

- Other AEs occurring more frequently with UTIBRON NEOHALER than with placebo, but with an incidence of <1% include dyspepsia, gastroenteritis, chest pain, fatigue, peripheral edema, rash/pruritus, insomnia, dizziness, bladder obstruction/urinary retention, atrial fibrillation, palpitations, tachycardia.
- In the 52-week trial, 614 subjects were treated for up to 52 weeks with indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg BID, indacaterol/glycopyrrolate 27.5 mcg/31.2 mcg BID or indacaterol 75 mcg once daily.
 - The AEs reported in this trial were consistent with those observed in the placebo-controlled trials of 12 weeks.
 - Additional AEs that occurred with a frequency of $\geq 2\%$ in the group receiving indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg BID that exceeded the frequency of indacaterol 75 mcg once-daily in this trial were: upper and lower respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis.

IMPORTANT SAFETY INFORMATION¹

WARNING: ASTHMA-RELATED DEATH

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

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

- All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. UTIBRON NEOHALER is contraindicated in patients who have demonstrated hypersensitivity to indacaterol, glycopyrrolate, or to any of the ingredients.
- UTIBRON NEOHALER should not be initiated in patients with acutely deteriorating or potentially life-threatening episodes of COPD, or used as rescue therapy for acute symptoms. Acute symptoms should be treated with an inhaled short-acting beta₂-agonist. Patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.
- UTIBRON NEOHALER should not be used more often or at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.
- UTIBRON NEOHALER can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing of UTIBRON NEOHALER, it should be treated immediately with an inhaled short-acting bronchodilator. UTIBRON NEOHALER should be discontinued immediately and alternative therapy instituted.
- Immediate hypersensitivity reactions have been reported after administration of indacaterol or glycopyrrolate, the components of UTIBRON NEOHALER. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, or swelling of tongue, lips, and face), urticaria, or skin rash, UTIBRON NEOHALER should be discontinued immediately and alternative therapy instituted. UTIBRON NEOHALER should be used with caution in patients with severe hypersensitivity to milk proteins.
- Indacaterol, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, UTIBRON NEOHALER may need to be discontinued. UTIBRON NEOHALER should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to consult a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema).
- Use with caution in patients with urinary retention. Instruct patients to consult a physician immediately if signs or symptoms of urinary retention develop (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction.
- Beta₂-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility for cardiac arrhythmias. Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose.
- Use with caution in patients treated with additional adrenergic drugs (sympathetic effects may be potentiated); xanthine derivatives, steroids, or diuretics (hypokalemic effect may be potentiated); non-potassium-sparing diuretics (ECG changes and/or hypokalemia can be acutely worsened); and beta-blockers (can inhibit the therapeutic effect of beta-agonists, which may produce severe bronchospasms in patients with COPD). Avoid coadministration of UTIBRON NEOHALER with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.
- Use with extreme caution in patients treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated. Drugs that are known to prolong the QTc interval may have an increased risk of ventricular arrhythmias.

References

1. UTIBRON NEOHALER [Prescribing Information]. Novartis Pharmaceuticals Corporation. October 2015.
2. Mahler DA, Kerwin E, Ayers T, et al. FLIGHT: Efficacy and safety of QVA149 (Indacaterol/Glycopyrrolate) versus its monocomponents and placebo in patients with COPD. *Am J Respir Crit Care Med*. 2015 Jul 15. [Epub ahead of print].

UTIBRON™ NEOHALER® (indacaterol and glycopyrrolate) inhalation powder
Clinical Summary for Formulary Review
Please consult complete Prescribing Information

INDICATIONS AND USAGE¹

UTIBRON NEOHALER is a combination of indacaterol, a long-acting beta₂-adrenergic agonist (LABA), and glycopyrrolate, an anticholinergic, indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: UTIBRON NEOHALER is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

DOSAGE AND ADMINISTRATION¹

- For oral inhalation only. Do not swallow UTIBRON capsules, as the intended effects on the lungs will not be obtained. UTIBRON capsules should only be used with the NEOHALER device.
- The recommended dosage of UTIBRON NEOHALER is the inhalation of the contents of one UTIBRON capsule twice-daily using the NEOHALER device.
- Utibron Neohaler should be administered at the same time of the day, (1 capsule in the morning and 1 capsule in the evening), every day. More frequent administration or a greater number of inhalations (more than 1 capsule twice-daily) of UTIBRON NEOHALER is not recommended.
- Store UTIBRON capsules in the blister, and only remove IMMEDIATELY BEFORE USE with the NEOHALER device.
- No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or patients with mild to moderate renal impairment.

