyrronium

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

Lactation

It is not known whether indacaterol and/or glycopyrronium passes into human breast milk. There are no data on the effects of indacaterol and/or glycopyrronium on the breastfed child or on milk production. Indacaterol and glycopyrronium (including its metabolites) have been detected in the milk of lactating rats after subcutaneous and intravenous administration. Glycopyrronium reached up to 10-fold higher concentrations in the milk than in the blood of the dam after intravenous administration. Therefore, the use of 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 also section Non-clinical safety data).

Females and males of child-bearing potential

There are no special recommendations.

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).

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

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: adrenergics in combination with anticholinergics, ATC code: R03AL04.

Mechanism of action (MOA)

ULTIBRO BREEZHALER

When indacaterol and glycopyrronium are administered together in ULTIBRO BREEZHALER, they provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve 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 a 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 M1-3 have a defined physiological function in the human lung. Glycopyrronium bromide is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human 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

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

Glycopyrronium

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

Biotransformation/metabolism

Indacaterol

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 is the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

Glycopyrronium

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

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

After inhalation, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. Since *in vitro* studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4% of parent drug C_{max} and AUC) after i.v. administration, it is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium bromide by pre-systemic hydrolysis and/or via first pass metabolism. After inhalation as well as i.v. administration, only minimal amounts of M9 were found in the urine (i.e. $\leq 0.5\%$ 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 $\geq 90\%$ 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 C_{max} of indacaterol were 1.2-fold higher in the [(TA)₇, (TA)₇] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

Glycopyrronium

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

Gender, smoking status and baseline FEV₁ had no apparent effect on systemic exposure.

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 C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

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

Renal impairment

Based on the clinical PK characteristics of its monotherapy components, 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 $eGFR \geq 30$ mL/min/1.73 m²) glycopyrronium can be used at the recommended dose.

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

These studies enrolled patients with a clinical diagnosis of moderate to very severe COPD, who were 40 years old or older, and had a smoking history of at least 10 pack years. Of these 5 studies, the [SHINE] and [ENLIGHTEN] studies had a post-bronchodilator FEV₁ <80% and $\geq 30\%$ of the predicted normal value and a post-bronchodilator FEV₁/FVC ratio of less than 70%. The 26-week active-controlled study, [ILLUMINATE], enrolled patients with a post-bronchodilator FEV₁ of <80% and $\geq 40\%$ of the predicted normal value. In comparison, the 64-week [SPARK] study enrolled patients with severe to very severe COPD, with a history of ≥ 1 moderate or severe COPD exacerbation in the previous year, and a post-bronchodilator FEV₁ <50% of the predicted normal value. The 52-week active-controlled study, [FLAME], enrolled moderate to very severe COPD patients with a history of ≥ 1 moderate or severe COPD exacerbation (19% had a history of ≥ 2 exacerbations) in the previous year, and a post-bronchodilator FEV₁ of ≥ 25 and <60% 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, FEV₁), 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 FEV₁

In the [SHINE] study, ULTIBRO BREEZHALER increased post-dose trough FEV₁ 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 FEV₁ (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 FEV₁ (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]. In the [FLAME] study, the mean pre-dose FEV₁ was clinically meaningful and statistically significant in favor of ULTIBRO BREEZHALER at all visits up to Week 52 compared to fluticasone/salmeterol (62-86 mL, p<0.001).

Peak FEV₁

ULTIBRO BREEZHALER produced statistically significant improvement in peak FEV₁ 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].

FEV₁ AUC

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**

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

* p<0.001 for all treatment comparisons

Serial spirometry subset

In the 26-week, placebo-controlled [SHINE] study, 12-hour serial spirometry was performed on Day 1 (Figure 1) and 24-hour serial spirometry at Week 26 (Figure 2) in a subset of 294 patients. Serial FEV₁ values over 12 hours at Day 1 and trough FEV₁ values at Day 2 are shown in Figure 1, and at Week 26 in Figure 2. Improvement of lung function was maintained for 24 hours after the first dose and consistently maintained over the 26-week treatment period with no evidence of tolerance.

Figure 1 24 hour profile of least squares means of FEV₁ (L) at Day 1 (FAS, serial spirometry subset)

