**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is the collective term for a lower respiratory tract condition that includes chronic bronchitis and emphysema. It is a partially reversible condition characterized by chronic, progressive difficulty with expiration of air from the lungs. COPD causes patients great distress and can have significant negative effects on their quality of life.

Mortality from COPD continues to increase. According to data from the 2008 National Center for Health Statistics, COPD has replaced stroke as the third leading cause of death in the U.S. It is estimated that 11.8 million people (7.4 million women, 4.4 million men) over 18 years of age are affected. The highest prevalence of COPD occurs in adults who have a family income below the federal poverty level and who are of Puerto Rican (6.9%) or non-Hispanic Caucasian (5.7%) descent. The change of COPD from the fourth leading cause of death to the third makes it the only deadly health condition whose incidence has increased over the past 30 years.

Recent data also suggest that COPD is the 12th leading cause of morbidity in the U.S.

COPD can be differentiated from asthma, another chronic lower respiratory tract condition, by its onset, frequency, and cause of symptoms, and its long-term responsiveness to treatment. Generally, COPD is diagnosed in patients 40 years of age or older who smoke or formerly smoked cigarettes, whereas asthma is diagnosed in early childhood or adolescence. Symptoms of COPD are ongoing and are commonly exacerbated by respiratory infection; however, some patients with asthma may be relatively symptom-free until they are exposed to certain irritants (e.g., cold air, allergens, and exercise) that prompt an attack.

Unlike asthma, the airflow limitation present in COPD is not fully reversible; however, the symptoms (cough, wheezing, breathlessness, and mucus production) can be improved and controlled with medications. It is possible for a patient to have both COPD and asthma.

There is no cure for COPD.

The diagnosis and management of COPD are described in two guidelines: the Global Initiative for Obstructive Lung Disease (GOLD) criteria and the American College of Physicians (ACP) Clinical Practice guidelines. These publications recommend a progressive addition of medication based on the stage of COPD (I = mild, II = moderate, III = severe, and IV = very severe), with the goals of improving symptoms (dyspnea, poor exercise tolerance, and cough) and of reducing the frequency and severity of exacerbations.

The stage of COPD is determined by spirometry, including forced expiratory volume in 1 second (FEV1) and the ratio of FEV1 to forced vital capacity (FVC), or FEV1:FVC. In general, dyspnea is controlled with short-acting bronchodilators (beta agonists), as needed, in stage I COPD (FEV1 ≥ 80% and FEV1:FVC < 70%), followed by the addition of long-acting bronchodilators (beta agonists or anticholinergics), which are used on a regular basis in stage II COPD (FEV1 50%–80% and FEV1:FVC < 70%). Inhaled glucocorticoids are initiated in stage III COPD (FEV1 30%–50% and FEV1:FVC < 70%) when patients experience repeated exacerbations. Long-term oxygen therapy is initiated in stage IV COPD (FEV1 ≤ 30% and FEV1:FVC < 70%).

Three long-acting beta-agonists (LABAs) are currently on the market in the U.S. Salmeterol (Serevent, GlaxoSmithKline) is available in a dry-powder inhaler and is administered twice daily. The once-daily formulations include formoterol, available in a dry-powder inhaler (Foradil, Schering) and as a solution for nebulization (Perforomist, Dey). Arformoterol (Brovana, Sunovion) is available only as a solution for nebulization. LABAs are used as single-ingredient or combination therapies. In addition to these agents, a long-acting, once-daily anticholinergic preparation, tiotropium (Spiriva, Pfizer) is available in a dry-powder inhaler.

On July 1, 2011, the FDA approved a new molecular entity, indacaterol maleate (Arcapta Neohaler, Novartis), for the treatment of airflow obstruction in patients with COPD. It is categorized as a LABA, and only once-daily administration is required. Tables 1 and 2 present a comparison of indacaterol with other available LABAs.

This article reviews and evaluates the available safety and efficacy data for indacaterol.

**PHARMACOLOGY**

Like the other LABAs, indacaterol is a highly lipophilic compound that demonstrates slow dissociation from lung fat-soluble tissues. This beneficial characteristic helps to extend the duration of action.

Indacaterol interacts with the receptor through the lipid bilayer and stimulates the formation of cyclic adenosine monophosphate (cAMP) and the activation of cAMP-dependent protein kinase (protein kinase A), which results in relaxation of airway smooth muscle. Indacaterol is a nearly full agonist of the beta2 adrenoceptor and has a binding affinity similar to that of formoterol but
higher intrinsic activity than that of salmeterol.\textsuperscript{12,13} It also decreases immunoglobulin E (IgE)–dependent release of inflammatory mediators from mast cells in the lungs.\textsuperscript{7}

Indacaterol has a rapid onset of action (approximately 5 minutes) with extended bronchodilation (approximately 24 hours).\textsuperscript{8} This is a longer duration of action than that of other LABAs, including formoterol and salmeterol, allowing once-daily dosing.\textsuperscript{7} The onset of action of indacaterol is similar to that of formoterol and is faster than that of salmeterol.

Indacaterol also demonstrates superior activity over salmeterol.\textsuperscript{10,13} Compared with tiotropium, indacaterol has a similar level of bronchodilation and is considered to be equally effective.\textsuperscript{14}

**PHARMACOKINETICS**

Pharmacokinetic data from multiple-dose studies have shown that indacaterol undergoes rapid absorption, with a mean elimination half-life of more than 30 hours.\textsuperscript{8,11} In single-dose studies, rapid absorption was observed, and maximum serum concentrations were reached within 15 minutes.\textsuperscript{12,15}

Although indacaterol undergoes rapid...
absorption after oral dosing, it does not have high bioavailability; after inhaled administration, its absolute bioavailability is approximately 43%. Indacaterol is approximately 95% bound to serum and plasma proteins and has extensive systemic distribution (2,361 to 2,557 L) after intravenous (IV) administration.\textsuperscript{8,11} The major routes of elimination for indacaterol and its metabolites are fecal and biliary.\textsuperscript{10,15}

No major active metabolites were identified in kinetic studies,\textsuperscript{8,11} probably because of the lack of glutathione/cysteine conjugates and the low potential for covalent protein binding.\textsuperscript{15} Several minor metabolites were identified, including a hydroxylated derivative (and its diastereomer), phenolic O-glucuronide, and N-glucuronide of indacaterol. UDP glucuronosyltransferase-1 family, polypeptide A1 (UGT1A1) is the UGT isoform responsible for the metabolism of the primary metabolite. Nevertheless, CYP3A4 is not expected to undergo significant interactions with medications metabolized by this pathway.\textsuperscript{8,11}

Indacaterol has low affinity for P-glycoprotein (P-gp), an efflux pump located mainly in the gastrointestinal (GI) tract, and P-gp is unlikely to affect the pharmacokinetics of indacaterol.\textsuperscript{8,11} Indacaterol is found in most tissues (except the brain, spinal column, and lymph nodes), with the highest concentrations occurring in the stomach, intestines, liver, and kidneys.\textsuperscript{10}

Table 3 summarizes the pharmacokinetic profiles of the currently available LABAs.

