UNILAB

Indacaterol maleate + Glycopyrronium bromide

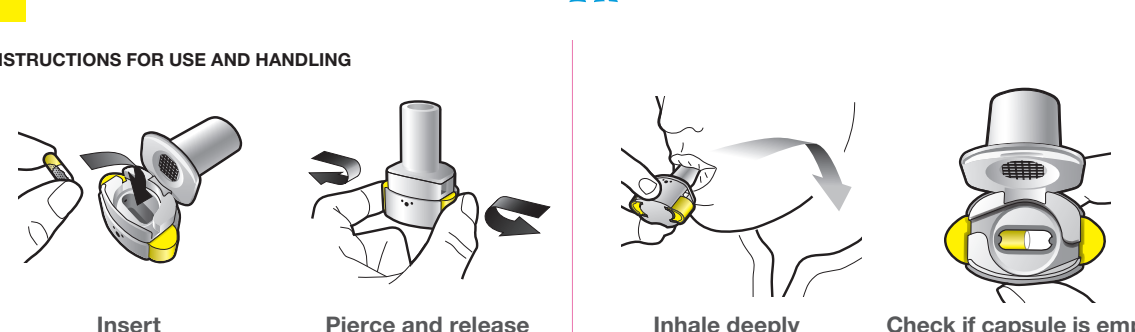
Glycoair® Breezhaler®

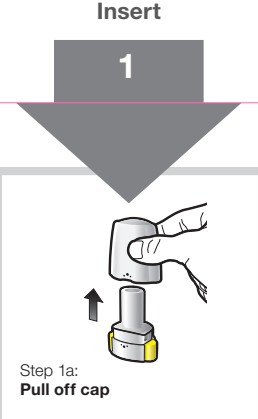
110 mcg/50 mcg Pre-metered Dose Dry Powder for Inhalation
Adrenergic-Anticholinergic Combination

Rx

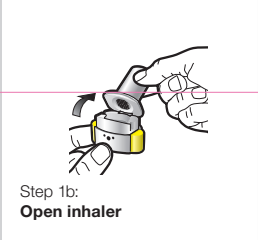
1143317-A23-PH

INSTRUCTIONS FOR USE AND HANDLING

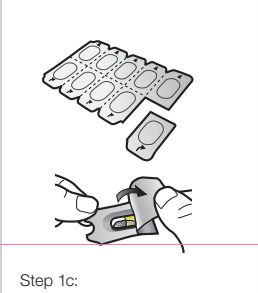




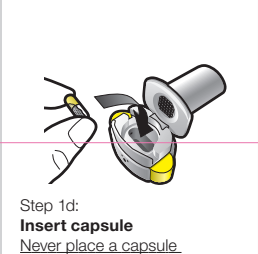
Step 1a:
Pull off cap



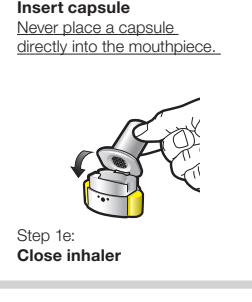
Step 1b:
Open inhaler



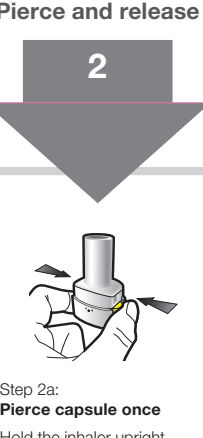
Step 1c:
Remove capsule
Separate one of the blisters from the blister card.
Peel open the blister and remove the capsule.
Do not push the capsule through the foil.
Do not swallow the capsule.



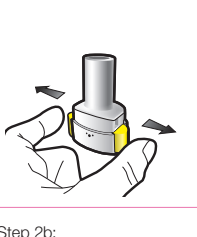
Step 1d:
Insert capsule
Never place a capsule directly into the mouthpiece.



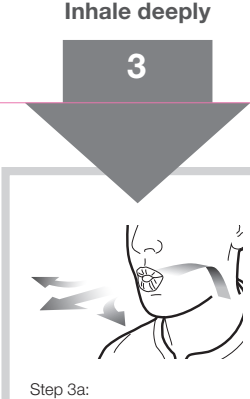
Step 1e:
Close inhaler



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



Step 2b:
Release side buttons

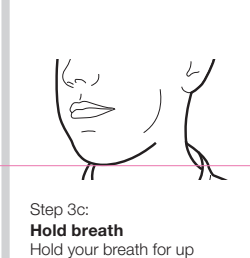


Step 3a:
Breathe out fully
Do not blow into the inhaler.

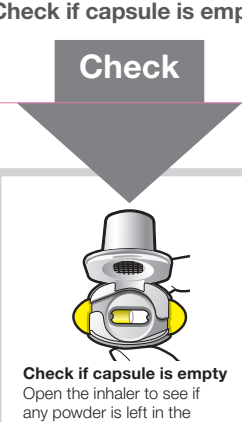


Step 3b:
Inhale medicine deeply
Hold the inhaler as shown in the picture.
Place the mouthpiece in your mouth and close your lips firmly around it.
Do not press the side buttons.