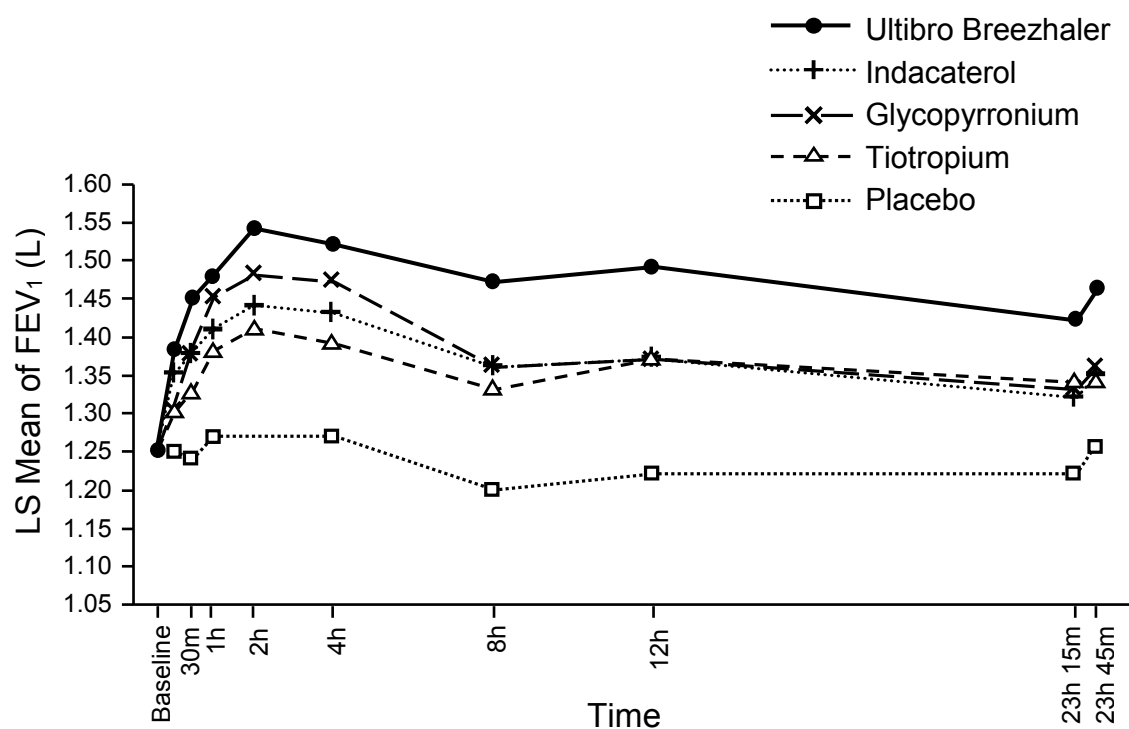
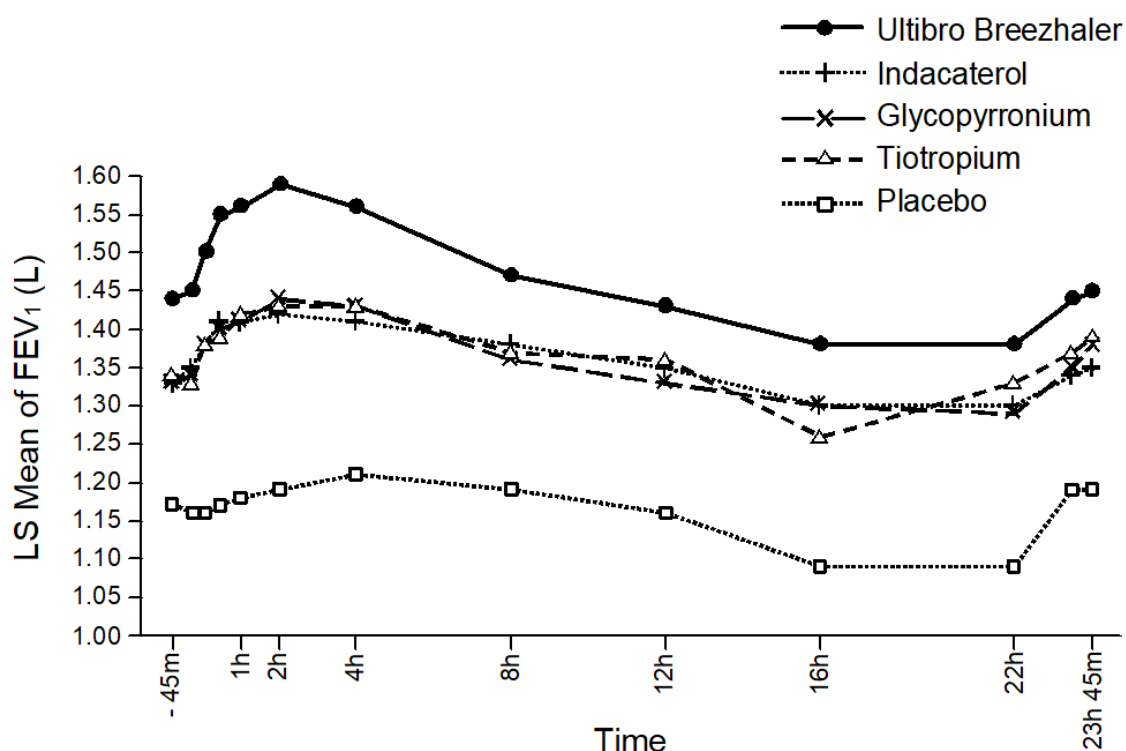


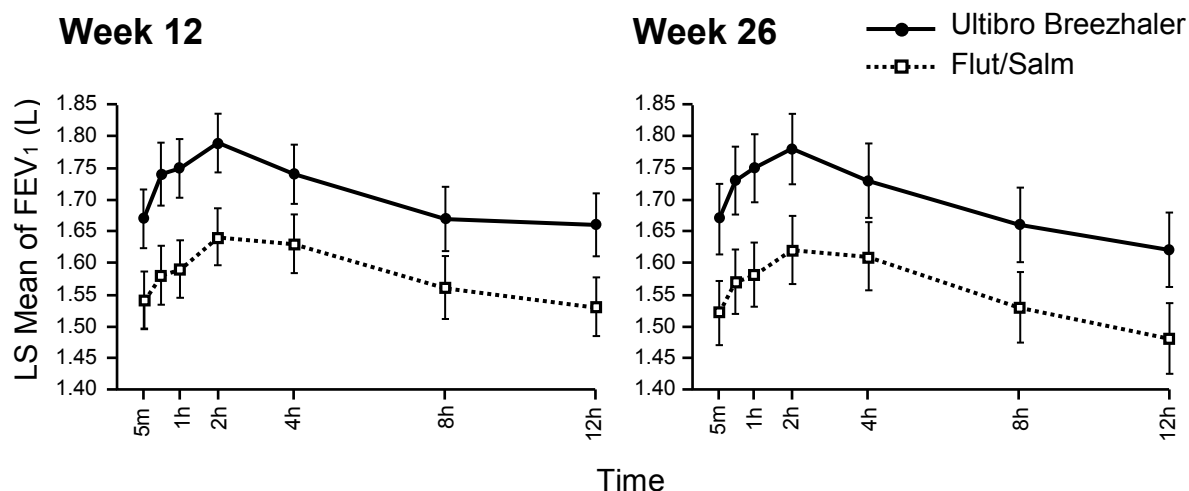
Figure 2 23 h 45 min profile of least squares means of FEV₁ (L) after 26 weeks of treatment (FAS, serial spirometry subset)



In the [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).

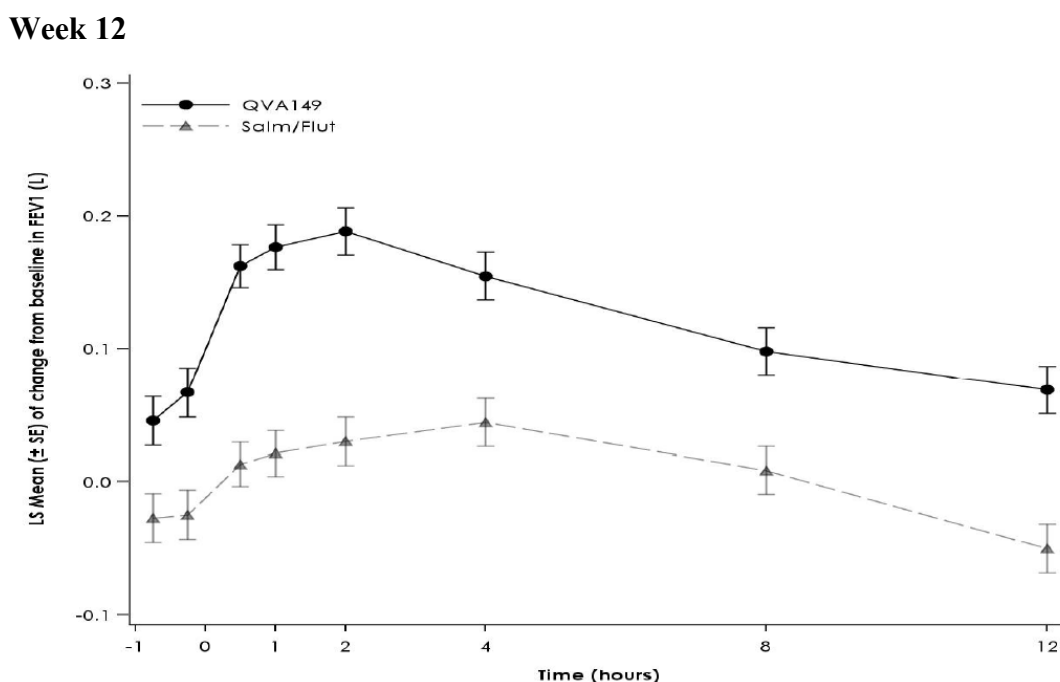
Figure 3 Profile of LS means of FEV₁ (L) from 5 min up to 12 h post-dose at Week 12 and Week 26 (Full analysis set)