### EFFICACY

The safety and efficacy of indacaterol in 6,968 patients with COPD were evaluated in 16 randomized, double-blind, placebo-controlled clinical trials.\textsuperscript{23,16–30} In general, the trials included patients with moderate-to-severe COPD, post-bronchodilator FEV\textsubscript{1} of less than 80% and greater than or equal to 30% predicted, and a post-bronchodilator FEV\textsubscript{1}:FVC ratio of less than 70%. The patients were 40 years of age or older and had a smoking history of 20 or more pack-years. Phase 2 dose-ranging studies lasted from 8 to 28 days,\textsuperscript{16–19} and phase 3 efficacy and safety studies lasted from 12 to 52 weeks.\textsuperscript{13,21–30}

Patients were excluded from enrollment if they had been hospitalized for a COPD exacerbation within 6 weeks before the first visit or run-in period or had a history of asthma, a recent respiratory tract infection; or any significant pulmonary disease or cardiovascular abnormality. Patients were also excluded if they were taking nonselective beta blockers, non–potassium-sparing diuretics, or certain antiarrhythmic agents. Most studies included a prescreening period, during which the patient’s COPD medications were reviewed to eliminate prohibited therapies (i.e., long-acting or short-acting anticholinergics, fixed-dose combinations of long-acting or short-acting beta-agonists and inhaled corticosteroids, xanthine derivatives, or oral corticosteroids). Chronic inhaled corticosteroid monotherapy was maintained at a constant dosing regimen during the studies.

The primary endpoint for most of the studies was the trough FEV\textsubscript{1} (measured at 23 hours 10 minutes and at 23 hours 45 minutes after administration) compared with placebo at the end of the study period. Many studies also included an active-treatment group who received formoterol, salmeterol, or tiotropium to set clinically significant thresholds for

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**Table 3 Pharmacokinetic Profiles of the Long-Acting Beta-Agonists (LABAs)**

<table>
<thead>
<tr>
<th></th>
<th>Indacaterol</th>
<th>Salmeterol</th>
<th>Formoterol</th>
<th>Arformoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>43%–45%</td>
<td>Undetectable to poor</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Time to C\textsubscript{max}</td>
<td>Approximately 15 minutes</td>
<td>Approximately 20 minutes</td>
<td>Approximately 15 minutes</td>
<td>0.5–3.0 hours</td>
</tr>
<tr>
<td>Protein binding</td>
<td>94%–96%</td>
<td>96%</td>
<td>61%–64%</td>
<td>52%–65%</td>
</tr>
<tr>
<td>Half-life</td>
<td>40–56 hours</td>
<td>5.5 hours</td>
<td>10–14 hours (inhaled powder)</td>
<td>26 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic and UGT1A1</td>
<td>Hepatic (hydroxylation by CYP3A4)</td>
<td>Hepatic via glucuronidation and O-demethylation</td>
<td>Hepatic via glucuronidation and secondarily via O-demethylation</td>
</tr>
<tr>
<td>CYP450 enzyme involvement</td>
<td>CYP3A4 (minor)</td>
<td>Metabolized by CYP3A4</td>
<td>CYP2D6, CYP2C8/9, CYP2C19, and CYP2A6 involved in O-demethylation</td>
<td>CYP2D6 and CYP2C19 (O-demethylation)</td>
</tr>
<tr>
<td>Elimination</td>
<td>• Feces: approximately 90% (54% as unchanged drug) • Urine: &lt;2% (as unchanged drug)</td>
<td>Feces: 60%</td>
<td>Urine: 25%</td>
<td>Urine: 15%–18% as direct glucuronide metabolites; 2%–10% as unchanged drug</td>
</tr>
</tbody>
</table>

\(C_{\text{max}}\) = maximum plasma concentration; CYP = cytochrome P450; UGT1A1 = UDP glucuronosyltransferase 1 family, polypeptide A1.

Data from references 8 and 31–33.
improvements in FEV₁; however, these studies were not powered to show the superiority or non-inferiority of indacaterol over the active treatments.

The clinical threshold for improvement in trough FEV₁ was 120 mL, and the threshold for the FEV₁ area-under-the-curve (AUC) concentration was 220 mL.14 Secondary endpoints included:

- peak FEV₁, FEV₁ AUC concentration, and FEV₁ at 5 minutes after administration
- safety outcomes, including (1) clinically meaningful changes in the corrected QT (QTc) interval (more than 60 msec over baseline or more than 500 msec); (2) mean pulse rate (exceeding 90 beats per minute); (3) mean blood pressure (BP) (higher than 200 mm Hg or an increase of more than 20 mm Hg over baseline); (4) blood glucose (above 7.7 mmol/L or 139 mg/dL); and (5) serum potassium (less than 3.5 mmol/L).13–20

Patients kept diaries to record adverse events (AEs), peak expiratory flow (PEF), the number of days of poor control, and the frequency of use of rescue medication (salbutamol or albuterol).16–20 Details of the studies are discussed next and are summarized in Table 4.

Phase 2 Studies16–19

Four phase 2, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging studies (N = 1,621) evaluated the safety, tolerability, and efficacy of indacaterol in COPD.16–19 Patients were randomly assigned to receive indacaterol 50, 75, 100, 200, 400, 600, or 800 mcg once daily over periods of 8 to 28 days. The primary endpoints included changes from baseline in trough FEV₁ and inspiratory capacity as well as safety measurements (e.g., hematology, blood chemistry, urinalysis, vital signs, and ECG changes). Patients who met the diagnostic criteria for moderate-to-severe COPD, as defined by GOLD criteria, were included in these studies.16–20 Overall, trough FEV₁ increased significantly in all indacaterol groups compared with placebo (P < 0.001).16–19 Indacaterol 50 and 100 mcg brought about similar results, increasing FEV₁ by 160 mL, with a 95% confidence interval (CI) of 100–220 mL, compared with placebo.17 Indacaterol 200 and 400 mcg increased FEV₁ by 200 mL (95% CI, 150–260 mL) and 220 mL (95% CI, 170–290 mL), respectively, compared with placebo.17 Although the 800-mcg dose significantly improved trough FEV₁ compared with placebo (P < 0.0001), it provided less improvement in trough FEV₁ compared with the 400-mcg dose.16 Moreover, indacaterol 600 mcg did not result in clinically significant improvement in FEV₁, compared with indacaterol 300 mcg, and provided similar improvement in FEV₁ compared with the 150-mcg dose.18

