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INDACATEROL MALEATE: A NEW ONCE-DAILY TREATMENT OPTION FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Chronic obstructive pulmonary disease (COPD) is a long-lasting and progressive obstruction of the airways that occurs with chronic bronchitis or emphysema resulting in irreversible expiratory airflow limitation.[1] Approximately 14.2 million people have been diagnosed with COPD in the United Sates with 12.5 million people having chronic bronchitis, and 1.7 million people having emphysema. These numbers may be an underestimate of the actual cases of COPD in the U.S., as half are potentially undiagnosed. The number of people with COPD has increased by 41.5% since 1982. It is estimated that in the U.S. 8 to 17% of men and 10 to 19% of women suffer from some form of COPD, and the number of women diagnosed has increased by 30% in the last decade.[1] While COPD has been recognized for many years, public health officials are growing more concerned about the increases in its prevalence and mortality, which has been largely attributed to the increasing use of tobacco products, both in the U.S. and internationally, and the changing age structure.[2] According to the National Heart Lung and Blood Institute (NHLBI), COPD is now the third leading cause of death in the United States.[1]

The diagnosis of COPD is based on symptomatic presentation, consisting of chronic cough, excess sputum production, or dyspnea, usually correlating with exposure to known risk factors, most notably cigarette smoke.[3] To gauge the extent of disease progression, spirometry is used and recommended by the NHLBI for routine use in all patients 45 years or older who currently or have formerly smoked.[4] The ratio of forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC) is used to diagnose the severity of obstructive impairment of the bronchioles.[5] A ratio of $FEV_1/FVC \leq 0.7$ after the use of a bronchodilator such as albuterol confirms the presence of airflow limitation that is not fully reversible. The percentage of predicated FEV_1 is used to stratify the severity of COPD into mild ($FEV_1 \geq 80\%$ predicted), moderate (FEV_1 50-80% predicted), severe (FEV_1 30-50% predicted), and very severe ($FEV_1 < 30\%$ predicted) COPD.[3]

The pharmacologic treatment of COPD is recommended in all patients who are symptomatic.[6] The current medications approved for the treatment of COPD include bronchodilators ($beta_2$-agonists, anticholinergics, methylxanthines), glucocorticoids, and inhaled corticosteroids (ICS). These medications reduce symptoms, increase exercise capacity, reduce the number of exacerbations, and improve health status; however, no drug treatment has been shown to modify the rate at which a patient's lung function declines. Short-acting bronchodilators can increase exercise tolerance acutely,[7] while long-acting inhaled $beta_2$-agonists (LABAs) improve health status to a greater extent.[8] LABAs re-

Inside This Issue:

duce symptoms, decrease rescue bronchodilator use and increase the time between COPD exacerbations compared with placebo.[8] However, combining medications results in more pronounced treatment benefits.[9,10] For example, combining two short-acting bronchodilators (i.e. albuterol and ipratropium) produces a greater change in spirometry than either agent alone.[11] Combining a LABA and an ICS produces better improvements in spirometry and symptoms than any single drug component.[12] Reflecting this, a recent study found that on average, patients used 3.5 ± 1.5 respiratory medications, which increased in number as the stages of COPD progressed.[12] While this increase in medication use provides proven gains in symptomatic improvement, compliance with this level of polypharmacy can be difficult for many patients.[12] Aside from compliance problems, the current twice-daily dosing of LABAs has been shown to lead to fluctuations in airway patency leading to poor breathing mechanics.[13] A potential solution to these problems is the development of once-daily dosing provided by an extended duration of action. Tiotropium utilized this once-daily dosing strategy and showed improved symptoms and quality of life, and reduced COPD exacerbations. Since then, a demand for once-daily options has increased.[14] Likewise, the development of once-daily dosing for LABAs may provide benefits in patient compliance and airway patency while meeting this demand. Indacaterol maleate, distributed by Novartis Pharmaceuticals under the trade name Arcapta Neohaler®, is the first once-daily LABA indicated for the long-term maintenance of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.[15] This article will focus on the safety, efficacy and tolerability of indacaterol for use in the management of COPD.