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



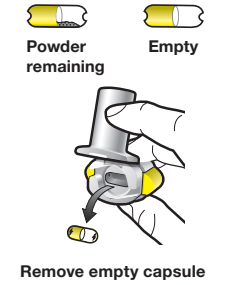
Step 3c:
Hold breath
Hold your breath for up to 5 seconds.



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

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

Powder remaining **Empty**



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

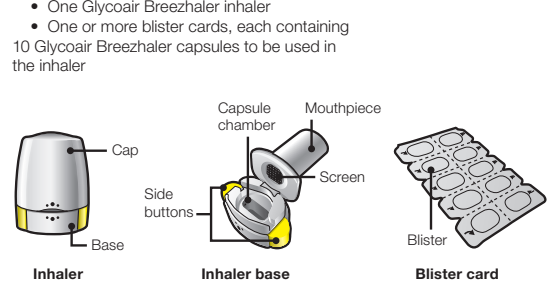
Close the inhaler and replace the cap.

Important Information

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

Your Glycoair Breezhaler Inhaler pack contains:

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



Frequently Asked Questions

Why didn't the inhaler make a noise when I inhaled?
The capsule may be stuck in the capsule chamber. If this happens, carefully loosen the capsule by tapping the base of the inhaler. Inhale the medicine again by repeating steps 3a to 3c.

What should I do if there is powder left inside the capsule?
You have not received enough of your medicine. Close the inhaler and repeat steps 3a to 3c.

I coughed after inhaling – does this matter?
This may happen. As long as the capsule is empty you have received enough of your medicine.

I felt small pieces of the capsule on my tongue – does this matter?
This can happen. It is not harmful. The chances of the capsule breaking into small pieces will be increased if the capsule is pierced more than once.

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

Disposing of the inhaler after use
Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

UNILAB

Indacaterol maleate + Glycopyrronium bromide

Glycoair® Breezhaler®

110 mcg/50 mcg Pre-metered Dose Dry Powder for Inhalation
Adrenergic-Anticholinergic Combination

DESCRIPTION AND COMPOSITION

Pharmaceutical form
Indacaterol/glycopyrronium 110/50 microgram, inhalation powder in hard capsules.
Transparent yellow cap and transparent body capsules containing a white to practically white powder, with the product code "IGP110.50" printed in blue under two blue bars on the body and logo printed in black on the cap.

Active substance
Each capsule contains 143 micrograms indacaterol maleate equivalent to 110 micrograms indacaterol and 63 micrograms glycopyrronium bromide equivalent to 50 micrograms glycopyrronium.
The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 85 micrograms indacaterol and 43 micrograms glycopyrronium.

Excipients
Capsule fill: Lactose monohydrate, magnesium stearate.
Capsule shell components: Hypromellose, purified water, carrageenan, potassium chloride, FD&C Yellow5/Tartrazine.

INDICATIONS

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

DOSAGE REGIMEN AND ADMINISTRATION

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

Special populations

Renal impairment
Indacaterol/glycopyrronium can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. See also sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY.

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

Pediatric patients (below 18 years)
Indacaterol/glycopyrronium should not be used in patients under 18 years of age.

Geriatric patients (75 years or above)
Indacaterol/glycopyrronium can be used at the recommended dose in elderly patients 75 years of age and older.

Method of administration
Indacaterol/glycopyrronium capsules must be administered only by the oral inhalation route and only using the Breezhaler® inhaler. Capsules must not be swallowed (see also section OVERDOSAGE).
It should be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.
Capsules must always be stored in the blister to protect from moisture, and only removed IMMEDIATELY BEFORE USE (see also section STORAGE).
When prescribing indacaterol/glycopyrronium 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

Patients with hypersensitivity to indacaterol or glycopyrronium, which are components of indacaterol/glycopyrronium, or to any of the excipients.

WARNINGS AND PRECAUTIONS

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

Asthma
Indacaterol/glycopyrronium should not be used for the treatment of asthma due to the absence of data in this indication.
Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

Not for acute use
Indacaterol/glycopyrronium 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 indacaterol/glycopyrronium. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, it should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm
As with other inhalation therapy, administration of indacaterol/glycopyrronium may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, treatment should be discontinued immediately and alternative therapy instituted.

Anticholinergic effects related to glycopyrronium
Like other anticholinergic containing drugs, indacaterol/glycopyrronium should be used with caution in patients with narrow-angle glaucoma or urinary retention. Patients should be advised about signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using it and to contact their doctor immediately should any of these signs or symptoms develop.

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

Systemic effects of beta-agonists
Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of indacaterol/glycopyrronium at the recommended dose, as with other compounds containing a $beta_2$-adrenergic agonist, it should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to $beta_2$-adrenergic agonists.
As with other drugs containing an inhaled $beta_2$-adrenergic agonist, it should not be used more often or at higher doses than recommended.