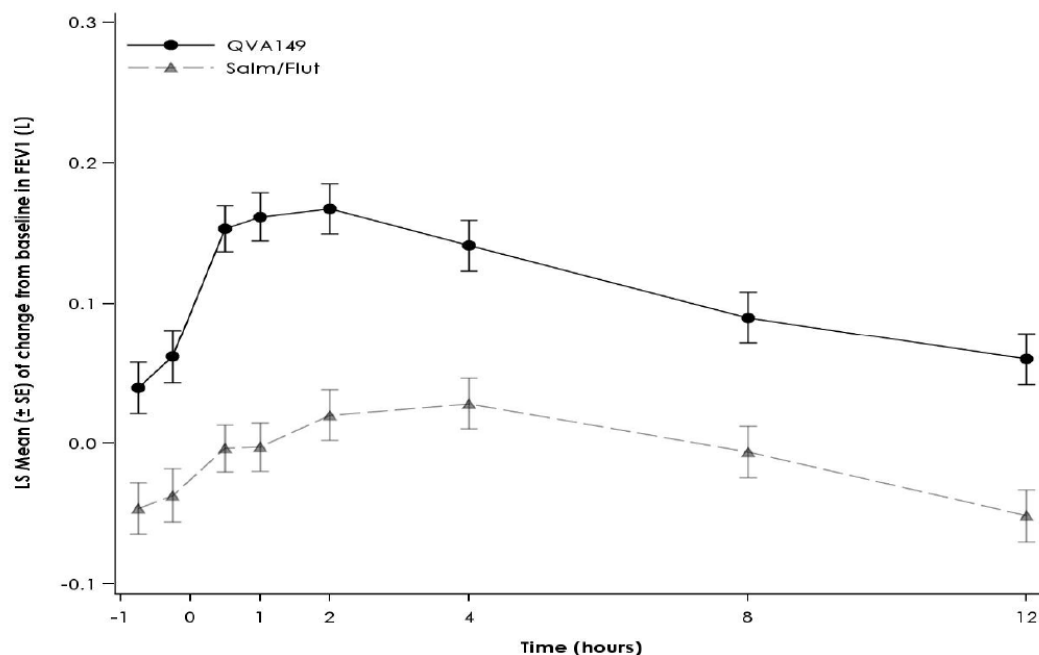
In the [ILLUMINATE] study, ULTIBRO BREEZHALER demonstrated significant overall improvements in lung function compared with fluticasone/salmeterol, across all key subgroups, including age, gender, smoking history, disease severity, and reversibility.

In the [FLAME] serial spirometry subset, ULTIBRO BREEZHALER demonstrated clinically meaningful and statistically significant improvements in FEV₁ AUC_{0-12h} at 52 weeks of treatment. The ULTIBRO BREEZHALER group was statistically superior to the fluticasone/salmeterol group from Day 1 onwards (all $p < 0.05$).

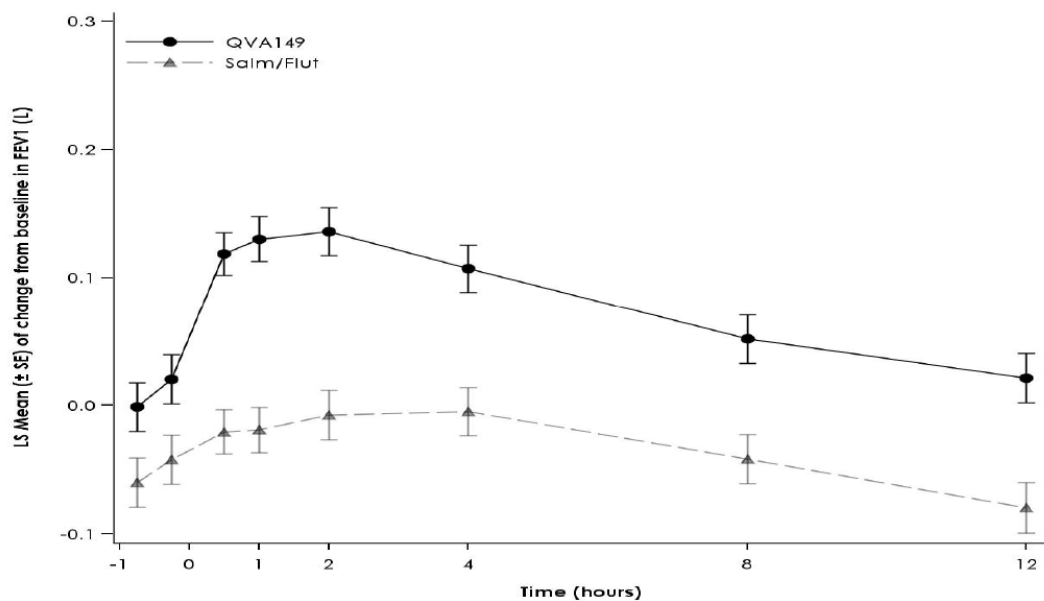
Figure 4 Profile of least squares mean change from baseline in FEV₁ (L) -45 min to 12 h at Week 12, Week 26, and Week 52 (Serial spirometry set)



Week 26



Week 52



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], at 64 weeks compared to tiotropium (-2.69, $p<0.001$) [SPARK], and at 52 weeks compared to fluticasone/salmeterol (-1.3, $p=0.003$) [FLAME]. In addition, improvements of the domains of the SGRQ score "symptoms", "activity" and "impact of daily life" were all statistically significant versus tiotropium at Week 64 ("symptoms": -3.06, $p=0.003$, "activity": -3.14, $p<0.001$, "impact of daily life": -2.24, $p=0.008$) [SPARK].

A higher percentage of patients receiving 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], 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], and at Week 52 compared to fluticasone/salmeterol (49.2% ULTIBRO BREEZHALER vs. 43.7% fluticasone/salmeterol, OR: 1.30, $p<0.001$) [FLAME].