In addition to significant improvements in trough FEV₁, compared with placebo (P < 0.001) and formoterol (P = 0.003), patients treated with indacaterol 300 mcg experienced significant improvements in inspiratory capacity at all time points relative to placebo (P < 0.001) and formoterol (P = 0.034).18 Indacaterol provided similar improvements in trough FEV₁ compared with tiotropium in the open-label extension phase of a dose-ranging study.17 In one trial with an adaptive seamless design, indacaterol 150 mcg was selected as the lowest effective dose;19 however, in another study, statistical and clinical differences were observed at doses as low as 50 mcg.17

In general, mild-to-moderate AEs were reported in patients taking indacaterol, and there were no drug-related serious AEs.16–18 No clinically significant differences in mean pulse rate, mean BP, QTc interval, blood glucose, or serum potassium were noted in patients treated with indacaterol 50 to 400 mcg compared with placebo.16–18 However, in one study, patients who were treated with indacaterol 800 mcg had serum potassium levels that were significantly lower than those in the placebo group (P = 0.029) and in the indacaterol 400-mcg group (P = 0.031). In addition, three indacaterol 400-mcg patients and one indacaterol 800-mcg patient showed an increase in the QTc interval that exceeded 60 msec from baseline when calculated with Friedman’s formula.16

Phase 3 Studies13,20–24

Six phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group studies evaluated the safety and efficacy of indacaterol over periods of 2 to 52 weeks.13,20–24 Patients in these trials (N = 2,633) were randomly assigned to receive indacaterol 150 or 300 mcg once daily. In one study, patients also received open-label tiotropium 18 mcg once daily.21

In three of the studies, the primary endpoint was trough FEV₁ at the end of the treatment period compared with placebo.13,21,22 However, one study used the FEV₁ at 5 minutes after administration as the primary outcome measure.23 A difference of 120 mL between indacaterol and placebo was prespecified as the smallest amount to be considered clinically significant for trough FEV₁.13,21–24 Although some phase 2 studies evaluated doses of indacaterol up to 800 mcg, doses greater than 300 mcg were avoided in the phase 3 studies.19 This was probably a result of the lack of improvement in patients who had received higher indacaterol doses and of the increased incidence of AEs in these patients.

At the end of the various study periods, indacaterol demonstrated greater efficacy than placebo, with a difference in trough FEV₁ of 130 to 180 mL with 150 mcg and 300 mcg, respectively (P < 0.001).13,20–23 Tiotropium also exceeded the 120-mL clinical threshold relative to placebo, with an increase in trough FEV₁ of 140 mL (P < 0.001).21

Indacaterol also performed significantly better than placebo in terms of increasing trough FEV₁ after the first dose (80-mL increase; P < 0.01) and at all other time points (P < 0.001).21 In two studies, indacaterol 150 mcg provided higher peak FEV₁ values on day 1 and at the end of the treatment period relative to placebo; differences were 190 mL (P < 0.001) and 160 mL (P < 0.001), respectively.13,22

Increases in FEV₁ 5 minutes after administration were significantly greater with both indacaterol 150 mcg and 300 mcg, when compared with placebo, with treatment differences of 100 mL (95% CI, 70–130 mL; P < 0.001) and 120 mL (95% CI, 90–150 mL; P < 0.001), respectively.23 This significant outcome was also noted in other studies as a secondary endpoint.13,22

Five minutes after administration, the FEV₁ was also higher with both indacaterol 150 mcg (a 10-mL difference) and 300 mcg (a 30-mL difference) than with salmeterol 50 mcg twice daily.21 Both indacaterol doses significantly increased text continues on page 93
Table 4 Controlled Clinical Trials of Indacaterol in Patients With Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Study Design, Duration</th>
<th>Regimen</th>
<th>Effects on FEV₁</th>
<th>Other Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beier et al. (2007)¹⁶</strong></td>
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<tr>
<td>Randomized</td>
<td>Double-blind</td>
<td>Placebo-controlled</td>
<td>Parallel-group</td>
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</table>

**Rennard et al. (2008)¹⁷** | IND 50 mcg daily (n = 103) | IND 100 mcg daily (n = 105) | IND 200 mcg daily (n = 105) | IND 400 mcg daily via multiple-dose DPI (n = 110) | IND 400 mcg daily via single-dose DPI (n = 105) | PBO once daily (n = 107) | TIO 19 mcg once daily, open-label for 8 days | FEV₁ AUC (22–24 hours) at day 7 (P < 0.001 vs. PBO for all): | IND 50: 160 mL (95% CI, 100–210) | IND 100: 160 mL (95% CI, 110–220) | IND 200: 200 mL (95% CI, 150–260) | IND 400 (multiple-dose DPI): 230 mL (95% CI, 180–290) | IND 400 (single-dose DPI): 220 mL (95% CI, 170–280) | IND trough FEV₁ levels compared favorably with improvement seen by day 8 in subjects receiving TIO in open-label extension | All IND doses well tolerated | IND 50 had fewest AEs |

**Kato et al. (2010)¹⁸** | IND 150 mcg once daily (n = 48) | IND 300 mcg once daily (n = 47) | IND 600 mcg once daily (n = 48) | PBO once daily (n = 46) | FEV₁ AUC (22–24 hours) at day 28 (P < 0.001 vs. PBO for all): | IND 150: 130 mL (95% CI, 100–160) | IND 300: 160 mL (95% CI, 130–190) | IND 600: 170 mL (95% CI, 140–200) | 5-minute post-dose FEV₁ was significantly better with all IND doses vs. PBO (P < 0.001) | IND well tolerated; showed no clinically meaningful effect on pulse rate, blood pressure, QTc interval, or laboratory parameters |

**Barnes et al. (2010)¹⁹** | IND 75 mcg once daily (n = 115) | IND 150 mcg once daily (n = 111) | IND 300 mcg once daily (n = 114) | IND 600 mcg once daily (n = 111) | FOR 12 mcg twice daily (n = 112) | PBO (n = 119) | TIO 18 mcg once daily, open-label (n = 119) | IND 150 mcg was lowest effective dose, exceeding criteria for trough FEV₁, (reference value, 140 mL vs. PBO) and FEV₁ AUC (1–4 hr) (reference value, 220 mL vs. PBO) | IND well tolerated; showed no safety signal observed with any dose of IND | IND 150 and IND 300 selected to continue to the second 26-week stage (Donohue et al., 2010) |

**Dahl et al. (2010)²⁰** | IND 300 mcg once daily + dummy PBO (n = 437) | IND 600 mcg once daily + dummy PBO (n = 428), FOR 12 mcg twice daily (n = 435) | PBO (n = 432) | Rescue med: SAL | Both IND doses increased FEV₁ by 170 mL vs. PBO and by 100 mL vs. FOR at week 12 (all P < 0.001); differences were maintained at week 52 | Increases in FEV₁ at 5 minutes post dose: | IND 150: 130 mL (95% CI, 110–150) | IND 300: 150 mL (95% CI, 140–170) | FOR: 140 mL (95% CI, 120–160) | IND was as effective as FOR in improving TDI score and reducing use of as-needed SAL | IND was well tolerated; good safety profile | Death (possibly related to treatment) occurred in one IND patient who discontinued study drug 3 days previously because of dyspnea | table continues
Table 4  Controlled Clinical Trials of Indacaterol in Patients With Chronic Obstructive Pulmonary Disease (cont.)

