PDL DRUG REVIEW

Proprietary Name: Utibron® Neohaler
Common Name: indacaterol & glycopyrrolate inhalation powder
PDL Category: Antiasthmatic- Adrenergic Combos

Comparable Products	Preferred Drug List Status
Anoro Ellipta	Non-Preferred
Bevespi Aerosphere	Non-Preferred
Stiolto Respimat	Non-Preferred

Summary

Pharmacology/Usage: Utibron® Neohaler is a combination product containing the active ingredients of indacaterol (a long-acting beta2-adrenergic agonist; LABA) and glycopyrrolate (a long-acting muscarinic antagonist (LAMA), often referred to as an anticholinergic). Indacaterol acts locally in the lung at the beta2 receptors in bronchial smooth muscle, working as a bronchodilator. In the airways, glycopyrrolate exerts its effect through inhibition of muscarinic receptor M3 at the smooth muscle, which leads to bronchodilation.

As do all LABA-containing products, Utibron® Neohaler has a box warning regarding the increased risk of asthma-related death. Data from a large US placebo-controlled study compared the safety of salmeterol (another LABA) with placebo and results demonstrated an increase in asthma-related deaths in the salmeterol group. This finding is considered a class effect of all LABAs, including indacaterol. The warning also indicates that the safety and efficacy of use in patients with asthma have not been established and that Utibron® Neohaler is not indicated for asthma.

Indication: A combination product for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Utibron® Neohaler is *NOT* indicated for the relief of acute bronchospasm or for the treatment of asthma.

This is a pregnancy category C medication. The safety and efficacy for use in the pediatric population have not been established.

Dosage Forms: A dry powder formulation for oral inhalation: Utibron® Neohaler consists of Utibron® capsules containing indacaterol/glycopyrrolate powder (27.5mcg/15.6mcg) for oral inhalation and the Neohaler device.

Recommended Dosage: Utibron® Neohaler is for oral inhalation only; the Utibron® capsules should only be used with the Neohaler device. Inhale the contents of one Utibron® capsule BID using the Neohaler device.

Dose adjustments are not required for patients with mild and moderate hepatic or renal impairment. Use Utibron® Neohaler only if the expected benefit outweighs the potential risk in patients with severe renal impairment or end-stage renal disease. Use has not been studied in patients with severe hepatic impairment.

Drug Interactions: It is recommended to avoid the concomitant use of Utibron® Neohaler with other anticholinergic-containing drugs. Due to the indacaterol component, Utibron® Neohaler should be used with extreme caution in patients being treated with MAO inhibitors, TCAs, or other drugs known to prolong the QTc interval. Although the clinical relevance is not known, it is recommended to use the combination of Utibron® Neohaler with non-potassium-sparing diuretics with caution. Concomitant use with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta2 adrenergic agonists, such as indacaterol. Due to the indacaterol component, use Utibron® Neohaler in combination with additional adrenergic agents with caution. Beta-blockers may block the effects of beta-agonists as well as produce severe bronchospasm in COPD patients. Thus, COPD patients should not normally be treated with beta-blockers; however, if there are no acceptable alternatives, it is recommended to consider cardioselective beta-blockers and use with caution.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Utibron® Neohaler) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included nasopharyngitis (2.3%), hypertension (0.6%), back pain (1.2%), and oropharyngeal pain (0.4%).

Utibron® Neohaler has not been studied in patients with acutely deteriorating COPD and thus treatment should not be started in this population or in those with potentially life-threatening episodes of COPD. In addition, Utibron® Neohaler can cause paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, discontinue treatment.

Indacaterol can produce clinically significant cardiovascular (CV) effects in some patients, as assessed by increases in pulse rate, SBP, DBP, or symptoms. In addition, beta-agonists have been reported to produce ECG changes. Thus, Utibron® Neohaler should be used with caution in patients with CV disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Utibron® Neohaler should be used with caution in patients with urinary retention or narrow-angle glaucoma.

Contraindications: In patients who have demonstrated hypersensitivity to indacaterol, glycopyrrolate, or to any of the ingredients of the compound; All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication (Utibron® Neohaler is not indicated for the treatment of asthma).

Manufacturer: Sunovion (note that the prescribing information still lists Novartis, but per Novartis they have sold this product to Sunovion and are not sure if/when the prescribing information will get changed)

Analysis: The safety and efficacy of Utibron® Neohaler were assessed in a clinical development program that included 3 dose-ranging studies, 2 lung function studies, and a 12-month long-term safety study. The confirmatory studies and the long-term safety study will be discussed here, with data obtained from the prescribing information.

The confirmatory studies were two randomized, double-blind, placebo- and active-controlled, parallel group 12-week studies (Trial 1 and Trial 2) that included COPD patients who were ≥40 years of age, had a smoking history of >10 pack-years, and had a post-albuterol FEV1 ≥30% and <80% of predicted normal values. Both studies evaluated Utibron® Neohaler BID as compared to glycopyrrolate 15.6mcg BID, indacaterol 27.5mcg BID, and placebo BID. The primary endpoint was the change from baseline in FEV1 AUC0-12h following the morning dose at day 85 (defined as the mean FEV1 change from baseline over 0 to 12 hours divided by 12 hours) as compared with placebo and both monotherapy groups. In both studies, results suggested that there was a larger increase in mean change from baseline in FEV1 AUC0-12h with Utibron® Neohaler as compared with placebo and monotherapy. The table below, which was adapted from the prescribing information, highlights the results.