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.

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

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

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

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

Use of rescue medication

Over 26 weeks, ULTIBRO BREEZHALER 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.

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

Exercise tolerance

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 significantly improved (250 mL, $p < 0.001$) compared to placebo. After three weeks of treatment, the improvement in inspiratory capacity with ULTIBRO BREEZHALER was greater (320 mL, $p < 0.001$) and exercise endurance time increased (59.5 seconds, $p = 0.006$) compared to placebo. 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 AUC_{0-24h} 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.

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 AUC_{0-24h}). 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 AUC_{0-24h}).

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 AUC_{0-24h}). 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.

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 (AUC_{0-24h}) 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.

Pharmaceutical information

Special precautions for storage

Do not store above 30°C. Protect from moisture.

ULTIBRO BREEZHALER must be kept out of the reach and sight of children.

Shelf life: the expiry date is indicated on the packaging.

Instructions for use and handling

For correct administration/use of the product please refer to section Dosage regimen and administration.

Pack size

Box, 3 blisters @ 10 capsules + 1 inhaler

Reg. No. DKI1897300767A1

ON MEDICAL PRESCRIPTION ONLY HARUS DENGAN RESEP DOKTER

Manufactured by Siegfried Barbera S.L., Barbera del Valles, Barcelona, Spain for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Product Information based on CDS v3.1 (23-Jun-2020).

ULTIBRO® BREEZHALER®

(kombinasi dosis tetap *indacaterol maleate* dan
glycopyrronium bromide)

serbuk inhalasi dalam kapsul

Informasi Produk untuk Pasien

(draf v1)

Berdasarkan BPL versi 3.1 (23-Jun-2020)

Bacalah seluruh brosur ini dengan saksama sebelum menggunakan obat ini.

Simpanlah brosur ini. Anda mungkin perlu membacanya kembali.

Jika Anda memiliki pertanyaan terkait dengan obat ini, tanyakan kepada dokter atau apoteker Anda.

Obat ini hanya diresepkan untuk Anda. Jangan memberikannya pada orang lain. Jangan menggunakan obat ini untuk mengobati penyakit lain.

Jika Anda mengalami efek samping, termasuk yang tidak tercantum pada brosur ini, hubungi dokter, apoteker, atau tenaga kesehatan Anda.

Daftar isi

- 1 Apa itu ULTIBRO™ BREEZHALER® dan apa kegunaannya
- 2 Apa yang perlu Anda ketahui sebelum dan ketika Anda menggunakan ULTIBRO BREEZHALER
- 3 Cara penggunaan ULTIBRO BREEZHALER
- 4 Efek samping yang mungkin terjadi
- 5 Cara penyimpanan ULTIBRO BREEZHALER
- 6 Isi kemasan dan informasi lainnya

INSTRUKSI PENGGUNAAN ALAT INHALASI ULTIBRO® BREEZHALER®

1 Apa itu ULTIBRO™ BREEZHALER® dan apa kegunaannya

Apa itu ULTIBRO BREEZHALER

ULTIBRO BREEZHALER mengandung zat aktif *indacaterol maleate* dan *glycopyrronium bromide*. *Indacaterol* adalah agonis adrenergik beta-2 dengan kerja panjang dan *glycopyrronium* adalah antagonis muskarinik dengan kerja panjang. Obat yang mengandung *indacaterol* dan *glycopyrronium* ini termasuk ke dalam golongan bronkodilator. Bronkodilator membantu membuka dan merelaksasi otot saluran pernapasan sehingga makin banyak udara yang masuk dan keluar paru-paru serta membantu mencegah napas pendek dan mengi.

Anda akan menggunakan alat yang disebut sebagai alat inhalasi atau *inhaler* (gunakan hanya alat inhalasi ULTIBRO BREEZHALER yang terdapat dalam kemasan). Dalam kemasan ini, Anda akan menemukan sebuah alat inhalasi dan kapsul (dalam *blister strip*) yang mengandung obat *indacaterol* dan *glycopyrronium bromide* dalam bentuk serbuk inhalasi. Alat inhalasi ULTIBRO BREEZHALER digunakan untuk menghirup obat yang terdapat di dalam kapsul tersebut.

Apa kegunaan ULTIBRO BREEZHALER

ULTIBRO BREEZHALER diindikasikan bagi penderita penyakit paru-paru yang disebut sebagai Penyakit Paru Obstruktif Kronik (PPOK):

- Untuk meringankan gejala dan mengurangi perburukan penyakit PPOK sedang hingga sangat berat bagi pasien yang masih merasakan gejala PPOK walaupun telah diobati dengan *indacaterol* saja, atau *glycopyrronium* saja, atau kombinasi salmeterol dan *fluticasone*.
- Untuk meringankan gejala penyakit PPOK sedang hingga berat bagi pasien yang masih merasakan gejala PPOK walaupun telah diobati dengan tiotropium saja.

Jika Anda menggunakan ULTIBRO BREEZHALER sekali sehari, hal tersebut akan membantu meringankan efek Penyakit Paru Obstruktif Kronik (PPOK) yang Anda rasakan setiap hari.

Bagaimana cara kerja ULTIBRO BREEZHALER

Pada Penyakit Paru Obstruktif Kronik (PPOK), otot-otot di sekeliling saluran napas akan mengencang, sehingga menyebabkan kesulitan bernapas. ULTIBRO BREEZHALER menghambat kontraksi otot saluran napas sehingga memudahkan udara untuk keluar dan masuk.

Jika Anda memiliki pertanyaan terkait dengan cara kerja ULTIBRO BREEZHALER atau alasan mengapa Anda diresepkan obat ini, tanyakan kepada dokter Anda.

2 Apa yang perlu Anda ketahui sebelum dan ketika Anda menggunakan ULTIBRO BREEZHALER

Ikuti seluruh petunjuk dokter dengan hati-hati. Hal tersebut mungkin berbeda dengan informasi umum yang terdapat dalam brosur ini.

Jangan gunakan ULTIBRO BREEZHALER

- **Jika Anda pernah mengalami reaksi alergi atau reaksi yang tidak biasa** terhadap zat aktif *indacaterol* atau *glycopyrronium* atau pun zat tambahan lain (“eksipien”) dari produk ini yang tertulis pada bagian akhir brosur.

Jika hal ini terjadi pada Anda, **hentikan penggunaan ULTIBRO BREEZHALER dan segera beri tahu dokter Anda.**

Jika Anda berpikir bahwa Anda mungkin alergi, tanyakan kepada dokter Anda.