<table>
<thead>
<tr>
<th>Study Design, Duration</th>
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</tr>
</thead>
</table>
| **Feldman et al. (2010)**<sup>13</sup> | • IND 150 mcg once daily (n = 211)  
• PBO once daily via single-dose DPI (n = 205) | • Mean difference between IND and PBO in trough FEV₁ at 24 hours post dose at week 12 was 130 ± 24 mL (P < 0.001)  
• Mean difference between IND and PBO in peak FEV₁ on day 1: 190 mL (P < 0.001)  
• Mean difference between IND and PBO in peak FEV₁ at week 12: 160 mL (P < 0.001) | • IND reduced percentage of days of poor control by 22.5% vs. PBO (P < 0.001)  
• IND was associated with less use of rescue medication vs. PBO (P < 0.001)  
• No decrease in effectiveness due to beta₂-adrenoreceptor down-regulation was noted  
• AE rates were comparable between treatment groups (IND, 49.3% vs. PBO, 46.8%)  
• Most common AEs were COPD worsening (IND, 8.5% vs. PBO, 12.2%) and cough (IND, 6.2% vs. PBO, 7.3%)  
• Serum potassium and blood glucose levels did not differ significantly between treatment groups  
• No patients had QTc > 500 msec |
| **Donohue et al. (2010)**<sup>14</sup> | • IND 150 mcg once daily (n = 349)  
• IND 300 mcg once daily (n = 361)  
• PBO once daily (n = 317)  
• TIO 18 mcg once daily, open-label (n = 356) | • IND 150 and IND 300 increased trough FEV₁ by 180 mL vs. PBO at week 12 (P < 0.001)  
• TIO increased trough FEV₁ by 140 mL vs. PBO at week 12 (P < 0.001)  
• Both IND doses were superior to TIO for improved FEV₁ (40–50 mL) (P < 0.01) | • At week 26, IND 150 and IND 300 increased TDI by 1.00 and 1.18 (P < 0.001 vs. PBO)  
• At week 26, TIO increased TDI by 0.87 (P < 0.001 vs. PBO)  
• Time to first exacerbation was reduced with IND 150 (HR, 0.69; 95% CI, 0.51–0.94; P = 0.019) but not with IND 300 or TIO  
• Overall rate of exacerbations was reduced with IND 150 (RR, 0.67; 95% CI, 0.46–0.99; P = 0.019) but not with IND 300 or TIO  
• Occurrence of low serum potassium, high blood glucose, and prolonged QTc interval was similar for all treatments |
| **Chapman et al. (2011)**<sup>22</sup> | • IND 150 mcg once daily (n = 144)  
• IND 300 mcg once daily (n = 146)  
• PBO once daily (n = 125)  
• ALB as needed | • IND groups increased trough FEV₁ by ≥170 mL vs. PBO at week 52 (P < 0.05)  
• IND 150 and IND 300 increased 5-minute post-dose FEV₁ by 90 mL and 100 mL, respectively, vs. PBO (P = 0.01) | • IND groups significantly reduced COPD exacerbations (P < 0.05) and use of as-needed ALB (P < 0.001) vs. PBO  
• No tolerance to bronchodilator effect of IND observed  
• IND had no clinically significant effect on QTc or on serum potassium or plasma glucose levels |
| **Kornmann et al. (2011)**<sup>23</sup> | • IND 150 mcg once daily (n = 289)  
• PBO (n = 265)  
• SAL 50 mcg twice daily (n = 284) | • At week 12, IND increased trough FEV₁ by 170 mL vs. PBO (P < 0.001) and by 60 mL vs. SAL (P < 0.001) | • Both active treatments improved SGRQ and TDI vs. PBO, with differences between them favoring IND  
• Safety profiles were similar across treatment groups  
• Both IND and SAL well tolerated |
Table 4 Controlled Clinical Trials of Indacaterol in Patients With Chronic Obstructive Pulmonary Disease (cont.)