Table 1 | Pharmacokinetics of Indacaterol [15,20]

Property	Indacaterol
Elimination half-life	40 hours
T-max	15 minutes
Bioavailability	43-45%
Protein binding	94-96%
Metabolism	Primary: CYP3A4 (hydroxylation) Secondary: UGT1A1 (glucuronidation)
Elimination	>90% excreted in

CYP: cytochrome P450; UGT: uridine diphosphate glucuronyltransferase; Tmax: time to maximum concentration.

Pharmacology and Pharmacokinetics

Indacaterol is a long acting beta$_2$-agonist. Stimulation of beta$_2$-receptors in the lung causes relaxation of bronchial smooth muscle, which produces bronchodilation and a resultant increase in bronchial airflow.[16] These effects are believed to be mediated, in part, by increased activity of adenyl cyclase, an intracellular enzyme responsible for the formation of cyclic-3',5'-adenosine monophosphate (cAMP). An increase in the level of cAMP subsequently causes a relaxation of bronchial smooth muscle reducing the airflow limitation.[16] In vivo studies show that indacaterol has a faster onset than salmeterol with a significantly longer duration of action than formoterol, salmeterol, or salbutamol.[17,18]

Indacaterol, like formoterol, has a 24-fold greater agonist activity at beta$_2$-receptors than at beta$_1$-receptors and does not inhibit the broncho-relaxant effect of a short-acting bronchodilator, indicating it is a full agonist.[15,17] However, 10% to 50% of the beta receptors in the heart are beta-2 receptors, which raises the possibility that even highly selective beta$_2$-adrenergic agonists may have cardiac effects. However, data from safety trials with indacaterol reveal that the risk of cardiac arrhythmias, based on QT_C interval and pulse rate, were not statistically significantly greater than placebo.[19]

The median time to reach peak serum concentrations of indacaterol is approximately 15 minutes after single or repeated inhaled doses with an absolute bioavailability of approximately 43-45% (**Table 1**). After repeated once-daily administration, steady state is reached within 12 to 15 days with a serum and plasma protein binding of 94.1-95.3% and 95.1-96.2%, respectively; indacaterol has a half-life of approximately 40 hours.[15,20] Indacaterol is primarily metabolized via hydroxylation through cytochrome P450 (CYP) 3A4 and to a lesser extent via glucuronidation to phenolic O-glucuronide through uridine diphosphate glucuronyltransferase (UGT) 1A1. In vitro investigations indicated that indacaterol is a low affinity substrate for the efflux pump P-glycoprotein (P-gp). Further in vitro investigations indicated that indacaterol has negligible potential to cause metabolic interactions with medications (by inhibition or induction of CYP enzymes, or induction of UGT1A1) at the systemic exposure levels achieved in clinical practice, and is unlikely to significantly inhibit transporter proteins such as P-gp.[15]

The results of pharmacokinetic studies in patients with COPD aged 40 to 88 years found that no dose adjustment is warranted based on the effect of age, gen-

der or weight.[15] Likewise, no dose adjustments are needed in patients with renal impairment or mild to moderate hepatic impairment. Indacaterol has not been studied in patients with severe hepatic impairment and specific recommendations for dose adjustments in this population are not currently available. Indacaterol is considered pregnancy category C, as there are no adequate and well-controlled studies in pregnant women.[15]