Peringatan dan perhatian

Sebelum menggunakan ULTIBRO BREEZHALER, beri tahu dokter Anda jika Anda memiliki salah satu atau lebih kondisi berikut:

- Jika Anda memiliki penyakit asma (dalam hal ini Anda seharusnya tidak diberikan terapi dengan ULTIBRO BREEZHALER)
- Jika Anda memiliki masalah dengan jantung
- Jika Anda mengalami gangguan kejang-kejang
- Jika Anda mengalami masalah dengan kelenjar tiroid (*thyrotoxicosis*)
- Jika Anda menderita diabetes
- Jika Anda sedang menggunakan obat yang sejenis untuk pengobatan penyakit paru (lihat bagian “Penggunaan obat lain”)
- Jika Anda memiliki masalah dengan ginjal
- Jika Anda memiliki masalah yang berat dengan organ hati
- Jika Anda memiliki masalah dengan mata yang disebut sebagai glaukoma sudut sempit
- Jika Anda memiliki kesulitan dalam berkemih
- Jika Anda tidak responsif terhadap agonis beta₂-adrenergik
- Jika Anda memiliki masalah intoleransi galaktosa secara keturunan, defisiensi Lapp laktase atau malabsorpsi glukosa-galaktosa sehubungan dengan zat tambahan dari ULTIBRO BREEZHALER

Selama pengobatan menggunakan ULTIBRO BREEZHALER:

- **Hentikan penggunaan ULTIBRO BREEZHALER dan segera beri tahu dokter Anda** jika Anda mengalami beberapa gejala sebagai berikut:
 - Sesak di dada, batuk, mengi atau sesak napas segera setelah menggunakan ULTIBRO BREEZHALER (tanda-tanda bronkospasme/penyempitan saluran napas).
 - Kesulitan bernapas atau menelan, pembengkakan lidah, bibir, dan wajah, ruam kulit, gatal dan bentol (gejala reaksi alergi).
 - Sakit atau rasa tidak nyaman di mata, penglihatan kabur sementara, halusinasi pada penglihatan, dan adanya gambar-gambar berwarna yang diikuti dengan mata merah, (tanda-tanda dari serangan akut glaukoma sudut sempit).
- **Segera beri tahu dokter Anda** jika gejala PPOK Anda (sesak napas, mengi, batuk) tidak membaik atau bahkan memburuk setelah pengobatan.

ULTIBRO BREEZHALER digunakan sebagai pengobatan pemeliharaan untuk PPOK. Jangan menggunakan ULTIBRO BREEZHALER untuk pengobatan serangan sesak napas atau mengi yang terjadi secara tiba-tiba.

Penggunaan obat lain

Beri tahu dokter atau apoteker Anda jika Anda sedang atau pun belum lama menggunakan obat-obatan lain, termasuk penggunaan obat non-resep. Secara khusus, hal tersebut mencakup antara lain obat-obat di bawah ini:

- Obat-obatan yang digunakan untuk terapi depresi (misalnya antidepresan trisiklik, inhibitor monoamin oksidase)

- Obat-obatan penyakit paru yang memiliki zat aktif sejenis (kelas yang sama) dengan zat aktif ULTIBRO BREEZHALER (penggunaan obat-obat ini secara bersamaan dapat meningkatkan risiko kemungkinan terjadinya efek samping).
- Obat-obatan yang menurunkan kadar kalium dalam darah. Obat-obatan ini termasuk diuretik (dikenal sebagai “pil air” dan digunakan untuk terapi tekanan darah tinggi, contohnya: hidroklorotiazid), beberapa bronkodilator lain seperti metilxantin yang digunakan untuk pengobatan kesulitan bernapas (contoh: teofilin) atau steroid (contoh: prednisolon).
- Penghambat beta (*beta blocker*) yang biasa digunakan untuk terapi tekanan darah tinggi atau gangguan jantung lain (contoh: propranolol) atau terapi glaukoma (contoh: timolol).

Kehamilan dan menyusui

Tidak ada data penggunaan obat ini pada wanita hamil dan tidak diketahui apakah zat aktif obat ini masuk ke dalam air susu ibu.

Jika Anda sedang hamil, berpikir bahwa Anda mungkin hamil, atau sedang merencanakan kehamilan, atau sedang menyusui, diskusikan dengan dokter Anda apakah Anda dapat menggunakan ULTIBRO BREEZHALER. Anda tidak boleh menggunakan ULTIBRO BREEZHALER kecuali dokter Anda mengizinkan.

Tanyakan kepada dokter Anda sebelum Anda menggunakan obat apapun.

Dokter Anda akan menjelaskan kepada Anda mengenai potensi risiko jika Anda menggunakan ULTIBRO BREEZHALER selama kehamilan atau menyusui.

ULTIBRO BREEZHALER mengandung laktosa

Obat ini mengandung laktosa (23,5 mg per kapsul). Jika Anda tahu atau pernah diberi tahu oleh dokter bahwa Anda mengalami intoleransi gula, beri tahu dokter Anda sebelum menggunakan obat ini.

Tanyakan kepada dokter Anda sebelum Anda menggunakan obat apapun.

3 Cara penggunaan ULTIBRO BREEZHALER

Gunakan selalu obat ini sesuai dengan petunjuk dokter Anda. Tanyakan kepada dokter Anda jika Anda merasa tidak yakin.

Jangan gunakan ULTIBRO BREEZHALER melebihi rekomendasi dosis yang diresepkan oleh dokter Anda.

Berapa banyak ULTIBRO BREEZHALER yang harus digunakan

Dosis lazim obat ini adalah menghirup isi satu kapsul sekali sehari. Jangan gunakan melebihi dosis yang disarankan oleh dokter Anda.

Kapan Anda harus menggunakan ULTIBRO BREEZHALER

Anda hanya perlu menggunakan ULTIBRO BREEZHALER sekali sehari untuk membantu memudahkan Anda untuk bernapas karena obat ini bekerja selama 24 jam.

Menggunakan ULTIBRO BREEZHALER pada saat yang sama setiap hari akan memudahkan Anda untuk meminimalkan gejala yang terjadi pada waktu siang dan malam serta mengingat waktu penggunaannya.

Makanan dan minuman

Anda dapat menggunakan ULTIBRO BREEZHALER kapanpun, terlepas dari waktu makan/minum. Anda disarankan untuk menggunakan ULTIBRO BREEZHALER pada waktu yang sama setiap hari (lihat bagian “Kapan Anda harus menggunakan ULTIBRO BREEZHALER” di atas). Kapsul ULTIBRO BREEZHALER digunakan dengan cara dihirup menggunakan alat inhalasi (lihat “Instruksi Penggunaan Alat Inhalasi ULTIBRO BREEZHALER” yang terdapat pada bagian akhir brosur ini). **Jangan menelan kapsul ULTIBRO BREEZHALER.**

Pasien usia lanjut (75 tahun ke atas)

Jika Anda berusia 75 tahun ke atas, Anda tetap dapat menggunakan ULTIBRO BREEZHALER dengan dosis yang sama dengan dosis dewasa.