<table>
<thead>
<tr>
<th>Study Design, Duration</th>
<th>Regimen</th>
<th>Effects on FEV₁</th>
<th>Other Key Results</th>
</tr>
</thead>
</table>
| **Balint et al. (2010)²⁴** | • Randomized  
• Double-blind  
• Placebo-controlled  
• Crossover  
• Phase 3  
• 2 weeks | • 89 patients assigned to receive:  
- IND 150 mcg once daily  
- IND 300 mcg once daily  
- PBO once daily  
- SAL 200 mcg once daily  
- SAL/FLU 50/500 mcg once daily | • IND 150 and IND 300 increased 5 minutes post-dose FEV₁ by 100 mL and 120 mL, respectively, vs. PBO (P < 0.001)  
• Percentages of patients with FEV₁ increase of at least 12% and 200 mL at 5 minutes post dose (P < 0.05 vs. PBO):  
- IND 150: 18.8%  
- IND 300: 27.6%  
- SAL 200: 23.3%  
- SAL/FLU 50/500 mcg: 9.1%  
- PBO: 3.4% | • AE rates were similar among treatment groups |
| **Korn et al. (2011)²⁵** | • Randomized  
• Double-blind  
• Double-dummy  
• Active-controlled  
• Parallel-group  
• Phase 3  
• 12 weeks | • IND 150 mcg once daily + dummy PBO (n = 560)  
- SAL 50 mcg twice daily (n = 563) | • IND increased FEV₁ AUC (5 minutes–11 hour 5 minutes) by 57 mL vs. SAL at week 12 (P < 0.001)  
• IND increased 24-hour trough FEV₁ by 60 mL vs. SAL at week 12 (P < 0.001)  
• IND improved mean total TDI score by 0.63 vs. SAL at Week 12 (P < 0.001)  
• IND was superior to SAL for percentage of patients with clinically relevant change from baseline in mean total TDI score (69.4% vs. 62.7%) (P < 0.05)  
• Patients on IND used fewer puffs per day of rescue med vs. SAL (mean difference, 0.18) (P < 0.05)  
• Patients on IND had greater percentage of days with no rescue use vs. SAL (mean difference, 4.4 days) (P < 0.05)  
• One patient in IND group had potassium level <3 mmol/L, and one patient had SBP > 200 mm Hg or increase from baseline > 20 mm Hg | |
| **Beier et al. (2009)²⁶** | • Randomized  
• Double-blind  
• Active-controlled  
• Crossover  
• Phase 3  
• 4 weeks | • On separate study days, 30 patients each received:  
- IND 300 mcg and matching PBO in randomized sequence, followed by:  
  - FOR 12 mcg twice daily, open-label | • IND had a greater effect than FOR on FEV₁ at 8 hours (1.47 L vs. 1.39 L) (P = 0.014) and 24 hours (1.44 L vs. 1.35 L) (P = 0.003)  
• At 24 hours, IND and FOR increased FEV₁ by 17.7% and 7.5% from pre-dose  
• IND and FOR increased FEV₁ at all time points vs. PBO (P < 0.001)  
• Effects on peak FEV₁ were similar for IND and FOR | • IND had a greater effect on resting IC from 4 to 24 hours vs. FOR (difference, 0.13–0.19 L; P < 0.05)  
• IND had greater effect on peak IC vs. FOR (31% vs. 23% from pre-dose) (P = 0.034)  
• IND improved IC significantly more than FOR at all post-baseline time points (P < 0.05)  
• AE rates similar among treatment groups  
• No changes in serum potassium, blood glucose, pulse rate, or QTc were observed |
| **Vogelmeier et al. (2010)²⁷** | • Randomized  
• Double-blind  
• Double-dummy  
• Placebo- and active-controlled  
• Noninferiority  
• Crossover  
• Phase 3  
• 2 weeks | • Patients received three of the following four treatments for 14 days:  
- IND 150 mcg once daily (n = 118)  
- IND 300 mcg once daily (n = 122)  
- TIO 18 mcg once daily (n = 120)  
- PBO once daily (n = 123) | • On day 1, at 5 minutes post dose, IND 150 and IND 300 increased mean FEV₁ by 120 and 130 mL, respectively, vs. PBO (P = 0.001)  
• On day 1, at 5 minutes post dose, both IND doses increased mean FEV₁ by 80 mL vs. TIO (P < 0.001)  
• At day 14, IND 150 and IND 300 increased trough FEV₁ by 170 and 150 mL, respectively, vs. PBO (both P < 0.001)  
• At day 14, IND 150 and IND 300 increased trough FEV₁ by 10 and 30 mL, respectively, vs. TIO (NS) | • AE rates similar across treatment groups  
• No increases in potassium, blood glucose, or QTc were noted |
Table 4 Controlled Clinical Trials of Indacaterol in Patients With Chronic Obstructive Pulmonary Disease (cont.)

<table>
<thead>
<tr>
<th>Study Design, Duration</th>
<th>Regimen</th>
<th>Effects on FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Other Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnussen et al. (2010)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Three 14-day treatment cycles in 96 patients:</td>
<td>At day 14, trough FEV&lt;sub&gt;1&lt;/sub&gt; was 200 mL higher with IND vs. PBO and 110 mL higher with IND vs. SAL (both P &lt; 0.001)</td>
<td>Both morning and evening IND improved percentage of nights with no awakenings (by 1.19 and 8.1 points, respectively) (P &lt; 0.01); percentage of days with no daytime symptoms (by 6.7 and 5.5 points) (P &lt; 0.05); and percentage of days able to perform usual activities (by 6.7 and 7.8 points) (P &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>• IND 300 mcg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SAL 50 mcg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PBO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laforce et al. (2011)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>68 patients assigned to receive:</td>
<td>On day 1, trough FEV&lt;sub&gt;1&lt;/sub&gt; was 150 mL higher with IND vs. PBO (P &lt; 0.001)</td>
<td>IND provided superior bronchodilation vs. PBO (P &lt; 0.001) across 24-hour assessment period on days 1 and 14</td>
</tr>
<tr>
<td></td>
<td>• IND 300 mcg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PBO once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SAL 50 mcg twice daily, open-label</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Donnell et al. (2011)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>90 patients assigned to receive:</td>
<td>IND increased FEV&lt;sub&gt;1&lt;/sub&gt; by 0.25 mL vs. PBO (P &lt; 0.001) at 75 minutes post dose after 3 weeks</td>
<td>IND increased resting IC by 0.17 mL (P = 0.001) and FVC by 0.26 mL (P &lt; 0.001) vs. PBO at 75 minutes post dose after 3 weeks</td>
</tr>
<tr>
<td></td>
<td>• IND 300 mcg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PBO once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE = adverse event; ALB = albuterol; AUC = area under the curve; BODE Index = body mass index, obstruction, dyspnea, and exercise; CI = confidence interval; DPI = dry-powder inhaler; ECG = electrocardiogram; FEV<sub>1</sub> = forced expiratory volume in 1 second; FOR = formoterol; FVC = forced vital capacity; HR = hazard ratio; IC = inspiratory capacity; IND = indacaterol; NS = not significant; PBO = placebo; QTc = corrected QT interval (Fridericia’s formula); RR = risk ratio; SAL = salbutamol; SAL/FLU = salmeterol/fluticasone; SBP = systolic blood pressure; SGRQ = St. George’s Respiratory Questionnaire; TDI = Transition Dyspnea Index; TIO = tiotropium. 

Data from references 13 and 16–30.

The FEV<sub>1</sub> 5 minutes after administration, compared with salmeterol/fluticasone 50/500 mcg once daily (a 50-mL increase with indacaterol 150 mcg; P = 0.003 and a 70-mL increase with indacaterol 300 mcg, P < 0.001).<sup>24</sup>

Two studies reported significant reductions in the number of COPD exacerbations in patients receiving indacaterol 150 mcg; P = 0.003 and a 70-mL increase with indacaterol 300 mcg, P < 0.001).<sup>24</sup>

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the FEV<sub>1</sub>, 5 minutes after administration, compared with salmeterol/fluticasone 50/500 mcg once daily (a 50-mL increase with indacaterol 150 mcg; P = 0.003 and a 70-mL increase with indacaterol 300 mcg, P < 0.001).<sup>24</sup>

Two studies reported significant reductions in the number of COPD exacerbations in patients receiving indacaterol 150 mcg and 300 mcg compared with placebo (relative risk [RR], 0.64; 95% CI, 0.43–0.96; P = 0.029 for 150 mcg, and RR, 0.62; 95% CI, 0.42–0.92; P = 0.018 for 300 mcg).<sup>23,24</sup> In one study, indacaterol 150 mcg also significantly reduced the time to the first exacerbation when compared with placebo (hazard ratio [HR], 0.69; 95% CI, 0.51–0.94; P = 0.019).<sup>24</sup> Compared with placebo, indacaterol reduced the number of days of poor control by 22.5% (P < 0.001) and significantly reduced the use of rescue inhaler medication by 1.2 to 1.4 puffs per day (P < 0.001).<sup>13,22</sup>