EFFICACY^{1,2}

- The clinical development program for UTIBRON NEOHALER included two (FLIGHT 1 and FLIGHT 2) 12-week, randomized, double-blinded, placebo- and active-controlled, parallel-group trials in subjects with COPD designed to evaluate the efficacy and safety of UTIBRON NEOHALER; and one 12-month, randomized, double-blind, active-controlled trial (FLIGHT 3) that evaluated bronchodilation and effects on long-term safety.
- FLIGHT 1 (N=1039) and FLIGHT 2 (N=996) evaluated UTIBRON NEOHALER (indacaterol/glycopyrrolate) 27.5 mcg/15.6 mcg (n=258 and n=249), indacaterol 27.5 mcg (n=260 and n=251), glycopyrrolate 15.6 mcg (n=261 and n=250), and placebo (n=260 and n=246), all dosed twice-daily (BID). The primary endpoint was the change from baseline in FEV₁ AUC_{0-12h} following the morning dose at Day 85 (defined as the mean FEV₁ change from baseline over 0 to 12 hours divided by 12 hours) compared with placebo, glycopyrrolate 15.6 mcg BID, and indacaterol 27.5 mcg BID. The comparison of UTIBRON NEOHALER with indacaterol 27.5 mcg and glycopyrrolate 15.6 mcg was assessed to evaluate the contribution of the individual comparators to UTIBRON NEOHALER.
- In both trials, UTIBRON NEOHALER demonstrated a larger increase in mean change from baseline in FEV₁ AUC_{0-12h} compared to placebo, indacaterol 27.5 mcg BID, and glycopyrrolate 15.6 mcg BID. The least squares mean treatment difference (95% CI) in FEV₁ AUC_{0-12h} at Day 85 with UTIBRON NEOHALER was:
 - FLIGHT 1: 0.231 L (0.192, 0.271) vs placebo, 0.094 L (0.055, 0.133) vs indacaterol 27.5 mcg BID group, and 0.098 L (0.059, 0.137) vs glycopyrrolate 15.6 mcg BID group
 - FLIGHT 2: 0.262 L (0.224, 0.300) vs placebo group, 0.112 L (0.075, 0.149) vs indacaterol 27.5 mcg BID group, and 0.079 L (0.042, 0.116) vs glycopyrrolate 15.6 mcg BID group
- With the limited data available, there was no suggestion of a difference in FEV₁ AUC_{0-12h} with respect to age, sex, degree of airflow limitation, GOLD stage, smoking status, or inhaled corticosteroid use.
- The peak FEV₁ was defined as the maximum FEV₁ recorded within 4 hours after the morning dose on Days 1 and 85. The mean peak FEV₁ improvement from baseline for UTIBRON NEOHALER compared with placebo at Day 1 and at Day 85 was 0.185 L and 0.290 (FLIGHT 2) and 0.151 L and 0.260 L (FLIGHT 1), respectively. The median time to onset on Day 1, defined as a 100-mL increase from baseline in FEV₁, was 12 minutes and 16 minutes in FLIGHT 2 and 1, respectively, in subjects receiving UTIBRON NEOHALER.
- In FLIGHT 1 and 2, patients treated with UTIBRON NEOHALER used less daily rescue albuterol compared to patients treated with placebo.
- In FLIGHT 1, the St. George's Respiratory Questionnaire (SGRQ) responder rate (defined as an improvement in score of 4 or more as threshold) was 57%, 46%, 48%, and 39%, for UTIBRON NEOHALER, glycopyrrolate, indacaterol, and placebo, respectively, with odds ratios of 1.6 (95% CI: 1.1, 2.3), 1.5 (95% CI: 1.1, 2.2), and 2.2 (95% CI: 1.5, 3.2), for UTIBRON NEOHALER vs. glycopyrrolate, UTIBRON NEOHALER vs. indacaterol, and UTIBRON NEOHALER vs. placebo, respectively. In FLIGHT 2, the trends were similar, with odds ratios of 1.4 (95% CI: 1.0, 2.0), 1.1 (95% CI: 0.8, 1.7), and 2.9 (95% CI: 1.9, 4.2), for UTIBRON NEOHALER vs. glycopyrrolate, UTIBRON NEOHALER vs. indacaterol, and UTIBRON NEOHALER vs. placebo, respectively.
- In FLIGHT 3, UTIBRON NEOHALER demonstrated a significant treatment effect with an increase of 0.080 L in pre-dose trough FEV₁ compared to indacaterol 75 mcg once-daily at Week 52.

ADVERSE EVENT PROFILE^{1,2}

- The UTIBRON NEOHALER safety database included 2654 subjects with COPD in two 12-week lung function trials and one 52-week long-term safety study. A total of 712 subjects received treatment with UTIBRON NEOHALER 27.5 mcg/15.6 mcg BID.
 - In the two 12-week, placebo-controlled trials (FLIGHT 1 and 2; N=1,042 and N=1,001):
 - The most common adverse reactions with UTIBRON NEOHALER (incidence ≥1% and higher than placebo) were nasopharyngitis, hypertension, back pain, and oropharyngeal pain.
 - The proportion of patients who discontinued treatment due to AEs was 2.95% for the UTIBRON NEOHALER-treated patients and 4.13% for placebo-treated patients.