Pasien anak dan remaja (di bawah 18 tahun)

Jika Anda berusia kurang dari 18 tahun, Anda tidak boleh menggunakan ULTIBRO BREEZHALER.

Bagaimana cara menggunakan ULTIBRO BREEZHALER

Di dalam kemasan obat ini, Anda akan menemukan sebuah alat inhalasi dan kapsul (dalam *blister strip*) yang mengandung obat dalam bentuk serbuk inhalasi.

- Gunakan hanya alat inhalasi yang terdapat dalam kemasan obat ini (alat inhalasi ULTIBRO BREEZHALER) untuk menghirup serbuk dalam kapsul obat tersebut.
- **Jangan menelan kapsul.**
- Kapsul harus selalu disimpan di dalam blister strip dan dikeluarkan dari blister hanya ketika akan segera digunakan.
- Untuk membuka blister, sobek bagian foil (bagian belakang blister yang tipis). Jangan mendorong kapsul menembus kemasan.
- Jika Anda memulai penggunaan kemasan obat yang baru, gunakan alat inhalasi ULTIBRO BREEZHALER yang terdapat pada kemasan baru tersebut.
- Buanglah setiap alat inhalasi setelah digunakan selama 30 hari.

Pastikan Anda membaca instruksi cara penggunaan alat inhalasi ULTIBRO BREEZHALER yang terdapat pada bagian akhir brosur ini.

Berapa lama penggunaan ULTIBRO BREEZHALER

Tetap gunakan ULTIBRO BREEZHALER selama dokter Anda masih menyarankannya.

PPOK merupakan penyakit jangka panjang dan Anda disarankan untuk menggunakan ULTIBRO BREEZHALER setiap hari, tidak hanya pada saat Anda mengalami kesulitan bernapas atau mengalami gejala-gejala PPOK.

Jika Anda memiliki pertanyaan mengenai berapa lama penggunaan ULTIBRO BREEZHALER, tanyakan kepada dokter atau apoteker Anda.

Jika Anda menggunakan ULTIBRO BREEZHALER lebih dari yang seharusnya

Jika Anda menggunakan terlalu banyak ULTIBRO BREEZHALER atau jika ada seseorang yang tidak sengaja menggunakan obat Anda, segera hubungi dokter atau rumah sakit. Tunjukkan kemasan ULTIBRO BREEZHALER. Perhatian medis mungkin diperlukan.

Jika Anda lupa menggunakan ULTIBRO BREEZHALER

Jika Anda lupa menggunakan satu dosis pada waktu yang biasa Anda menggunakan obat, gunakanlah sesegera mungkin satu dosis yang terlewat tersebut pada hari itu. Kemudian, gunakan dosis obat di hari berikutnya pada waktu yang biasa. Jangan menggunakan dua dosis obat (dosis ganda) pada satu hari yang sama.

4 Efek samping yang mungkin terjadi

Seperti pada penggunaan semua obat, pasien yang menggunakan ULTIBRO BREEZHALER dapat mengalami efek samping, walaupun tidak semua pasien akan mengalaminya.

Beberapa efek samping yang dapat menjadi serius

Jika Anda mengalami efek samping yang serius, **hentikan penggunaan obat ini dan segera hubungi dokter Anda.**

Umum: *dapat dialami hingga 1 dari setiap 10 pasien*

- Rasa haus berlebih, volume urin (air kemih) yang tinggi, meningkatnya nafsu makan yang disertai dengan penurunan berat badan, rasa lelah (hal ini dapat merupakan gejala tingginya kadar gula dalam darah yang disebut sebagai hiperglikemia).
- Kesulitan bernapas atau menelan, bengkak pada lidah, bibir dan wajah, ruam kulit, gatal-gatal (hal ini dapat merupakan gejala/tanda-tanda reaksi alergi).

Tidak umum: *dapat dialami hingga 1 dari setiap 100 pasien*

- Perubahan penglihatan, peningkatan tekanan mata, penglihatan yang buram untuk sementara, melihat bundaran/lingkaran putih atau gambar berwarna yang disertai mata merah (hal ini dapat merupakan tanda-tanda glaukoma).

- Nyeri dada yang disertai dengan peningkatan produksi keringat (tanda kurangnya suplai darah dan oksigen ke jantung dan dapat merupakan gangguan jantung serius seperti penyakit jantung iskemik).
- Detak jantung yang tidak beraturan.
- Kesulitan bernapas yang disertai dengan bersin dan batuk (tanda penyempitan saluran napas).

Tidak diketahui frekuensinya: *frekuensi tidak dapat diestimasi dari data yang ada*

- Terjadi pembengkakan terutama pada lidah, bibir, wajah dan tenggorokan (hal ini dapat merupakan tanda-tanda angioedema).

Efek samping lainnya yang mungkin terjadi

Efek samping lainnya tertera pada daftar di bawah ini. Jika efek samping ini bertambah parah, beri tahu dokter, apoteker atau tenaga kesehatan Anda.

Sangat Umum: *dapat dialami pada lebih dari 1 dari 10 pasien*

- Hidung tersumbat, bersin, batuk, sakit kepala dengan atau tanpa demam (hal ini dapat merupakan gejala-gejala infeksi saluran napas atas).

Umum: *dapat dialami hingga 1 dari setiap 10 pasien*

- Kombinasi dari sakit tenggorokan, dan hidung berair (hal ini dapat merupakan gejala/tanda-tanda nasofaringitis).
- Infeksi saluran kemih: nyeri saat buang air kecil dan sering buang air kecil (hal ini dapat merupakan gejala/tanda infeksi saluran kemih yang disebut sistitis).
- Merasa tertekan atau nyeri pada pipi dan dahi (kemungkinan gejala sinusitis atau kongesti sinus).
- Hidung berair atau tersumbat.
- Pusing.
- Sakit kepala.
- Batuk.
- Sakit tenggorokan.
- Rasa tidak nyaman pada perut, gangguan pencernaan.
- Gigi berlubang.
- Demam.
- Nyeri dada.
- Kesulitan dan nyeri ketika buang air kecil (hal ini dapat merupakan gejala dari obstruksi kandung kemih atau retensi urin).

Tidak umum: *dapat terjadi hingga 1 dari 100 pasien.*

- Nyeri otot, ligamen, tendon, sendi, dan tulang.
- Sulit tidur.
- Detak jantung cepat.
- Palpitasi (gejala detak jantung yang abnormal).
- Mulut kering.

