New Drug Evaluation: indacaterol/glycopyrrolate and glycopyrrolate inhalation powder, oral

Date of Review: May 2016
Generic Name: indacaterol/glycopyrrolate inhalation powder
glycopyrrolate inhalation powder
PDL Class: LAMA/LABA Inhalers; Anticholinergics, Inhaled
End Date of Literature Search: February 1, 2016
Brand Name (Manufacturer): Utibron™ Neohaler® (Novartis)
Seebri™ Neohaler® (Novartis)
Dossier Received: Utibron™ Neohaler® - yes
Seebri™ Neohaler® - no

Research Questions:
• Is there any evidence that glycopyrrolate (GLY) or the fixed dose combination indacaterol (IND)/GLY are more effective than other long-acting muscarinic antagonists (LAMAs) or LAMA/long-acting beta-2 agonists (LABAs) when important outcomes such as mortality, hospitalizations, and quality of life are compared?
• Is there any evidence that GLY or IND/GLY are associated with less harms than other LAMAs or combination LAMA/LABA products?
• Is there any evidence that GLY is more effective or more harmful in certain subpopulations?

Conclusions:
• There is insufficient evidence that GLY or IND/GLY decreases hospitalizations or mortality. There is insufficient comparative efficacy between GLY and other LAMA products and between IND/GLY and other LAMA/LABA products.
• There is insufficient evidence for the efficacy of GLY due to the lack of published trials. Prescribing information reports GLY to be superior to placebo in two, 12-week randomized control trials.¹
• There is low strength of evidence from two, 12-week trials that IND/GLY increases the primary endpoint, FEV1 AUC 0-12 hours, more than GLY or IND alone. The first trial found changes in the primary endpoint of 0.171 L for IND/GLY and 0.083 L for IND (TD 0.094 L; 95% CI 0.055 to 0.133; P < 0.001) and changes of 0.128 L for GLY (TD 0.098 L; 95% CI 0.059 to 0.137; P < 0.001).² The magnitude of change for FEV1 values are at the lower end of a clinically relevant difference of 0.100 L to 0.140 L. In the second trial, FEV1 AUC 0-12 changes were higher for the IND/GLY group compared to IND alone, 0.184 L vs. 0.080 L (TD 0.112 L; 95% CI 0.075 to 0.149; P < 0.001) and compared to GLY, 0.184 vs. 0.135 L (TD 0.079 L; 95% CI 0.042 to 0.116; P < 0.001).² Demographic data was pooled for both studies, therefore, it is unknown if patient characteristics account for a larger treatment effect of IND/GLY seen in the second study.
• There is low strength of evidence from the pre-specified secondary endpoint comparison between IND/GLY and placebo that active treatment was more effective than placebo in improving St. George’s Respiratory Questionnaire (SGRQ) scores in the first and second study with a treatment difference of, -3.8 and -6.4 units, respectively (P < 0.001).²

Recommendations:
• Recommend GLY be non-preferred on the preferred drug list (PDL) due to insufficient evidence for review.

Author: Kathy Sentena, PharmD
Date: May 2016
• Recommend IND/GLY be non-preferred on the PDL and subject to prior authorization criteria for LAMA/LABA fixed dose combination treatments.

**Background:**
Chronic cough, sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of FEV1/FVC < 0.70), symptom severity, risk of exacerbations and comorbidities. COPD is classified into four stages based on spirometric measurements of FEV1/FVC; grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (very severe) (Table 1). The GOLD guidelines recommend therapeutic approaches based on disease burden as well as FEV1, which classifies patients into groups A-D (low to high risk of symptoms and exacerbations). This type of classification system shifts the focus from including just FEV1 measurements, as these are not always indicative of COPD status.

**Table 1. Classification of COPD Based on GOLD Guidelines**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Severity</th>
<th>Post-Bronchodilator FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>Mild</td>
<td>FEV₁ ≥ 80% predicted</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very severe</td>
<td>FEV₁ &lt; 30% predicted</td>
</tr>
</tbody>
</table>

* For patients with a FEV₁/FVC < 0.70

Mortality, hospitalizations, functional capacity, quality of life (QoL), dyspnea, and exacerbation rates are all important outcomes in the management of COPD patients. FEV1 is the most common surrogate outcome used in studies to determine therapy effectiveness. Minimally important FEV1 values for COPD changes have not been clearly defined but are suggested to range from 100-140 ml. The SGRQ is a validated quality of life assessment used to quantify the health and well-being of patients with COPD. The scores range from 0-100, with higher scores indicative of worse health. A change of four points has been determined as the minimally clinical important difference. The COPD Assessment Test (CAT) is another validated instrument used to measure health status. It is less complex than the SGRQ but scores correlate well with SGRQ results. CAT scores range from 0-40 points with higher scores representing worse disease severity.