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

Hypokalemia with beta-agonists
$Beta_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see section INTERACTIONS) which may increase the susceptibility to cardiac arrhythmias.
Clinically relevant effects of hypokalemia have not been observed in clinical studies of indacaterol/glycopyrronium at the recommended therapeutic dose (see section CLINICAL PHARMACOLOGY).

Hyperglycemia with beta-agonists
Inhalation of high doses of $beta_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with indacaterol/glycopyrronium, plasma glucose should be monitored more closely in diabetic patients. During long-term clinical studies ([ENLIGHTEN] and [RADIATE]), more patients on indacaterol/glycopyrronium experienced clinically notable changes in blood glucose (4.9%) than on placebo (2.7%). It has not been investigated in patients for whom diabetes mellitus is not well controlled.

ADVERSE DRUG REACTIONS

The presentation of the safety profile is based on the experience with combination indacaterol/glycopyrronium and the individual monotherapy components.

Summary of the safety profile
The safety experience was comprised of exposure of up to 15 months at the recommended therapeutic dose (110/50 microgram).
The Phase III clinical development program consisted of 11 studies and enrolled over 10000 patients with a clinical diagnosis of moderate to very severe COPD. Safety data from 9 of these studies with treatment durations of 4 weeks or longer pooled from 4352 patients exposed to indacaterol/glycopyrronium 110/50 microgram once-daily.
The safety profile was characterized by typical anticholinergic and beta-adrenergic symptoms related to the individual monotherapy components of the combination. Other most common adverse drug reactions related to the drug product (≥3% and greater than placebo) were headache, cough and nasopharyngitis.
At the recommended dose, the adverse drug reaction profile in patients with COPD showed clinically insignificant systemic effects of $beta_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per min, and tachycardia was infrequent and reported at a lower rate than with placebo. Relevant prolongations of QTcF were not detectable in comparison to placebo. The frequency of notable QTcF 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 studies of 6 and 12 months in duration. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000, <1/1,000); and very rare (<1/10,000).
Combination indacaterol/glycopyrronium showed similar adverse drug reactions as the individual monotherapy components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of the monotherapy components may be expected in the combination.

Table 1 Kaplan-Meier cumulative incidence (%) of 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 (0.32, 1.41)	0.78 (0.29, 2.12)	Uncommon
Atrial fibrillation	0.8 (0.33, 1.95)	0.24 (0.03, 1.68)	Uncommon
Tachycardia	0.39 (0.15, 1.04)	0.7 (0.29, 1.66)	Uncommon
Palpitations	0.73 (0.34, 1.56)	1.38 (0.68, 2.80)	Uncommon
Respiratory, thoracic and mediastinal disorders			
Cough	6.84 (5.38, 8.68)	5.94 (4.30, 8.17)	Common
Oropharyngeal pain incl throat irritation	2.95 (2.05, 4.23)	2.71 (1.70, 4.29)	Common
Epistaxis	0.28 (0.09, 0.85)	0.24 (0.03, 1.68)	Uncommon
Paradoxical bronchospasm	0.18 (0.05, 0.73)	0.51 (0.16, 1.64)	Uncommon
Gastrointestinal disorders			
Dyspepsia	2.29 (1.49, 3.51)	2.25 (1.32, 3.81)	Common
Dental caries	1.39 (0.79, 2.44)	0.97 (0.43, 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
Fatigue	0.83 (0.41, 1.68)	0.54 (0.20, 1.43)	Uncommon

Of the 1106 patients on indacaterol/glycopyrronium, 946 (86%) were exposed for at least 26 weeks, and 447 (40%) were exposed for at least 52 weeks. Of the 748 patients on placebo, 588 (79%) were exposed for at least 26 weeks, and 339 (45%) were exposed for at least 52 weeks.
*adverse drug reaction observed with the combination indacaterol/glycopyrronium but not with the monotherapy components.

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

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

Immune system disorders	
Angioedema	
Respiratory, thoracic and mediastinal disorders	
Dysphonia	

Description of selected adverse drug reactions
The most common anticholinergic adverse event was dry mouth (0.64% versus 0.45% for placebo), however, this adverse event was reported at a lower frequency with indacaterol/glycopyrronium combination than with glycopyrronium monotherapy. The majority of the reports of dry mouth were suspected to be drug related and of mild degree, none was severe. Cough was common, but usually of mild intensity.
Some serious adverse events, including hypersensitivity and ischemic heart disease, have been reported as ADRs for indacaterol administered as monotherapy. The reported frequencies for indacaterol/glycopyrronium for hypersensitivity and ischemic heart disease were 2.06% versus 1.9% for placebo and 0.67% versus 0.78% for placebo, respectively.