Clinical Trials

Dose-ranging efficacy studies

INVOLVE, a 52-week, randomized, double-blind, double-dummy, active control, multicenter, 5 period crossover, dose-ranging study by Dahl et al., assessed the bronchodilatory efficacy and safety of single doses of indacaterol 300 mcg and 600 mcg delivered via single dose dry powder inhaler versus formoterol 12 mcg twice daily (BID) in 1,732 patients with moderate to severe COPD (**Table 2**).[21] The study included patients aged 40-65 years with a clinical diagnosis of COPD according to the GOLD Guidelines and a history of characteristic COPD symptoms. The primary efficacy endpoint was 24-hour post-dose trough FEV_1 evaluated at week 12 and week 52. Trough FEV_1, measured prior to first dosing of inhaled medications, has been associated with proportional improvements in overall patient health status.[22] Thus, trough FEV_1 at 24 hours post dose would demonstrate the effectiveness of one dose of indacaterol on lung function improvement. The study found statistically significantly greater trough FEV_1 values for all doses of indacaterol compared to placebo and a significantly greater trough FEV_1 values for indacaterol 300 mcg once daily (OD) vs. formoterol 12 mcg BID ($p < 0.001$).[21]

Secondary endpoints included time to first COPD exacerbation, days of poor control (a composite measure used in formoterol registration studies,[7,23] defined as the number of days with a score of ≥ 2 on a 0–3 scale for at least two of the following symptoms: coughing, wheezing, production/color of sputum and breathlessness), and St. George's Respiratory Questionnaire (SGRQ), a surrogate marker of overall treatment effect which measures the overall impact of symptoms on patient activity and quality of life, with higher scores correlating with poorer health.[21,24] Of these endpoints, there was a significant improvement in the time to first COPD exacerbation for both indacaterol 300 mcg OD and formoterol 12 mcg BID (HR 0.77; 95% CI 0.61 - 0.98) versus placebo, with no significant difference between indacaterol and formoterol. The percentage of patients who experienced exacerbations was 32.8% in the indacaterol 300 mcg OD group, 31.5% in the formoterol group, and 36.3% in the placebo group. Both indacaterol 300 mcg OD and formoterol BID had statistically significantly less days of poor control versus placebo (mean days of poor control: placebo=38.3%, indacaterol= 33.6%, formoterol= 33.5%, both $p < 0.05$ vs. placebo). In regards to SGRQ, clinically important improvements (≥ 4 points) versus placebo were seen for patients receiving indacaterol; however, there were no significant differences in SGRQ scores between indacaterol and formoterol at the 12- or 52-week assessments.[21]

Kato et al. conducted a randomized, double-blind, placebo controlled, four-period crossover, multicenter, dose-ranging study assessing the efficacy and safety of indacaterol in 45 Japanese patients with COPD at 150 mcg OD, half the 300 mcg starting dose used in the INVOLVE trial.[25] The primary endpoint was improvement in pulmonary function as represented by changes in FEV_1 and FVC for indacaterol 150 mcg, 300 mcg, and 600 mcg versus placebo. Overall, the 300 mcg and 600 mcg doses of indacaterol were associated with sustained efficacy in improving $FEV_1$and FVC; however, the maximum benefit was seen at the 300 mcg dose as there was no significant improvement in FEV_1 or FVC at 600 mcg dose compared to the 300 mcg dose. The 150 mcg dose, which showed statistically significant differences to placebo, appeared to be less effective than the 300 mcg and 600 mcg doses in the trough FEV_1 measured by the area-under-the-curve (AUC) at 22-24 hours and peak FEV_1.[25] However, this difference did not translate into a clinically significant effect on patient outcomes as further efficacy trials, most notably the INHANCE trial by Donohue et al., which found the 150 mcg and 300 mcg doses to be equivalent in terms of patient-related outcomes.[26]

Pivotal COPD Studies

Indacaterol versus Placebo (INLIGHT-1)[27]

INLIGHT-1, a randomized, double-blind, placebo controlled, multicenter, parallel group study by Feldman et al., assessed the efficacy and safety of indacaterol (150 mcg OD) for 12 weeks in 416 patients with moderate to severe COPD. Eligible patients were randomly assigned (randomization ratio 1:1, with stratification for smoking status) to inhaled indacaterol 150 mcg OD or placebo.[28] Patients were required to take study medication once a day in the morning between 8 and 11 am. Salbutamol was permitted as a rescue medication but not within 6 hours prior to the study visits. Daily ICS monotherapy was