Pharmacotherapy prescribed in a step-wise manner is recommended for COPD management. Treatment often starts with monotherapy and progress to combination regimens. Currently available treatments are the following: short-acting beta-2 agonists (SABA), LABAs, short-acting muscarinic antagonists, LAMAs and inhaled corticosteroids (ICS). Short-acting beta-2 agonists SABA are recommended for acute management. Bronchodilator therapy (LABAs and LAMAs) is recommended for patients with symptoms despite SABA treatment and are used as monotherapy or in combination for maintenance treatment for chronic, stable COPD. Inhaled corticosteroids are reserved for patients requiring additional treatment for chronic disease, despite LAMA and LABA use. Glycopyrrolate is one of four LAMAs used to treat COPD. Other available treatment options are: aclidinium bromide, tiotropium and umeclidinium. No treatment has been shown to alter the long-term progression and decline in lung function associated with COPD. The 2016 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that tiotropium has the most evidence for reducing exacerbations and hospitalizations. Indirect evidence suggests outcomes of lung function and breathlessness are similar for tiotropium, aclidinium and GLY. A systematic review and meta-analysis found no significant difference between the LABA/LAMA combinations of umeclidinium/vilanterol, GLY/IND, tiotropium/olodaterol and aclidinium/formoterol.

See Appendix 1 for Highlights of Prescribing Information from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Author: Kathy Sentena, PharmD

Date: May 2016
Clinical Efficacy:
Glycopyrrolate is a long-acting anticholinergic inhaler approved in 2015 for the long-term maintenance treatment of airflow obstruction in patients with COPD. Glycopyrrolate is provided in a powder form, administered in a 15.6 mcg dose by the Neohaler® twice daily. Approval of GLY was based on two efficacy trials and one safety trial, none of which have been published. Data from the prescribing material show that GLY 15.6 mcg twice daily was compared to placebo twice daily in two, 12-week, double-blind randomized controlled trials. Patients had a COPD diagnosis, were a mean age of 63 years, 58% were male, 57% were currently smoking and baseline post-bronchodilator FEV1 was 55%. The primary endpoint was change from baseline in FEV1 AUC 0-12 hours at day 85. In the first trial GLY was shown to produce a greater change in the primary endpoint compared to placebo, 0.125 L vs. -0.014 L (ETD 0.139; 95% CI 0.095 to 0.184). The second trial produced similar results, change in FEV1 AUC 0-12 hours was 0.115 L for GLY and -0.008 L for placebo (ETD 0.123; 95% CI 0.081 to 0.165). The percent of patients who experienced a clinically significant change of 4 points in their SGRQ score was found to be improved with GLY compared to placebo, 49% vs. 41% (OR 1.43; 95% CI 0.95 to 2.15) in the first trial and 55% vs. 42% (OR 1.78; 95% CI 1.17 to 2.71) in the second trial.

Clinical Safety:
Data from a 52-week study found adverse reactions occurred at an incidence of ≥2% in the GLY group 15.6 mcg (twice daily) compared to indacaterol 75 mcg (once-daily) to be the following: diarrhea, nausea, upper abdominal pain, fatigue, bronchitis, pneumonia, rhinitis, back pain, arthralgia, dyspnea, and wheezing.

Table 2. Adverse Reactions of Glycopyrrolate in ≥1% incidence and higher than placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Glycopyrrolate (N=951)</th>
<th>Placebo (N=938)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>3.4%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1.8%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Indacaterol/glycopyrrolate

Clinical Efficacy:
The fixed dose combination of IND/GLY is a LABA/LAMA product approved for the long-term maintenance treatment of airflow obstruction in patients with COPD. Glycopyrrolate is provided in a powder form, administered in a 27.5 mcg dose of indacaterol and a 15.6 mcg dose of glycopyrrolate via the Neohaler® device twice daily. Two studies were published for the approval or the IND/GLY combination. Studies utilizing higher doses to support approval in other countries have also been published but will not be the focus of this monograph.