INTERACTIONS

Interactions linked to the indacaterol/glycopyrronium
Concomitant administration of orally inhaled indacaterol and glycopyrronium under steady-state conditions of both drugs did not affect the pharmacokinetics (PK) of either drug.
No specific drug-drug interaction studies were conducted. Information on the potential for interactions is based on the potential for each of its two monotherapy components.

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

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

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

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

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

Metabolic and transporter based drug interactions
Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, raises the systemic exposure of indacaterol by up to two-fold. 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 2-fold increase in AUC and 1.5-fold increase in C_{max}. Coadministration of erythromycin resulted in an increase in AUC of 1.4- to 1.6-fold and for C_{max} of 1.2 fold. 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 up to 600 microgram.

Interactions linked to glycopyrronium
In vitro studies showed that glycopyrronium is not likely to inhibit or induce the metabolism of other drugs, or processes involving drug transporters. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see section CLINICAL PHARMACOLOGY – Biotransformation/metabolism and elimination). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

Anticholinergics
The co-administration of indacaterol/glycopyrronium with other anticholinergic-containing drugs has not been studied and is therefore, not recommended.

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy
Risk Summary
There are no adequate and well-controlled studies 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 during either inhalation embryo-fetal development study in rats. Indacaterol and glycopyrronium were not teratogenic in rats or rabbits following subcutaneous and inhalation administration respectively.
The potential risk for humans is unknown. Therefore, indacaterol/glycopyrronium should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Clinical Considerations
Labor and delivery
Information related to indacaterol
Like other $beta_2$-adrenergic agonist containing drugs, Indacaterol may inhibit labor due to a relaxant effect on uterine smooth muscle.
Information related to glycopyrronium
In pregnant women undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide, the umbilical plasma concentration of glycopyrronium in the umbilical venous (0.28 (0.25) ng/mL) and in the umbilical arterial (0.18 (0.11) ng/mL) plasma were low (clinically insignificant).

Data
Animal data
Indacaterol: Adverse effects with respect to pregnancy and embryonal/fetal development could only be demonstrated in rabbits following subcutaneous application at doses more than 500-fold than achieved following the daily inhalation of 150 microgram in humans (based on AUC0-24h).
Glycopyrronium: Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Fertility and pre- and post-natal development were not considerably affected in rats. Glycopyrronium and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Published data for glycopyrronium in animals do not indicate any reproductive toxicity issues.

Lactation
It is not known whether indacaterol and/or glycopyrronium pass 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. Glycopyrronium reached up to 10-fold higher concentrations in the milk of lactating rats than in the blood of the dam after intravenous administration. The use of indacaterol/glycopyrronium by breastfeeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Females and males of reproductive potential
There are no special recommendations.

Infertility
Information related to indacaterol and glycopyrronium
Reproduction studies or other data in animals did not indicate a concern regarding fertility in either males or females.

OVERDOSAGE

Information related to indacaterol/glycopyrronium
In a single dose study in healthy volunteers the 4-fold of the therapeutic dose of indacaterol/glycopyrronium 110/50 microgram, administered in 4 inhalations separated by one hour, each, was well tolerated with no increase in heart rate, QTc interval, serum potassium or blood glucose.
In COPD patients, doses of up to 600/100 microgram were inhaled over two weeks and were well tolerated with only minor effects on heart rate, QTc interval, blood glucose or serum potassium. There was an increase in ventricular ectopics after 14 days of dosing with 300/150 and 600/100 microgram indacaterol/glycopyrronium, but low prevalence and small patient numbers (N=49 and N=51 for 600/100 microgram and 300/100 microgram indacaterol/glycopyrronium, respectively) did not 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 $beta_2$-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 $beta_2$-adrenergic effects, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

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

CLINICAL PHARMACOLOGY

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

Indacaterol
The pharmacological effects of $beta_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. In vitro studies have shown that indacaterol has more than 24-fold greater agonist activity at $beta_2$-receptors compared to $beta_1$-receptors and 20-fold greater agonist activity compared to $beta_3$-receptors. This selectivity profile is similar to formoterol.
When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human $beta_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.
Although $beta_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the human heart, there are also $beta_2$-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of $beta_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-adrenergic agonists may have cardiac effects.

Glycopyrronium
Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) for once-daily maintenance bronchodilator treatment of COPD. Parasympathetic nerves are the major bronchoconstrictive neural pathway in airways, and cholinergic tone is the key reversible component of airflow obstruction in COPD. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.
Of the five known muscarinic receptor subtypes (M_{1-5}), only subtypes M_{1-3} have a defined physiological function in the human lung. Glycopyrronium bromide is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M_3 and M_1 receptors over the human M_2 receptor in competition binding studies. It has a rapid onset of action as evidenced by observed receptor association/dissociation kinetic parameters and the onset of action after inhalation in clinical studies.
The long duration of action can be partly attributed to sustained drug concentrations in the lungs as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the inhaler in contrast to the half-life after i.v. administration (see section CLINICAL PHARMACOLOGY – Pharmacokinetics (PK)). Pharmacokinetic data in the lungs in rats following inhalation of glycopyrronium bromide provides further evidence for this.