Table 2 | Summary of Indacaterol Clinical Trials

Study	Design	Dose	Results
INVOLVE Dahl et al. (2010)[21]	-52-week, R, DB, DD, active PCB, multicenter, 5 period crossover, dose-ranging study - Patients aged 40-65 yrs with a clinical diagnosis of symptomatic COPD (n=1,732) -P.E.: 24 hour post-dose, trough FEV_1 at wks 12 & 52	Indacaterol 300 mcg (n=437) and 600 mcg (n=428) vs. PCB (n=432) vs. for-moterol 12 mcg BID as active control (n=435)	-Inc trough FEV_1 values for all doses of indacaterol vs. PCB ($p<0.001$) -Inc trough FEV_1 values for indacaterol 300 mcg once daily (OD) vs formoterol 12 mcg BID ($p<0.001$). -Improvement in the time to first COPD exacerbation for both indacaterol 300 mcg OD and formoterol 12 mcg BID (HR 0.77; 95% CI 0.61, 0.98) vs. PCB, with no difference between indacaterol and formoterol. -COPD exacerbations were 32.8% in the indacaterol 300 mcg OD group, 31.5% in the formoterol group and 36.3% in PCB group. -Indacaterol 300 mcg OD and formoterol BID had sta-tistically significantly less days of poor control vs. PCB ($p<0.05$) -Significant SGRQ improvements (≥4 points) vs. PCB for both indacaterol doses -No significant differences in SGRQ scores between indacaterol and formoterol at 12- or 52-wks
INHANCE Donohue et al. (2010)[26]	-26-wk, R, DB, DD, PCB-controlled, MC, PG - Patients ≥40 yrs with a smoking history of ≥20 pack-yrs and moder-ate-to-severe COPD (n=1683) - P.E.: trough FEV_1 at 12 wks.	Indacaterol 150 (n=2611) and 300 mcg QD vs. tiotro-pium 18 mcg QD vs. PCB	-Inc trough FEV_1 vs. PCB at 150/300 mcg doses ($p<0.001$) -40 mL higher trough FEV_1 vs. PCB than tiotropium for both indacaterol doses -Inc TDI for 150/300 mcg dose respectively vs. PCB (1.00/1.18, respectively, $p<0.001$) - Dec total SGRQ score for 150/300 mcg dose respec-tively vs. PCB (−3.3/−2.4, respectively, $p<0.01$) -Note: tiotropium resulted in a TDI of 0.87 ($p<0.001$) and a SGRQ total score of -1.0 (p=NS) –No significant difference in incidence of AE across treatments
INLIGHT-1 Feldman et al. (2010)[27]	- 12-wk, R, DB, PCB-controlled, MC, PG - Patients ≥40 years with a smok-ing history of ≥20 pack-yrs and moderate-to-severe COPD (n = 416, mean age 63 yrs) - P.E.: 24-h trough FEV_1 at week 12, and the percentage of COPD days with poor control	Indacaterol 150 mcg QD (n = 211) vs. PCB (n = 205)	-Trough FEV_1 (LSM ± SEM) at wk 12 difference of 130 ± 24 mL vs. PCB ($p < 0.001$). -Trough FEV_1 after one dose was significantly higher with indacaterol than placebo ($p < 0.001$). -Inc peak FEV_1 than PCB, both on day 1 and at wk 12, with indacaterol-placebo differences (LSM ± SEM) of 190 ± 28 ($p < 0.001$) and 160 ± 28 mL ($p < 0.001$), re-spectively. -Dec in the percentage of days of poor control versus PCB by 22.5% ($p < 0.001$) -Dec in use of rescue medication ($p < 0.001$), with simi-lar rates of AE (indacaterol 49.3%, placebo 46.8%)
INLIGHT-2 Kornmann et al. (2011)[28]	- 26-wk, R, DB, PCB-controlled, MC, PG - Patients ≥40 yrs with a smoking history of ≥20 pack-yrs and moder-ate-to-severe COPD (n = 998) - P.E.: 24-h trough FEV_1 at Week 12	Indacaterol 150 mcg QD (n = 330) vs. PCB (n = 335) vs. salmeterol 50 mcg BID (n=333)	-Inc trough FEV_1 at week 12 by 170 mL vs. PCB ($p<0.001$) and by 60 mL vs salmeterol ($p<0.001$ -Mean±SE percentage of days of poor COPD control over 26 wks: 34.1±1.82% for indacaterol and salmet-erol vs 38.1±1.85% with PCB ($p>0.05$) -Better improvement from baseline SGRQ total score of ≥4 units vs salmeterol at wk 12 (OR 1.59, 95% CI 1.12–2.25; $p<0.01$) -No significant difference in incidence of AE across treatments