Two identical double-blind, phase 3, 12-week studies comparing IND/GLY to the monotherapy components and placebo in 2,038 patients provides evidence for the efficacy and safety of IND/GLY. The patients were predominately white males (63%) and females (37%) with moderate to severe COPD and a baseline post-
bronchodilator FEV1% of 55%. The primary endpoint for both studies was comparison of FEV1 AUC 0-12 hours at 12-weeks. A key pre-specified secondary endpoint was change in SGRQ total score.²

In the first study (FLIGHT1) there was greater improvement in the primary endpoint with combination IND/GLY compared to IND, 0.171 L vs. 0.083 L (TD 0.088 L; 95% CI 0.055 to 0.133; P < 0.001) and compared to GLY, 0.171 L vs. 0.128 L (TD 0.068 L; 95% CI 0.039 to 0.107; P < 0.001).² Results were similar in the second study (FLIGHT2) with more improvement in the IND/GLY group compared to IND, 0.184 L vs. 0.080 L (TD 0.098 L; 95% CI 0.075 to 0.122; P < 0.001) and compared to GLY, 0.184 vs. 0.135 L (TD 0.085 L; 95% CI 0.076 to 0.095; P < 0.001). In a pooled analysis of both studies the combination product of IND/GLY demonstrated more benefit in the change of FEV1 AUC 0-12 compared to IND (TD 0.103 L; 95% CI 0.076 to 0.130; P < 0.001) and compared to GLY (TD 0.099 L; 95% CI 0.065 to 0.133; P < 0.001).² FEV1 changes with IND/GLY, compared to its monotherapy components, were at the low end of what is considered a clinically relevant change. Non-pooled changes in SGRQ total scores were found to be improved with IND/GLY compared to placebo in both studies, -3.8 for the FLIGHT1 trial and -6.4 for the FLIGHT2 trial (p <0.001 for both comparisons). The SGRQ total score was also improved with IND/GLY compared to GLY in the FLIGHT1 trial (TD -1.7; 95% CI -3.6 to 0.2; P < 0.05).² All other SGRQ comparisons were not statistically different between groups. A clinically relevant change, drop of 4 units or more in the SGRQ score, was only demonstrated in the FLIGHT 2 comparison between IND/GLY and placebo.

Longer trial durations would be helpful in determining the durability of the efficacy of IND/GLY and long-term safety. Patient demographics divided by trial may help explain the differences in the magnitude of change seen between the two studies for the primary endpoint. Some individual results and statistics were missing, limiting efficacy comparisons. There is a potential for high detection bias due to no details on blinding status of outcome assessment. Only one short-term, small study suggests clinically relevant FEV1 changes. Only one study found a clinically significant decrease of at least 4 units in the SGRQ quality of life outcome when IND/GLY was compared to placebo and difference in scores between IND/GLY and monotherapy components were not considered clinically relevant, suggesting little benefit of a combination device.

Clinical Safety:
Safety data from the two efficacy trials above found nasopharyngitis and hypertension to be the most common adverse reactions experienced with IND/GLY (occurring in ≥ 2% compared to placebo).⁸

Table 3. Adverse Reactions of Indacaterol/Glycopyrrolate occurring ≥ 1% incidence than placebo⁸

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Indacaterol/glycopyrrolate (N=508)</th>
<th>Indacaterol (N=511)</th>
<th>Glycopyrrolate (N=513)</th>
<th>Placebo (N=508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.0%</td>
<td>1.0%</td>
<td>0.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.1%</td>
<td>2.5%</td>
<td>2.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1.8%</td>
<td>1.4%</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1.6%</td>
<td>0.8%</td>
<td>1.6%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
Pharmacology and Pharmacokinetic Properties:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glycopyrrolate</th>
<th>Indacaterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Bronchodilation due to inhibition of the muscarinic receptor M3</td>
<td>Bronchodilation via beta2-receptors</td>
</tr>
<tr>
<td>Inhaled Bioavailability</td>
<td>40%</td>
<td>43-45%</td>
</tr>
<tr>
<td>Distribution and Protein Binding</td>
<td>83 L</td>
<td>2,361 to 2,557 L</td>
</tr>
<tr>
<td>Protein Bound</td>
<td>38-41% protein bound</td>
<td>95.1-96.2%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal 60-70%, non-renal 30-40%</td>
<td>54% fecal and 23% hydroxylation</td>
</tr>
<tr>
<td>Half-Life</td>
<td>33-53 hours (inhaled)</td>
<td>40-56 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP isoenzymes</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