Pharmacodynamics (PD)
Primary pharmacodynamic effects
Indacaterol/glycopyrronium
The combination of indacaterol and glycopyrronium showed a rapid onset of action within 5 minutes after dosing (see section CLINICAL STUDIES, Table 4). The effect remains constant over the whole 24 h dosing interval (see section CLINICAL STUDIES, Figures 1 and 2).
The mean bronchodilator effect derived from serial FEV_1 measurements over 24 hours was 320 mL after 26 weeks of treatment. The effect was significant greater for indacaterol/glycopyrronium compared to indacaterol, glycopyrronium or tiotropium alone (difference 110 mL, for each comparison).
There was no evidence for tachyphylaxis to the effect of indacaterol/glycopyrronium over time compared to placebo or its monotherapy components.

Secondary pharmacodynamic effects
The systemic side effects of inhaled $beta_2$-adrenergic agonists and inhaled muscarinic receptor antagonists result from activation of systemic $beta_2$-adrenergic receptors and blockade of muscarinic receptors after systemic absorption of the drugs. The side effect profile of indacaterol/glycopyrronium was explored in healthy volunteers and in COPD patients.

Effects on heart rate
Heart rate effects in healthy volunteers were investigated after a single dose of 4-times the therapeutic dose of indacaterol/glycopyrronium administered in four dosing steps separated by one hour and compared to the effects of placebo, 440/200 microgram indacaterol/glycopyrronium, 600 microgram indacaterol and 200 microgram glycopyrronium.
The largest time matched heart rate increase compared to placebo was +5.69 bpm, the largest decrease was -2.51 bpm. Overall the effect on heart rate over time did not show a consistent PD effect.
Heart rate in COPD patients at supratherapeutic dose levels was investigated up to 600/100 microgram. There were no relevant effects on mean heart rate over 24 hours 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 microgram did not demonstrate a clinically relevant effect on the QT-interval. Also for glycopyrronium, no QT prolongation has been observed in a TQT study after an inhaled dose of 400 microgram.
The effects on QTc-interval were investigated in healthy volunteers after inhalation of indacaterol/glycopyrronium up to 440/200 microgram in four dose steps separated by one hour. The largest time matched difference versus placebo was -2.71 ms (90% CI: -6.97, 1.54 ms), indicating that it had no relevant impact on QT-interval.

Serum potassium and blood glucose
In healthy volunteers, after administration of 440/200 microgram indacaterol/glycopyrronium, 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.

Pharmacokinetics (PK)
Absorption
Indacaterol/glycopyrronium
Following inhalation, the median time to reach peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 minutes and 5 minutes, respectively.
Based on the in vitro performance data, the dose of indacaterol delivered to the lung is expected to be similar for indacaterol/glycopyrronium 110/50 microgram and indacaterol 150 microgram monotherapy product. The steady state exposure to indacaterol after indacaterol/glycopyrronium 110/50 microgram inhalation was either similar or slightly lower than systemic exposure after indacaterol 150 microgram monotherapy product inhalation.
The exposure to glycopyrronium after indacaterol/glycopyrronium inhalation was similar to systemic exposure after glycopyrronium 50 microgram monotherapy product inhalation.

CLINICAL STUDIES

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

Trough FEV_1
In the [SHINE] study, it increased post-dose trough FEV_1 by 200 mL compared to placebo at the 26-week primary endpoint (p<0.001) and showed significant increases compared to each monotherapy component treatment arm (indacaterol and glycopyrronium) as well as the tiotropium treatment arm (see Table 3).

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

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

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

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

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

Onset of action
In the [SHINE and ILLUMINATE] studies, indacaterol/glycopyrronium demonstrated a statistically significant rapid onset of bronchodilator effect on Day 1 and at Week 26.