- Gatal-gatal atau ruam kulit.
- Kejang otot.
- Nyeri/sakit pada otot.
- Hidung berdarah.
- Bengkak pada tangan, pergelangan kaki, dan kaki.
- Rasa kelelahan.
- Mual, muntah, diare dan nyeri perut/abdomen (kemungkinan gejala dari gastroenteritis).
- Nyeri pada ekstremitas/bagian ujung tubuh (seperti lengan atau kaki).

Jarang: *dapat terjadi hingga 1 pada setiap 1000 pasien*

- Rasa kesemutan atau mati rasa, penurunan sensitivitas kulit.

Tidak diketahui frekuensinya: *frekuensi tidak dapat diestimasi dari data yang ada*

- Perubahan suara atau serak (parau)

Jika Anda mengalami efek samping, termasuk yang belum tercantum pada brosur ini, beri tahu dokter, apoteker, atau tenaga kesehatan Anda.

5 Cara penyimpanan ULTIBRO BREEZHALER

- Jangan gunakan obat setelah tanggal kedaluwarsa yang tercantum pada kemasan.
- Simpan obat pada suhu tidak lebih dari 30°C.
- Simpan obat di dalam kemasannya agar terlindung dari kelembapan. Jangan mengeluarkan kapsul dari blister kecuali ketika akan segera digunakan.
- Jauhkan obat ini dari jangkauan dan penglihatan anak-anak.
- Setiap alat inhalasi harus dibuang setelah 30 hari penggunaan.
- Jangan gunakan obat jika kemasannya rusak atau menunjukkan adanya cacat.

Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak Anda gunakan.

6 Isi kemasan dan informasi lainnya

Apakah kandungan ULTIBRO BREEZHALER

Zat aktif ULTIBRO BREEZHALER adalah *indacaterol maleate* dan *glycopyrronium bromide*. Tiap kapsul mengandung 143 mikrogram *indacaterol maleate* setara dengan 110 mikrogram *indacaterol* dan 63 mikrogram *glycopyrronium bromide* setara dengan 50 mikrogram *glycopyrronium*. Dosis yang dihantarkan (dosis yang keluar dari mulut inhaler dan dihisap pasien) sebanding dengan 85 mikrogram *indacaterol* dan 43 mikrogram *glycopyrronium*.

Zat tambahan (atau yang disebut “eksipien”) ULTIBRO BREEZHALER adalah:

- Isi kapsul: laktosa monohidrat, magnesium stearat.
- Komponen cangkang kapsul: hipromelosa, air terpurifikasi, karagenan, kalium klorida, *FD&C Yellow5/Tartrazine*.

Bagaimana bentuk dari ULTIBRO BREEZHALER dan isi kemasannya

Di dalam kemasannya, Anda akan menemukan sebuah alat inhalasi beserta kapsul dalam blister strip.

Kapsul berwarna kuning transparan pada bagian tutup kapsul dan transparan natural pada bagian badan kapsul, mengandung serbuk berwarna putih. Pada kapsul terdapat kode produk “IGP110.50” berwarna biru yang tercetak di bawah dua garis biru pada badan kapsul dan logo perusahaan berwarna hitam (b) yang tercetak pada bagian tutup kapsul.

Kemasan

Dus, 3 blister @ 10 kapsul + 1 inhaler

No. Reg.: DK11897300767A1

HARUS DENGAN RESEP DOKTER

Pemegang Nomor Ijin Edar

PT Novartis Indonesia

Pabrik pembuat

Diproduksi oleh Siegfried Barbera S.L., Barbera del Valles, Barcelona, Spanyol untuk Novartis Pharma AG, Basel, Swiss.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Jika Anda memiliki pertanyaan mengenai obat ini, tanyakan kepada dokter atau apoteker Anda.

Informasi Produk untuk Pasien berdasarkan BPL versi 3.1 (23-Jun-2020).

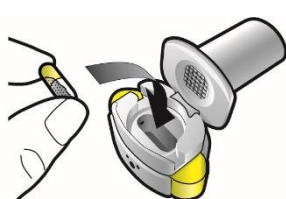
INSTRUKSI PENGGUNAAN ALAT INHALASI ULTIBRO® BREEZHALER®

Bagian akhir brosur ini menjelaskan mengenai cara penggunaan alat inhalasi ULTIBRO BREEZHALER. . Bacalah dan ikuti seluruh instruksi penggunaan ini dengan saksama.

Lihat juga bagian **3. Bagaimana cara menggunakan ULTIBRO BREEZHALER** pada brosur ini.

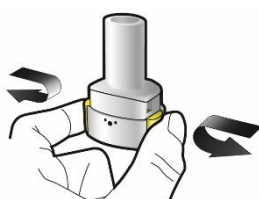
Jika Anda memiliki pertanyaan, **tanyakan kepada dokter atau apoteker Anda.**

Bacalah **seluruh Instruksi Penggunaan** sebelum Anda menggunakan ULTIBRO BREEZHALER.



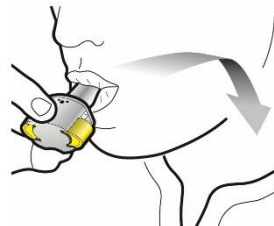
Masukkan kapsul

1



Tekan dan lepas

2



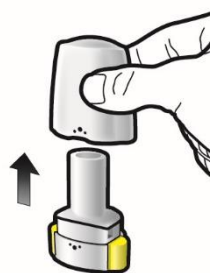
Bernapaslah dengan dalam

3

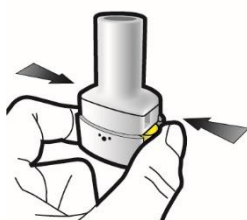


Periksa apakah kapsul sudah kosong

Periksa



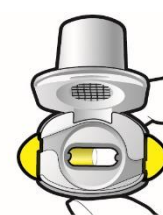
Langkah 1a:
Buka penutup *inhaler*



Langkah 2a:
Lubangi kapsul sekali dengan alat
Pegang *inhaler* menghadap ke atas.
Lubangi kapsul dengan cara menekan kuat kedua tombol yang ada di sisi samping *inhaler* pada waktu yang bersamaan. Anda akan mendengar



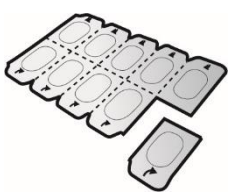
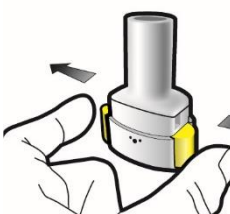
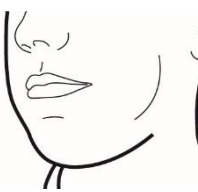
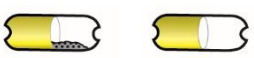
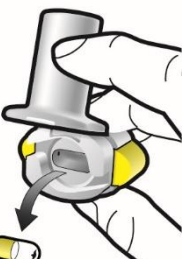
Langkah 3a:
Hembuskan napas secara penuh
Jangan menghembuskan napas ke dalam *inhaler*.