* Only in IND/GLY combination inhaler
Abbreviations: CYP = cytochrome P-450 enzymes; L= liters;

Comparative Clinical Efficacy:
Clinically Relevant Endpoints:
1) Mortality
2) Hospitalizations
3) Exacerbations
4) Changes in FEV1
5) Quality of life

Comparative Evidence Table

<table>
<thead>
<tr>
<th>Ref./ Study Design</th>
<th>Drug Regimens/ Duration</th>
<th>Patient Population (pooled events*)</th>
<th>N</th>
<th>Efficacy Endpoints</th>
<th>ARR/NNT</th>
<th>Safety Outcomes (pooled events*)</th>
<th>ARR/NNH</th>
<th>Risk of Bias/ Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maler, et al (FLIGHT1)²</td>
<td>Indacaterol/glycopyrrolate (IND/GLY) 15.6/27.5 mcg twice daily</td>
<td>Demographics: Age: 63 Male: 63% White: 91% Moderate COPD: 61% Severe COPD: 39% Smoker: 52% Post-bronchodilator FEV1%: 55%</td>
<td>mITT: 1. 260 2. 261 3. 260 4. 261 PP: 1. 244 2. 243 3. 244 4. 220</td>
<td>Primary Endpoint: FEV, AUC 0-12 hours: IND/GLY 0.171 L GLY 0.128 L IND 0.083 L P 0.016 L</td>
<td>IND/GLY vs. IND: TD 0.094 (95% CI, 0.055 to 0.133) P &lt; 0.001</td>
<td>IND/GLY 16 (3.2%) GLY 20 (3.9%) IND 18 (3.5%) P 21 (4.1%)</td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear): Selection Bias: (low) randomized 1:1:1:1 via Interactive Response Technology (IRT) Performance Bias: (low) double – blind with masked drug delivery devices Detection Bias: (high) no details were provided Attrition Bias: (low) overall attrition was low (9%), however, placebo rates were higher. mITT was used for analysis with LOCF for missing data Reporting Bias: Study protocol was followed but individual study results were only reported for the primary outcome measure and some p-values were missing.</td>
</tr>
<tr>
<td>2. Glycopyrrolate (GLY) 15.6 mcg twice daily</td>
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<tr>
<td>3. Indacaterol (IND) 27.5 mcg twice daily</td>
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<tr>
<td>4. Placebo (P)</td>
<td></td>
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</tbody>
</table>

Author: Kathy Sentena, PharmD Date: May 2016
previous smoking history of at least 10 pack years - FEV1 ≥ 30% and < 80%

Key Exclusion Criteria:
- Diabetes
- Cardiac, renal or lab abnormalities
- BMI of > 40 kg/m2

4. 16%

IND/GLY vs. P:
TD 0.231 (95% CI, 0.192 to 0.271)
P < 0.001

Secondary Endpoint:
SGRQ:
IND/GLY vs. IND:
TD -1.9 points (95% CI, -3.8 to 0.0)
NS: P-value not given

IND/GLY vs. GLY:
TD -1.7 points (95% CI, -3.6 to 0.2)
P < 0.05

IND/GLY vs. P:
TD -3.8 points (95% CI, -5.7 to -1.8)
P < 0.001

Phase 3, DB, PG, PC and active – controlled, RCT
12 weeks

Demographics:
Age: 63
Male: 63%
White: 91%
Moderate COPD: 61%
Severe COPD: 39%
Smoker: 52%
Post-bronchodilator FEV1%: 55%

Key Inclusion Criteria:
- Moderate to severe stable COPD
- ≥ 40 years
- Current or previous smoking history of at least 10 pack years
- FEV1 ≥ 30% and < 80%

Primary Endpoint:
FEV1 AUC 0-12 hours:
IND/GLY 0.184 L
GLY 0.135 L
IND 0.080 L
P -0.003 L

IND/GLY vs. IND:
TD 0.112 (95% CI, 0.075 to 0.149)
P < 0.001

IND/GLY vs. GLY:
TD 0.079 (95% CI, 0.042 to 0.116)
P < 0.001

IND/GLY vs. P:
TD 0.262 (95% CI, 0.224 to 0.300)
P < 0.001

Risk of Bias (low/high/unclear):
Selection Bias: (low) randomized 1:1:1:1 via Interactive Response Technology (IRT)
Performance Bias: (low) double – blind with masked drug delivery devices
Detection Bias: (high) no details were provided
Attrition Bias: (low) overall attrition was low (9%), however, placebo rates were higher.
mITT was used for analysis with LOCF for missing data
Reporting Bias: Study protocol was followed but individual study results were only reported for the primary outcome measure and some p-values were missing.