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

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

* p < 0.001 for all treatment comparisons

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

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

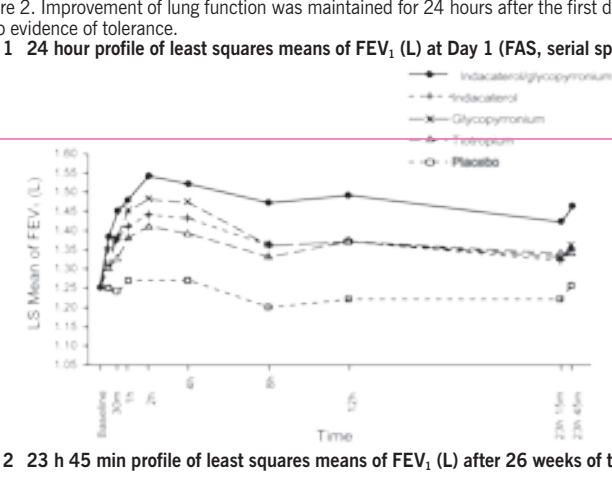
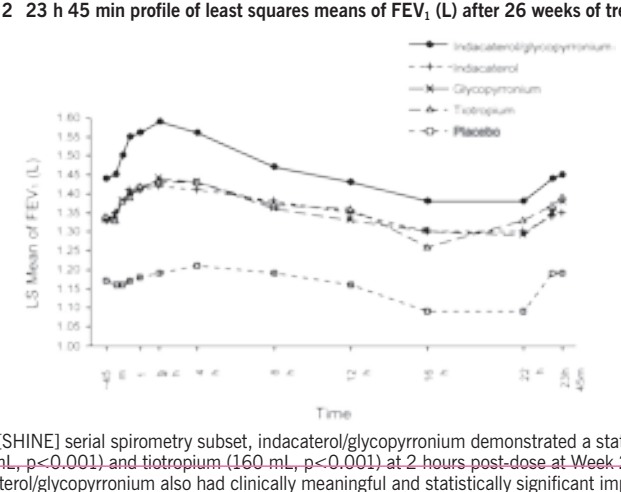
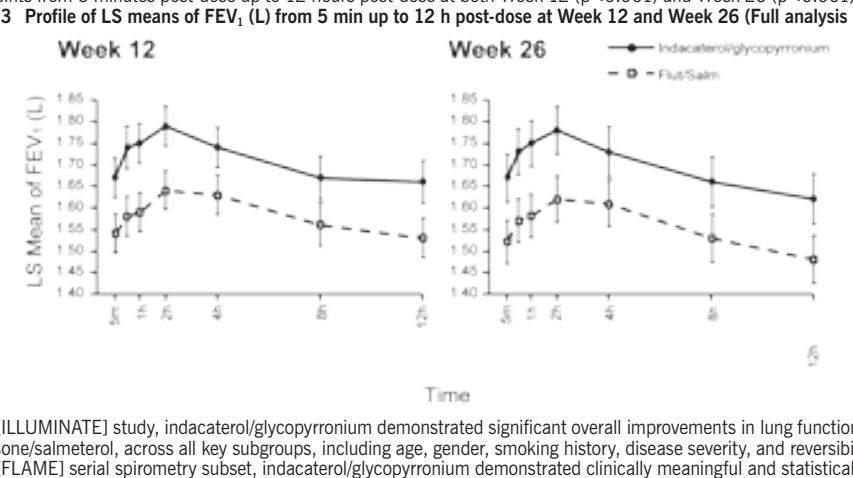


Figure 2 23 h 45 min profile of least squares means of FEV_1 (L) after 26 weeks of treatment (FAS, serial spirometry subset)



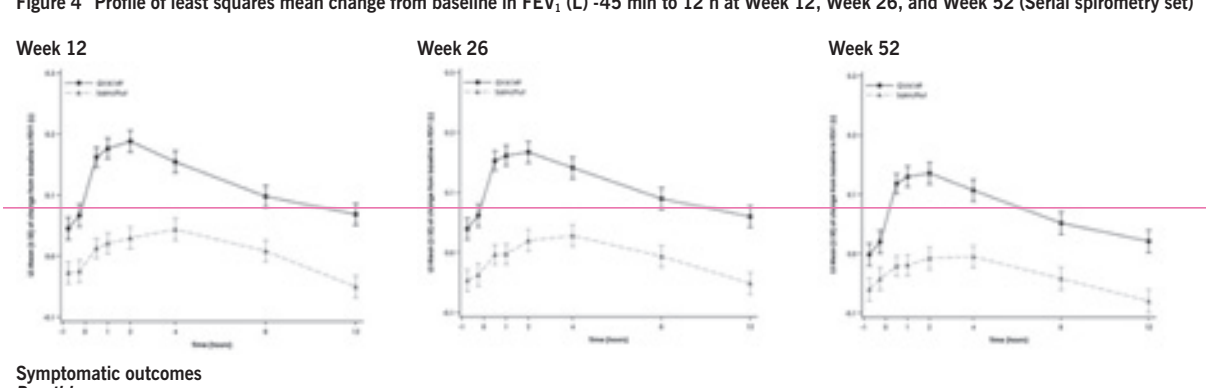
In the [SHINE] serial spirometry subset, indacaterol/glycopyrronium demonstrated a statistically significant improvement in FEV_1 compared to placebo (400 mL, p<0.001) and tiotropium (160 mL, p<0.001) at 2 hours post-dose at Week 26.
Indacaterol/glycopyrronium also had clinically meaningful and statistically significant improvements in FEV_1 compared to fluticasone/salmeterol across all time points from 5 minutes post-dose up to 12 hours post-dose at both Week 12 (p<0.001) and Week 26 (p<0.001) [ILLUMINATE] (see Figure 3).