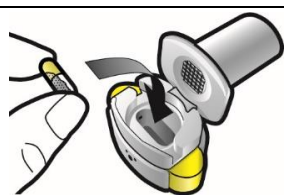


Periksa apakah kapsul sudah kosong

Buka *inhaler* untuk melihat apakah masih ada serbuk obat yang tertinggal dalam kapsul. Jika masih ada serbuk yang tersisa dalam kapsul:

- Tutup kembali *inhaler*.
- Ulangi Langkah 3a

 Langkah 1b: Buka <i>inhaler</i>-nya  Langkah 1c: Keluarkan kapsul dari blister Pisahkan satu bagian blister yang berisi satu kapsul. Buka (sobek) bagian belakang (foil) dan keluarkan kapsulnya. <u>Jangan mengeluarkan kapsul dari dalam foil dengan cara mendorong kapsul sehingga menembus foil.</u> <u>Jangan menelan kapsul (lihat instruksi selanjutnya).</u>	bunyi saat kapsul dilubangi. <u>Lubangi kapsul hanya sekali.</u>  Langkah 2b: Lepaskan kedua tombol samping	 Langkah 3b: Hirup obat secara dalam Pegang <i>inhaler</i> tanpa menekan tombol sampingnya, seperti yang ditunjukkan pada gambar. Masukkan corong <i>inhaler</i> ke dalam mulut Anda dan tutup rapat dengan menggunakan bibir Anda. <u>Jangan menekan tombol samping pada saat memegang <i>inhaler</i>.</u> Bernapaslah dengan cepat dan dalam semampu Anda. Selama inhalasi, Anda akan mendengar bunyi mendesing. Anda juga mungkin merasakan obat ini selama Anda menghirupnya.  Langkah 3c: Tahan napas Anda Tahan napas Anda selama 5 detik.	hingga 3c.  Serbuk masih tertinggal Kosong  Keluarkan kapsul yang telah kosong Buang kapsul yang telah kosong pada tempat pembuangan limbah rumah tangga Anda. Tutup <i>inhaler</i> dan pasang kembali penutup alat.
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Langkah 1d:

Masukkan kapsul ke dalam *inhaler*

Jangan memasukkan kapsul langsung pada corong mulut *inhaler*.



Langkah 1e:

Tutup *inhaler*

Membersihkan *inhaler*

Gosok corong mulut bagian dalam dan luar dengan sebuah kain yang bersih, kering, bebas serat untuk menghilangkan serbuk-serbuk yang mungkin masih tertinggal. Jaga *inhaler* tetap kering. Jangan mencuci *inhaler* dengan air.

Membuang *inhaler*

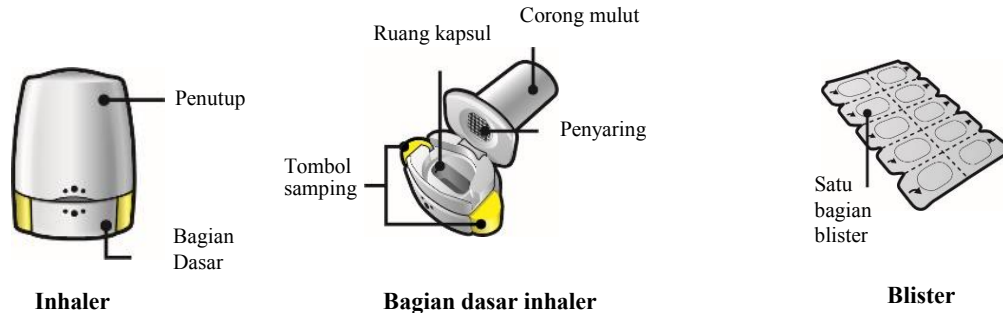
Buang *inhaler* ketika seluruh kapsul yang terdapat dalam kemasan obat telah habis digunakan. Tanyakan kepada apoteker Anda terkait bagaimana cara membuang obat dan alat inhalasi (*inhaler*) yang tidak lagi Anda gunakan.

Informasi Penting

- Kapsul ULTIBRO BREEZHALER harus selalu disimpan pada blister dan hanya dikeluarkan ketika akan segera digunakan.
- Jangan mendorong kapsul menembus foil untuk mengeluarkannya dari blister.
- Jangan menelan kapsul.
- Jangan menghirup kapsul ULTIBRO BREEZHALER menggunakan alat inhalasi lain.
- Jangan menggunakan alat inhalasi ULTIBRO BREEZHALER untuk menghirup obat lain.
- Jangan meletakkan kapsul pada mulut Anda atau pada corong mulut *inhaler*.
- Jangan menekan tombol samping *inhaler* lebih dari sekali.
- Jangan meniup atau menghembuskan napas ke dalam corong mulut *inhaler*.
- Jangan menekan tombol samping *inhaler* ketika sedang bernapas/menghirup obat menggunakan *inhaler*.
- Jangan memegang kapsul dengan tangan basah.
- Jangan mencuci alat/*inhaler* Anda dengan air.

Kemasan (satu dus obat) ULTIBRO BREEZHALER berisi:

- Satu alat inhalasi (*inhaler*) ULTIBRO BREEZHALER
- Tiga kartu blister (atau secara singkat disebut “blister”) dimana masing-masing kartu blister berisi 10 kapsul ULTIBRO BREEZHALER.



Pertanyaan yang Sering Diajukan

Mengapa *inhaler* tidak mengeluarkan bunyi ketika saya sedang menghirup obat?

Kemungkinan kapsul macet/tertahan di dalam ruang kapsul. Jika hal ini terjadi, cobalah bebaskan kapsul dengan cara mengetuk bagian dasar *inhaler* secara hati-hati. Hirup kembali obat dengan mengulangi Langkah 3a hingga 3c.

Apa yang saya harus lakukan jika masih terdapat serbuk yang tertinggal di dalam kapsul?

Jika hal tersebut terjadi, Anda mungkin belum mendapatkan dosis obat yang cukup. Tutuplah kembali *inhaler* dan ulangi Langkah 3a hingga 3c.

Saya batuk setelah menghirup obat – apakah hal ini berpengaruh?

Hal ini mungkin terjadi. Namun, selama kapsul sudah kosong, Anda telah mendapatkan dosis obat yang cukup.

Saya merasakan beberapa partikel kecil kapsul di dalam mulut saya – apakah hal ini bermasalah?

Hal ini mungkin terjadi, namun tidak membahayakan. Kemungkinan kapsul pecah menjadi partikel-partikel kecil dapat meningkat apabila Anda melubangi kapsulnya (menekan tombol samping *inhaler*) lebih dari sekali.