Applicability:
Patient: Primarily patients with GOLD B or D COPD. GOLD guidelines recommend combination LAMA/LABA therapy for these patients.
Intervention: Doses appropriate.
Comparator: The primary endpoint was a comparison to the individual components of IND/GLY, which is appropriate. The secondary endpoints were compared to placebo which limits external validity to most COPD patients with moderate to severe COPD as they would likely be on active treatment.
Outcomes: FEV1 is a common surrogate outcome used in clinical trials.
Hospitalizations, mortality and long-term safety data are more clinically useful outcomes.
Setting: Conducted in 8 countries.
<table>
<thead>
<tr>
<th>Key Exclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diabetes</td>
</tr>
<tr>
<td>- Cardiac, renal or lab abnormalities</td>
</tr>
<tr>
<td>- Diabetes</td>
</tr>
<tr>
<td>- BMI of &gt; 40 kg/m²</td>
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</table>

<table>
<thead>
<tr>
<th>SGRQ*:</th>
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<tbody>
<tr>
<td>IND/GLY vs. IND:</td>
</tr>
<tr>
<td>TD -1.5 points (95% CI, -3.6 to 0.6)</td>
</tr>
<tr>
<td>NS: P-value not given</td>
</tr>
<tr>
<td>IND/GLY vs. GLY:</td>
</tr>
<tr>
<td>TD -1.4 points (95% CI, -3.5 to 0.7)</td>
</tr>
<tr>
<td>NS: P-value not given</td>
</tr>
<tr>
<td>IND/GLY vs. P:</td>
</tr>
<tr>
<td>TD -6.4 points (95% CI, -8.5 to -4.2)</td>
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<tr>
<td>P &lt; 0.001</td>
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<tr>
<th>provided</th>
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<tbody>
<tr>
<td>NS</td>
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<tr>
<td>NA</td>
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<td>NA</td>
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</tbody>
</table>

| Comparison to the individual components of IND/GLY, which is appropriate. The secondary endpoints were compared to placebo which limits external validity to most COPD patients with moderate to severe COPD as they would likely be on active treatment. |
| Outcomes: FEV1 is a common surrogate outcome used in clinical trials. Hospitalizations, mortality and long-term safety data are more clinically useful outcomes. |
| Setting: Conducted in 9 countries. |

* Values are from pooled results of FLIGHT1 and FLIGHT2 studies. Individual results not reported.

**Abbreviations** [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PP = per protocol; TD = treatment difference
References:


Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use UTIBRON NEOHALER safely and effectively. See full prescribing information for UTIBRON NEOHALER.

UTIBRON™ NEOHALER® (indacaterol and glycopyrrolate) inhalation powder, for oral inhalation use
Initial U.S. Approval: 2015

--- WARNING: ASTHMA-RELATED DEATH ---
See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists (LABAs), such as indacaterol, one of the active ingredients in UTIBRON NEOHALER, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding of an increased risk of asthma-related death with salmeterol is considered a class effect of all LABAs, including indacaterol. (5.1)

- 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. (5.1)

--- INDICATIONS AND USAGE ---
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) (1)

Limitations of Use: Not indicated for the relief of acute bronchospasm or for the treatment of asthma. (1, 3.1, 5.2)

--- DOSAGE AND ADMINISTRATION ---
- For oral inhalation only. Do not swallow UTIBRON capsules. Only use UTIBRON capsules with the NEOHALER device. (2)
- Maintenance treatment of COPD. The inhalation of the powder contents of one UTIBRON capsule twice-daily (2)

--- DOSAGE FORMS AND STRENGTHS ---
- Inhalation powder. UTIBRON capsules contain 27.5 mcg of indacaterol and 15.6 mcg glycopyrrolate inhalation powder for use with the NEOHALER device (3)

--- CONTRAINDICATIONS ---
- All LABAs are contraindicated in patients with asthma without use of a long-term asthma controller medication. (4) UTIBRON NEOHALER is not indicated for the treatment of asthma. (1)
- History of known hypersensitivity to indacaterol, glycopyrrolate, or to any of the ingredients. (4, 5.5)