Figure 3 Profile of LS means of FEV_1 (L) from 5 min up to 12 h post-dose at Week 12 and Week 26 (Full analysis set)



In the [ILLUMINATE] study, indacaterol/glycopyrronium demonstrated significant overall improvements in lung function compared with fluticasone/salmeterol, across all key subgroups, including age, gender, smoking history, disease severity, and reversibility.
In the [FLAME] serial spirometry subset, indacaterol/glycopyrronium demonstrated clinically meaningful and statistically significant improvements in FEV_1 AUC_{0-12h} at 52 weeks of treatment. The indacaterol/glycopyrronium group was statistically superior to the fluticasone/salmeterol group from Day 1 onwards (all p<0.05).

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



Symptomatic outcomes

Breathlessness
Indacaterol/glycopyrronium significantly reduced breathlessness as evaluated by the Transitional Dyspnea Index (TDI). Indacaterol/glycopyrronium demonstrated a clinically meaningful and statistically significant improvement in the TDI focal score at Week 26 as compared to placebo (1.09, p<0.001), tiotropium (0.51, p=0.007) [SHINE], and fluticasone/salmeterol (0.76, p=0.003) [ILLUMINATE].
A significantly higher percentage of patients receiving indacaterol/glycopyrronium responded with a 1 point or greater improvement in the TDI focal score at Week 26 compared to placebo (68.1% and 57.5% respectively, p=0.004). A higher proportion of patients demonstrated clinically meaningful response at Week 26 on indacaterol/glycopyrronium as compared to tiotropium (68.1% indacaterol/glycopyrronium vs. 59.2% tiotropium, p=0.016) [SHINE] and fluticasone/salmeterol (65.1% indacaterol/glycopyrronium vs. 55.5% fluticasone/salmeterol, p=0.088) [ILLUMINATE].

Health related quality of life
Indacaterol/glycopyrronium once daily has also shown a statistically significant effect on health related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ) at 26 weeks as indicated by a reduction in SGRQ total score compared to placebo (-3.01, p=0.002) and tiotropium (-2.13, p=0.009) [SHINE]at 64 weeks compared to tiotropium (-2.69, p<0.001) [SPARK], and at 52 weeks compared to fluticasone/salmeterol (-1.3, p=0.003) [FLAME]. In addition, improvements of the domains of the SGRQ score "symptoms", "activity" and "impact of daily life" were all statistically significant versus tiotropium at Week 64 ("symptoms": -3.06, p=0.003, "activity": -3.14, p < 0.001, "impact of daily life": -2.24, p=0.008) [SPARK].
A higher percentage of patients receiving indacaterol/glycopyrronium responded with a clinically meaningful improvement in SGRQ score (defined as a decrease of at least 4 units from baseline) at Week 26 compared to placebo (63.7% and 56.6% respectively, p=0.088) and tiotropium (63.7% indacaterol/glycopyrronium vs. 56.4% tiotropium, p=0.047) [SHINE], at Week 64 compared to glycopyrronium and tiotropium (57.3% indacaterol/glycopyrronium vs. 51.8% glycopyrronium, p=0.055; vs. 50.8% tiotropium, p=0.051, respectively) [SPARK], and at Week 52 compared to fluticasone/salmeterol (49.2% indacaterol/glycopyrronium vs. 43.7% fluticasone/salmeterol, OR: 1.30, p<0.001) [FLAME].

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

COPD exacerbations
At 64 weeks in the [SPARK] study, indacaterol/glycopyrronium once daily reduced the rate of moderate or severe COPD exacerbations by 12% compared to glycopyrronium (p=0.038) and by 10% compared to tiotropium (p=0.096).
In addition, it was shown to be clinically and statistically superior to glycopyrronium and tiotropium in reducing the rate of all COPD exacerbations (mild, moderate, and severe), with a rate reduction of 15% for indacaterol/glycopyrronium as compared to glycopyrronium (p=0.001) and 14% as compared to tiotropium (p=0.002).
For time to first moderate or severe COPD exacerbation, indacaterol/glycopyrronium demonstrated a 7% risk reduction compared to glycopyrronium (p=0.319). Glycopyrronium and tiotropium showed no difference in risk reduction.
In the 52-week active-controlled [FLAME] study, indacaterol/glycopyrronium once daily met the primary study objective of non-inferiority in rate of all COPD exacerbations (mild, moderate, or severe) compared to fluticasone/salmeterol. It 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 indacaterol/glycopyrronium vs. 51 days for fluticasone/salmeterol, p<0.001).
Indacaterol/glycopyrronium reduced the annualized rate of moderate or severe exacerbations by 17% versus fluticasone/salmeterol (0.98 vs. 1.19, p<0.001) and prolonged time-to-first moderate or severe exacerbation with a 22% reduction in risk of an exacerbation (25th percentile: 127 days for indacaterol/glycopyrronium vs. 87 days for fluticasone/salmeterol, p<0.001). Less than 50% of patients in the indacaterol/glycopyrronium group had an exacerbation, therefore the time to the first moderate or severe exacerbation in the first quartile of patients was calculated instead.
It numerically reduced the annualized rate of severe exacerbations by 13% versus fluticasone/salmeterol (0.15 vs. 0.17, p=0.231). Further, it prolonged time-to-first severe exacerbation with a 19% reduction in risk of an exacerbation (p=0.046).
The incidence of pneumonia (as confirmed by radiographic imaging i.e. chest x-ray or CT scan) was 3.2% in the indacaterol/glycopyrronium arm compared to 4.8% in the fluticasone/salmeterol arm (p=0.017). Time to first pneumonia was prolonged with indacaterol/glycopyrronium compared to fluticasone/salmeterol (p=0.013).