Indacaterol improved patients’ health status, as demonstrated by a mean total deterioration of more than 4 units in St. George’s Respiratory Questionnaire (SGRQ) scores.<sup>22,24</sup> No decrease in efficacy resulting from beta<sub>2</sub>-adrenoreceptor down-regulation was reported.<sup>13,22</sup> AE rates were comparable between active-treatment groups and were not greater than those associated with placebo.<sup>13,21–23</sup> The most frequently reported AE in the indacaterol and placebo groups were COPD worsening (8.5% to 12%, respectively) and cough (6.2% and 7.3%).<sup>13</sup> Indacaterol had no clinically significant effects on serum potassium levels, plasma glucose levels, or the QTc interval.<sup>13,21–24</sup>

Two phase 3, randomized, double-blind, double-dummy, active-controlled, parallel-group studies (N = 2,455) evaluated the safety and efficacy of indacaterol. <sup>20,21</sup> Dahl et al. assigned patients to receive indacaterol 300 mcg or 600 mcg plus dummy placebo, formoterol 12 mcg twice daily, or placebo for 52 weeks.<sup>20</sup> Korn et al. assigned patients to receive indacaterol 150 mcg plus dummy placebo or salmeterol 50 mcg twice daily for 12 weeks.<sup>25</sup>
The primary endpoint in the Dahl study was trough FEV₁ at week 52, and the primary endpoint in the Korn study was FEV₁ AUC (5 minutes to 11 hours 45 minutes) at week 12. Secondary endpoints in both studies included the Transition Dyspnea Index (TDI), the use of rescue medication, COPD exacerbations, the patients’ health status (as determined by SGRQ scores), the BODE Index (body mass index, obstruction, dyspnea, and exercise capacity), safety, and tolerability.²⁰²⁵

In the Dahl study, the 300-mcg and 600-mcg doses of indacaterol significantly improved trough FEV₁.²⁶ Indacaterol 300 mcg increased FEV₁ by 110 mL (95% CI, 120–200 mL) and indacaterol 600 mcg increased FEV₁ by 150 mL (95% CI, 110–190 mL), compared with an increase of 50 mL (95% CI, 10–90 mL) with formoterol (P < 0.001 for both comparisons). These differences were maintained at 52 weeks.²⁰

Increases in FEV₁ at 5 minutes after administration were significantly greater with indacaterol 300 mcg (a 130-mL increase; 95% CI, 110–150 mL) and indacaterol 600 mcg (a 150-mL increase; 95% CI, 140–170 mL) when compared with placebo (P < 0.001) but not when compared with formoterol (a 140-mL increase; 95% CI, 120–160 mL). Indacaterol and formoterol were equally effective in improving TDI scores and in reducing the need for rescue medication. Compared with formoterol, both doses of indacaterol significantly improved morning and evening PEF measures.²⁰

In general, indacaterol was well tolerated. One patient who had discontinued indacaterol 3 days previously because of dyspnea died, a possible result of treatment.²⁰

Korn et al. found that indacaterol 150 mcg was superior to salmeterol in increasing the FEV₁ AUC (5 minutes to 11 hours 45 minutes) after 12 weeks of treatment (mean difference, 57 mL; 95% CI, 37–79 mL; P < 0.001).²⁵ Indacaterol also significantly improved trough FEV₁ (mean difference, 60 mL; 95% CI, 37–83 mL; P < 0.001); FVC (mean difference, approximately 0.09 L; P < 0.05) compared with salmeterol; and the TDI (difference, 0.63; 95% CI, 0.30–0.97; P < 0.001). It also reduced the number of puffs of rescue medication needed per day (mean difference, −0.18; 95% CI, −0.36 to 0.00; P < 0.05) versus salmeterol.²⁵

In general, AE rates were similar between the two treatment groups. One indacaterol patient had a potassium level of less than 3 mmol/L, and one patient had systolic BP that exceeded 200 mm Hg, or an increase from baseline of more than 20 mm Hg.²⁵

Four phase 3, randomized, double-blind, placebo-controlled and active-controlled, multicenter, crossover studies (N = 515) evaluated the safety and efficacy of indacaterol.²⁶²⁰

In a 4-week, randomized, double-blind, double-dummy, active-controlled, multicenter, crossover study (N = 30), Beier et al. compared the bronchodilator effects of indacaterol 300 mcg plus a dummy placebo with formoterol 12 mcg twice daily.²⁶ The primary efficacy endpoint was the change in inspiratory FEV₁ (95% CI, 10–90 mL) with formoterol (P < 0.001 for both comparisons). These differences were maintained at 52 weeks.²⁰

Increases in FEV₁ at 5 minutes after administration were significantly greater with both indacaterol and formoterol than with placebo (P < 0.0001 and P < 0.001, respectively) at all post-dose time points (5 minutes–24 hours). Five minutes after administration, both indacaterol and formoterol increased FEV₁ by 0.22 L compared with placebo. At 24 hours, the mean difference in FEV₁ between indacaterol and formoterol was 0.09 L (P = 0.0003). Indacaterol significantly increased peak FEV₁ (32.3%; 95% CI, 26.4–38.3) compared with placebo (P < 0.001) and significantly improved inspiratory capacity compared with placebo (31.2%; 95% CI, 23.7–38.7; P < 0.001) and formoterol (22.9%; 95% CI, 18.2–27.7; P < 0.05).²⁰

AE rates were similar among treatment groups, except for cough, which occurred in 20% of the indacaterol-treated patients. No serious AEs were reported during the study.²⁶

Vogelmeier et al. evaluated the safety and efficacy of indacaterol in a 2-week, phase 3, randomized, double-blind, double-dummy, placebo- and active-controlled, multicenter, crossover study (N = 483).²⁷ Patients received three of four treatments at separate periods: indacaterol 150 mcg, indacaterol 300 mcg, tiotropium 18 mcg, or placebo. The primary endpoint was trough FEV₁ after 14 days.