--- WARNINGS AND PRECAUTIONS ---
- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3, 7.1)
- If paradoxical bronchospasm occurs, discontinue UTIBRON NEOHALER immediately and institute alternative therapy. (5.4)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, sensitivity to sympathomimetic drugs, diabetes mellitus, and ketoadiposis. (5.6, 7.1)
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur. (5.8, 5.9)
- Be alert to hypokalemia and hyperglycemia. (5.11)

--- ADVERSE REACTIONS ---
Most common adverse reactions (incidence ≥2% and higher than placebo) are nasopharyngitis and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-5682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---
- Other adrenergic drugs may potentiate effect: Use with caution (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (7.2, 7.3)
- Monoamine Oxidase inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness: Use with caution and only when medically necessary. (7.5)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of UTIBRON NEOHALER with other anticholinergic-containing drugs. (7.6)

--- USE IN SPECIFIC POPULATIONS ---
- Use in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SEEBR™ NEOHALER® safely and effectively. See full prescribing information for SEEBR™ NEOHALER.

SEEBR™ NEOHALER® (glycopyrrolate) inhalation powder, for oral inhalation use
Initial U.S. Approval: 1961

--------------------INDICATIONS AND USAGE-----------------------

SEEBR™ NEOHALER is an anticholinergic indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) (1)

--------------------DOSAGE AND ADMINISTRATION-------------------

• For oral inhalation only. Do not swallow SEEBR™ capsules. Only use SEEBR™ capsules with the NEOHALER® device. (2)
• Maintenance treatment of COPD: The inhalation of the powder contents of one SEEBR™ capsule (15.6 mcg) twice-daily (2)

--------------------DOSAGE FORMS AND STRENGTHS-------------------

• Inhalation powder: SEEBR™ capsules contain 15.6 mcg of glycopyrrolate inhalation powder for use with the NEOHALER® device (3)

--------------------CONTRAINDICATIONS-----------------------------

• History of known hypersensitivity to glycopyrrolate or to any of the ingredients. (4, 5.3)

--------------------WARNINGS AND PRECAUTIONS---------------------

• Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.1)

• If paradoxical bronchospasm occurs, discontinue SEEBR™ NEOHALER immediately and institute alternative therapy. (5.2)
• Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a physician immediately if symptoms occur. (5.4)
• Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder neck obstruction and instruct patients to consult a physician immediately if symptoms occur. (5.5)

--------------------ADVERSE REACTIONS-----------------------------

Most common adverse reactions (incidence greater than or equal to 2% and higher than placebo) are upper respiratory tract infection and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--------------------DRUG INTERACTIONS-----------------------------

• Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SEEBR™ NEOHALER with other anticholinergic-containing drugs. (7.2)

--------------------USE IN SPECIFIC POPULATIONS-------------------

• Use in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2015
**Long-acting Muscarinic Antagonist/Long-acting Beta-agonist Combination (LAMA/LABA)**

**Goals:**
- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also:
- Promote COPD therapy that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also:
  - Step-therapy required prior to coverage:
    - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LAMA and LABA products do NOT require prior authorization.

**Length of Authorization:**
- Up to 12 months

**Requires PA:**
- All LAMA/LABA products

**Covered Alternatives:**
- Preferred alternatives listed at

### Approval Criteria

<table>
<thead>
<tr>
<th>1. What diagnosis is being treated?</th>
<th>Record ICD10 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Will the prescriber consider a change to a preferred product?</td>
<td>Yes: Inform prescriber of preferred LAMA and LABA products in each class</td>
</tr>
<tr>
<td><strong>Message:</strong></td>
<td>Preferred products do not require PA or a copay.</td>
</tr>
<tr>
<td>Approval Criteria</td>
<td>Yes: Pass to RPh. Deny; medical appropriateness.</td>
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</tr>
<tr>
<td>3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522, J45901-45998)?</td>
<td>Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.</td>
</tr>
<tr>
<td>4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?</td>
<td>Yes: Go to #5</td>
</tr>
<tr>
<td>5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?</td>
<td>Yes: Go to #6</td>
</tr>
<tr>
<td>6. Has the patient been assessed with GOLD C/D COPD?</td>
<td>Yes: Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.</td>
</tr>
<tr>
<td>7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol)?</td>
<td>Yes: Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).</td>
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