Treatment	N for Utibron®	Difference from placebo	Difference from indacaterol	Difference from glycopyrrolate
Trial 1 FEV1 (L) AUC0-12h at week 12				
Utibron® Neohaler	249	0.262 L (N=246)	0.112 L (N=251)	0.079 L (N=250)
Study 2 FEV1 (L) AUC0-12h at week 12				
Utibron® Neohaler	258	0.231 L (N=260)	0.094 L (N=260)	0.098 L (N=261)

The mean peak FEV1, defined as the max FEV1 recorded within 4 hours after the morning dose on days 1 and 85, improved from baseline for Utibron® Neohaler compared with placebo at day 1 and day 85 in Trial 1 (0.185L and 0.290L, respectively) and in Trial 2 (0.151L and 0.260L, respectively). Less daily rescue albuterol was used in patients treated with Utibron® Neohaler as compared to the placebo group in both studies. Results of the St. George's Respiratory Questionnaire (SGRQ) are illustrated in the table below. The SGRQ responder rate was defined as an improvement in score of ≥4 as threshold. Note that only the odds ratio, not the responder rates, were available for Trial 1.

Treatment	SGRQ Responder Rate	Odds Ratio vs Utibron®
Trial 1		
Utibron® Neohaler	NA	
glycopyrrolate	NA	1.4
indacaterol	NA	1.1
placebo	NA	2.9
Trial 2		
Utibron® Neohaler	57%	
glycopyrrolate	46%	1.6
indacaterol	48%	1.5
placebo	39%	2.2

Results of the 52 week study (Trial 3) suggested that Utibron® Neohaler had a significant treatment effect on lung function, with an increase of 0.080L in pre-dose trough FEV1 as compared to indacaterol 75mcg BID.

Place in Therapy: The 2017 GOLD COPD guidelines suggest the use of a long-acting antimuscarinic (LAMA) OR long-acting beta2-agonist (LABA) for patients with a GOLD Grade B, or for those with GOLD Grade B with persistent symptoms it recommends to use the combination of a LABA plus a LAMA.[2] Utibron® Neohaler is a newly FDA approved combination product containing a long-acting anticholinergic and LABA indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It was found to be safe and effective as compared to either monotherapy in this patient population in phase 3 studies. The two studies below are representative of those found that illustrate the effectiveness of this new combination product as compared to other active ingredients.

A 2015 blinded, triple-dummy, parallel-group, non-inferiority study (N=934) by Buhl et al[3] compared the safety and efficacy of the fixed-dose combination indacaterol/glycopyrronium as compared with the combination of tiotropium inhaler plus formoterol. The primary endpoint was to show non-inferiority of health-related quality of life (HRQoL) as assessed using the St. George's Respiratory Questionnaire-COPD. Results suggested that non-inferiority for SGRQ-COPD was met (p=0.399); however, there was a significantly higher percentage of patients who achieved a clinically relevant ≥1-point improvement in Transition Dyspnea Index (TDI) total score with indacaterol/glycopyrronium as compared with tiotropium plus formoterol (49.6% vs 42.4%; p=0.033). In addition, it significantly increased pre-dose FEV1 (+68ml; p<0.001) as compared with tiotropium plus formoterol at week 26.

A 2013 double-blind, double-dummy superiority 26-week study (N=523) by Vogelmeier et al[4] assessed the safety and efficacy of indacaterol/glycopyrronium as compared with salmeterol/fluticasone 50/500mcg in COPD patients. The primary endpoint was to demonstrate superiority as assessed per the standardized area under the curve from 0 to 12 hr post dose for FEV1 (FEV1 AUC0-12h). Results suggested that at 26 weeks, FEV1 AUC0-12h was significantly higher with indacaterol/glycopyrronium as compared with salmeterol/fluticasone (treatment difference 0.138L; p<0.0001).

There is evidence that Utibron® Neohaler is more effective as compared to both its individual components used as monotherapy (indacaterol and glycopyrrolate), and also that there is some evidence to support that Utibron® Neohaler is potentially more effective than some other available combination products for some measures. However, it is recommended that Utibron® Neohaler remain non-preferred and require prior authorization and be available to those who are unable to achieve therapeutic goals on preferred, more cost effective alternatives. Specifically, according to 2017 GOLD guidelines, a single agent long acting beta agonist inhaler, alone or in combination with a single agent long acting antimuscarinic inhaler or as a combination with an inhaled corticosteroid.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Utibron Neohaler [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017.
[2] Global Initiative for Chronic Obstructive Lung Disease (GOLD): Pocket guide to COPD diagnosis, management, and prevention. A guide for healthcare professionals. Updated 2017. Website: http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf. Accessed September 2017.
[3] Buhl R, Gessner C, Schuermann W, et al. Efficacy and safety of once-daily QVA149 compared with the free combination of once-daily tiotropium plus twice-daily formoterol in patients with moderate-to-severe COPD (QUANTIFY): a randomized, non-inferiority study. *Thorax*. 2015; 70(4): 311-9.
[4] Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily slameterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomized, double-blind, parallel group study. *Lancet Respir Med*. 2013; 1(1): 51-60.