Indacaterol 150 mcg and 300 mcg were significantly more effective than placebo for increasing trough FEV₁ (mean differences, 170 mL [95% CI, 120–220] for 150 mcg and 150 mL [95% CI, 100–200] for 300 mcg; P < 0.001 for both). The two indacaterol doses also provided significantly higher mean FEV₁ after 5 minutes compared with placebo (differences, 120 mL and 130 mL for 150 mcg and 300 mcg, respectively; P < 0.001) and tiotropium (difference with both doses, 80 mL; P < 0.001).²⁷

Indacaterol 150 mcg and 300 mcg also demonstrated superiority over placebo and non-inferiority to tiotropium in terms of increases in trough FEV₁.²⁷ AEs occurred at similar rates in all treatment groups. No increases in potassium, blood glucose, or the QTc interval occurred.²⁷

Two phase 3, randomized, double-blind, double-dummy, multicenter, crossover studies (N = 164) compared 2 weeks of treatment with indacaterol 300 mcg once daily versus salmeterol 50 mcg twice daily and placebo.²⁸²⁹ The primary endpoint in both studies was trough FEV₁ with indacaterol compared with salmeterol. Secondary endpoints included the percentage of nights with no nighttime awakenings, the percentage of days without symptoms, and the percentage of days on which patients were able to perform their usual activities.²⁸²⁹

In both studies, trough FEV₁ with indacaterol 200 mL higher than in the placebo group (P < 0.001) whether or not the dose was given in the morning or evening. Trough FEV₁ was 90 mL and 110 mL higher with indacaterol than with salmeterol at 12 hours (P = 0.011 and P < 0.001, respectively).²⁸²⁹ Bronchodilation with indacaterol was superior to that with placebo at all time points (P < 0.001). Moreover, in the study by Laforce et al., indacaterol increased FEV₁ better than salmeterol (P < 0.05) 5 minutes after administration and at all subsequent time points.²⁸²⁹ In the Magnussen study, indacaterol improved the percentage of nights with no awakenings (by 8.1 to 11 points; P < 0.01); the percentage of days with no daytime symptoms (by 5.5 to 6.7 points; P < 0.05); and the percentage of days that patients were able to perform their usual activities (by 6.7 to 7.8 points; P < 0.05).²⁸

All treatments were well tolerated in
both studies, and AE rates were similar for all treatment groups. Cough was the most frequently reported AE. There were no drug-related serious AEs.28,29

In a phase 3, double-blind, crossover study, O’Donnell et al. evaluated the effect of indacaterol on exercise endurance and lung hyperinflation during exercise and at rest in 90 patients with moderate-to-severe COPD.30 Patients were randomly assigned to receive indacaterol 300 mg once daily or placebo. The primary efficacy endpoint was exercise endurance time after 3 weeks of treatment.30

Exercise endurance time was significantly greater with indacaterol than with placebo (treatment difference, 101 seconds; \( P < 0.001 \)). Indacaterol also provided a significant increase in end-exercise inspiratory capacity compared with placebo (0.28 L; \( P = 0.002 \)).30

Significant improvements were noted in resting inspiratory capacity (0.17 L; \( P = 0.001 \)), FEV1 (0.25 L; \( P < 0.001 \)), and FVC (0.26 L; \( P < 0.001 \)) after 3 weeks of treatment, when compared with placebo, 75 minutes after administration.30

**DOSAGE AND ADMINISTRATION**

Until the approval of indacaterol, all available LABAs had been administered twice daily either by a dry-powder inhaler or by a solution for nebulization.31–33

Indacaterol is available in a 75-mcg dose for once-daily administration via a dry-powder inhaler device called a Neohaler.8 The dry powder is derived from hard, gelatin capsules that the patient must insert into the Neohaler device before administration. The capsules are provided in blister packs of 30 and should remain in the blister packaging until immediately before administration.9 Patients should be informed that the medication is effective only if delivered via the Neohaler device and that the capsules should not be swallowed.

As with any of the dry-powder inhalers that require manual loading of doses prior to administration, consideration should be given to patients’ cognitive ability to follow instructions and their physical ability (dexterity and strength) to prepare the dose for administration.33

Table 5 lists dosage, administration, and monitoring considerations for the available LABAs.

Currently, indacaterol is indicated only for long-term maintenance treatment of COPD and should not be used acutely to treat exacerbations.8 However, the FDA has requested that studies be conducted in patients with asthma, and it is anticipated that the manufacturer will seek FDA approval for this indication.11

**PHARMACOECONOMIC CONSIDERATIONS**

Pharmacoeconomic considerations are especially important in patients with COPD because this condition occurs most commonly in adults who have a family income below the federal poverty level.2 In addition, because a large proportion of patients with COPD may have health insurance coverage through Medicare, it is likely that they will ex-

| Table 5 Dosage, Administration, and Monitoring for the Long-Acting Beta-Agonists |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Indacaterol**                 | **Salmeterol**  | **Formoterol**  | **Arformoterol** |
| **Dose, route, and frequency** | 75 mcg inhaled, once daily | 50 mcg inhaled, twice daily, at least 12 hours apart | 12 mcg inhaled, twice daily (inhalation powder) or 20 mcg nebulized, twice daily, at least 12 hours apart (inhalation solution) | 15 mcg nebulized, twice daily, at least 12 hours apart |
| **Renal impairment**            | Not studied; no dosage adjustment expected | No dosage adjustment needed | N/A (solution) | No dose adjustment needed |
| **Hepatic impairment**          | No dosage adjustment needed | Not well studied; patients should be monitored closely | N/A (solution) | No dose adjustment needed |
| **Age**                         | No dosage adjustment needed; safety has not been established in pediatric patients | No dosage adjustment needed; however, elderly patients should be counseled on which inhaler to use and on proper scheduling of doses | Not studied in the elderly; should not be used in children | Sensitivity has not been established for younger and older patients |
| **Patient counseling**          | • Patients should be counseled on proper insertion of capsules into the product devices for indacaterol and formoterol and on the proper use, technique, and care of a nebulizer. • Patients should be counseled on which inhaler to use and on the proper scheduling of doses (if multiple inhalers are used). | | |
| **Monitoring parameters**       | Periodic measurements of FEV1, peak flow, and/or other pulmonary function tests; blood pressure, heart rate, serum glucose, serum potassium. | | |

Data from references 8 and 31–33.
ceed the annual $2,830 expense threshold and will become subject to the coverage gap (‘donut hole’) that requires them to pay 100% of medication costs, at least until copayments are reinstated after $4,550.33 Based on the average wholesale prices of the available LABAs (see Table 1, page 87), patients with COPD could easily exceed Medicare thresholds if they are taking multiple medications for COPD or for comorbidities.9,34

Pharmacists can improve patient adherence to the medication regimen by being mindful of cost and reimbursement issues and by providing assistance with product selection for patients with COPD. The once-daily dosing schedule of indacaterol is convenient and could improve patient compliance and drug affordability.

SAFETY

Indacaterol has been available in Europe since 2009 and has been sold around the world for the treatment of COPD.34 The postmarketing safety database includes AE reports of exposures totaling 57,000 patient-years.