Use of rescue medication
Over 26 weeks, indacaterol/glycopyrronium once daily significantly reduced the use of rescue medication (salbutamol) by 0.96 puffs per day (p<0.001) compared to placebo and 0.54 puffs/day (p <0.001) compared to tiotropium in the [SHINE] study, as well as 0.39 puffs per day (p=0.019) compared to fluticasone/salmeterol in the [ILLUMINATE] study.
Over 64 weeks, indacaterol/glycopyrronium reduced the use of rescue medication (salbutamol) by 0.76 puffs per day (p<0.001) compared to tiotropium in the [SPARK] study.
Over 52 weeks, indacaterol/glycopyrronium once daily reduced the use of rescue medication by 1.01 puffs per day from baseline and fluticasone/salmeterol had a reduction of 0.76 puffs per day from baseline. The difference of 0.25 puffs per day was statistically significant (p<0.001).

Exercise tolerance
In a 3-week study [BRIGHT] where exercise tolerance was tested via cycle ergometry at submaximal (75%) workload (submaximal exercise tolerance test), indacaterol/glycopyrronium, 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 indacaterol/glycopyrronium was greater (320 mL, p<0.001) and exercise endurance time increased (59.5 seconds, p=0.006) compared to placebo. Similar findings were seen with tiotropium.
Whole-Body Plethysmography measurements of Residual Volume (RV) and Functional Residual Capacity (FRC) give insights on airway closure and reflects the presence of gas trapping, considered a hallmark of COPD. On the first day of treatment, 60 min post-dose, indacaterol/glycopyrronium reduced RV by 380 mL (p<0.001) compared to placebo and FRC by 350 mL (p< 0.001) compared to placebo. On day 21, 60 min post-dose, further reductions were seen with RV by 520 mL (p< 0.001) and FRC by 520 mL (p< 0.001).

NON-CLINICAL SAFETY DATA

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

Information related to indacaterol
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction. The effects of indacaterol seen in toxicity studies in dogs were mainly on the cardiovascular system and consisted of tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological effects and could be explained by the $beta_2$-agonistic properties of indacaterol. Other relevant effects noted in repeated-dose toxicity studies were mild irritancy of the upper respiratory tract in rats consisting of rhinitis and epithelial changes of the nasal cavity and larynx. All these findings were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Studies on genotoxicity did not reveal any mutagenic or clastogenic potential. The carcinogenic potential of indacaterol has been evaluated in a 2-year inhalation study in rats and a 26-week oral transgenic mouse study. Lifetime treatment of rats resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle at doses approximately 30-times the dose of 150 microgram once-daily for humans (based on AUC0-24h). Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other $beta_2$-adrenergic agonist drugs. A 26- week oral study in CB6F1/TgrasH2 hemizygous mice with indacaterol did not show any evidence of tumorigenicity at doses of at least 103-times the dose of 150 microgram once-daily for humans (based on AUC0-24h).

Information related to glycopyrronium
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.
The effects seen during repeated-dose inhalation toxicity studies were attributable to exacerbations of the expected pharmacological action of glycopyrronium or mild local irritation. These included mild to moderate increases in heart rate in dogs and a number of reversible changes in rat and dogs associated with reduced secretions from the salivary, lacrimal and Harderian glands and pharynx. Lens opacities observed during chronic studies in rats have been described for other muscarinic antagonists and are considered to be species-specific changes with limited relevance for therapeutic use in patients. Findings in the respiratory tract of rats included degenerative/regenerative changes and inflammation in the nasal cavity and larynx that are consistent with mild local irritation. Minimal epithelial changes in the lung at the bronchioloalveolar junction were also observed in rats and are regarded as a mild adaptive response. All these findings were observed at exposures considered to be sufficiently in excess of the maximum human exposure and therefore indicate limited relevance during clinical use.
Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium. Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity at systemic exposures (AUC0-24h) of approximately 53-fold higher in mice and 75-fold higher in rats than the dose of 50 microgram once-daily for humans.

INCOMPATIBILITIES

Not applicable.

AVAILABILITY

PA/AL/PVC Blister Pack of 10 capsules (Box of 10's) and 1 inhaler device
PA/AL/PVC Blister Pack of 10 capsules (Box of 30's) and 1 inhaler device

STORAGE

Store at temperatures not exceeding 25°C. Protect from moisture.
Do not use after the date marked "EXP" on the pack.
Drugs must be kept out of the reach and sight of children.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1- 800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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

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