Similar to the other LABAs, indacaterol (especially the 300-mcg dose) has been associated with possible asthma exacerbation and asthma-related deaths, as well as with an increase in beta-agonistic effects. The labeling for indacaterol includes a boxed warning regarding the risk of asthma-related death associated with LABA therapy.8 The safety and efficacy of indacaterol have not been established in patients with asthma, and indacaterol is not indicated for the treatment of asthma.8

At the time of FDA approval in July 2011, there were no new safety concerns with indacaterol.25 Therefore, only a communication plan and a timetable for assessment are mandated by the FDA as part of the product’s Risk Evaluation and Mitigation Strategy (REMS). The manufacturer has voluntarily provided patients with a medication guide to communicate the potential risks of misusing the Neohaler device.11

Overall, studies of indacaterol have reported a good safety profile.12,14,35 The rates of AEs characteristic of beta agonists, including muscle spasm, headache, and tremor, were comparable between indacaterol and placebo.13 Beta agonists are also known to increase the risk of QTc interval prolongation. However, cardiac safety studies of indacaterol at doses two to four times the therapeutic dose showed no clinically relevant effects on the QTc interval.30,14,36 Compared with placebo, indacaterol did not significantly increase the risk of cardiac or cerebrovascular AEs.

The QTc interval was evaluated as a secondary safety endpoint in clinical studies of indacaterol in patients with COPD.12,13,18,19,21–26 In these studies, the threshold for discontinuation was an increase in QTc of more than 500 msec or more than 60 msec from baseline. In general, no significant differences were observed between indacaterol and placebo with regard to changes in the QTc interval, and no patients discontinued indacaterol treatment because of cardiovascular safety concerns.13,18,19,21–26 Further, the risks of myocardial infarction, stroke, arrhythmias, and cardiovascular-related death were not significantly increased with indacaterol compared with placebo.37

The down-regulation of beta2-adrenoceptors can occur during chronic administration of LABAs, resulting in tachyphylaxis. However, tachyphylaxis has not been observed during long-term treatment with indacaterol.20 In clinical studies, cough was the most commonly

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**Table 6** Contraindications, Warnings, and Precautions Associated With the Long-Acting Beta-Agonists (LABAs)

<table>
<thead>
<tr>
<th>Contraindications, Warnings, Precautions</th>
<th>Indacaterol</th>
<th>Salmeterol</th>
<th>Formoterol</th>
<th>Arformoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy in treatment of status asthmaticus, other acute episodes of asthma, or COPD</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Severe hypersensitivity to milk proteins</td>
<td>C</td>
<td>C</td>
<td>W/P</td>
<td>—</td>
</tr>
<tr>
<td>Asthma-related death</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W</td>
</tr>
<tr>
<td>Deterioration of disease and acute episodes</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W</td>
</tr>
<tr>
<td>Excessive use and use with other LABAs</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W</td>
</tr>
<tr>
<td>Cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension)</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
</tr>
<tr>
<td>Strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin)</td>
<td>—</td>
<td>W/P</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Paradoxical bronchospasm</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W</td>
</tr>
<tr>
<td>Coexisting conditions (e.g., convulsive disorders or thyrotoxicosis)</td>
<td>W/P</td>
<td>W/P</td>
<td>W/P</td>
<td>W</td>
</tr>
</tbody>
</table>

C = contraindication; COPD = chronic obstructive pulmonary disease; CYP = cytochrome P450; P = precaution; W = warning.

Data from references 8 and 31–33.
reported AE associated with indacaterol, occurring in 20% of patients. Indacaterol-associated cough is of short duration (less than 2 minutes after administration) and is not related to bronchospasm. The cough usually does not occur after the first month of treatment.8,12,14

DRUG INTERACTIONS
Caution should be exercised with the concomitant use of indacaterol and other adrenergic drugs because the effects of indacaterol may be potentiated. The concomitant treatment with steroids and diuretics may also increase the risk of hypokalemia. Hypokalemia that is sometimes caused by non–potassium-sparing diuretics may be acutely worsened by beta-agonists.8,13–33

Extreme caution should be exercised when indacaterol is used in patients taking monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval; the concomitant use of these drugs may potentiate the QTc prolongation associated with LABA therapy.8,13–33

Beta blockers interfere with the therapeutic effect of indacaterol; and they may produce severe bronchospasm in COPD patients.8,13–33

CONTRAINDICATIONS AND PRECAUTIONS
The use of indacaterol is contraindicated in patients with acutely deteriorating COPD and who require acute symptom relief. After the initiation of indacaterol therapy, the use of short-acting beta-agonists should be reserved for symptomatic relief of acute respiratory symptoms. No dose adjustments are required for geriatric patients or patients with hepatic or renal impairment.8

Table 6 (see page 96) compares the contraindications, warnings, and precautions of the currently available LABAs.

CONCLUSION
Indacaterol, a LABA, is used for the treatment of COPD because of its ability to relax bronchial smooth muscle.8 Current disease-state standards of care indicate that LABAs should be started in patients with stage II (moderate) COPD.3,6

Indacaterol is administered at a dosage of 75 mcg once daily. No dosage adjustments are required in elderly patients or in those with mild-to-moderate renal or hepatic impairment.8

The safety and efficacy of indacaterol at doses ranging from 75 mcg to 800 mcg have been demonstrated in the treatment of COPD in numerous controlled clinical trials.36–39 However, because of the clinically insignificant differences in efficacy between indacaterol 75 mcg and the higher doses studied, and because of the increased frequency of serious AEs compared with placebo and formoterol, the FDA approved only the 75-mcg dose for marketing in the U.S.11

As with the other LABAs, the labeling for indacaterol includes a boxed warning regarding the risk of asthma-related death.6,23–25 Indacaterol is being studied in asthma, but it is not currently indicated for the treatment of this disorder.8

No statistically or clinically relevant differences in AE rates were observed between indacaterol, placebo, and active controls in clinical studies.16–30 Assessment of specific safety endpoints, including changes in the QTc interval, BP, blood glucose levels, and serum potassium levels, showed no significant differences between indacaterol and placebo.26–30

Because of the chronic dosing of LABAs, some studies have shown a decrease in effectiveness due to beta2-adrenoceptor down-regulation; however, this effect has not been observed in clinical trials of indacaterol.13,28 Indacaterol and the other LABAs have the same contraindications, warnings, and precautions.8,13–33

Pharmacists and health care practitioners will find that indacaterol is an effective bronchodilator, offering convenient once-daily administration with a favorable safety profile and a reasonable price compared with that of the other LABAs. Further, after sufficient efficacy and safety data are available in other conditions, such as asthma and exercise-induced bronchospasm, and if the acquisition costs of the LABAs remain stable, indacaterol will probably replace the other agents as the formulary representative for the LABAs in many institutions.

REFERENCES