Continued on page 4.

Table 2 | Summary of Indacaterol Clinical Trials, continued

Kerwin et al. (2011)[29]	-2 identical, 12-wk, R, DB, PCB-controlled trials - Patients with moderate-to-severe COPD and smoking history ≥10 pack-yrs (Study 1: n=323; Study 2: n=318 from Study 1) -P.E.: trough FEV1 after 12 weeks.	Study 1 (n=323; 85% completed): indacaterol 75 mcg vs. PCB Study 2 (n=318; 91% completed): indacaterol 75 mcg vs. PCB	-Inc trough FEV1 at Week 12 (≥120mL) (p<0.001 vs. PCB) -Inc likelihood of achieving a clinically relevant improvement in TDI total score (≥1 point) in Study 1 (Study 1: OR 2.19, p=0.002; Study 2: OR 1.58, p=0.065) -Inc probability of a clinically relevant improvement (≥4 units) in SGRQ total vs PCB (OR 1.80 and 1.71, both p<0.05).

AE = adverse effects, DB = double-blind, DD = double-dummy, Dec = decreased, FEV1 = forced expiratory volume in 1 second, Inc = increased, LSM = least squares mean, MC = multi-center, NS = not statistically significant, OR = odds ratio, PG = parallel-group, PCB = Placebo, P.E.= primary endpoint, QD = once-daily, R = randomized, SEM = standard error of the mean, SGRQ = St. George's Respiratory Questionnaire, TDI = Transition Dyspnea Index, wk = week, yrs = years.

maintained at a constant dose and regimen throughout the study in patients who were previously on an ICS. The primary endpoint was a composite of spirometry measurements of FEV_1 and FVC, peak expiratory flow (PEF), COPD exacerbations, the composite score of the SGRQ, patient reported symptoms, and rescue medication use (albuterol/salbutamol). The primary objective was to demonstrate superiority of indacaterol 150 mcg versus placebo at 24 hours post-dose using trough FEV_1 after 12 weeks of treatment as the outcome measure.[27]

The results demonstrated a statistically and clinically significantly greater trough FEV_1 for indacaterol 150 mcg compared with placebo at week 12 (1.49 L versus 1.35 L, respectively, $p < 0.001$; absolute difference=0.13 L, 95% CI: 0.09 - 0.18).[27] Similar results were observed in the per protocol primary analysis and with FEV_1 AUC values evaluated between 5 minutes and 4 hours, 5 minutes and 1 hour, and 1 and 4 hours at day 1 and after 12 weeks of treatment (at all time points, $p < 0.001$). The percentage of COPD days of poor control (based on patient-reported symptoms captured in the patient's diary) over 12 weeks of treatment was significantly lower in the indacaterol 150 mcg group (31.2%) compared with placebo (40.2%) ($p < 0.001$; absolute difference = 9.1%, 95% CI: - 13.3 to -4.8). The SGRQ total score at week 12 was significantly lower for indacaterol 150 mcg (43.38) compared with placebo (48.13). The percentage of days with no rescue medication use was also significantly higher with indacaterol 150 mcg than with placebo ($p < 0.001$). There was no significant difference in the incidence of hospitalizations, emergency room visits, or unscheduled outpatient visits between the indacaterol and placebo groups.[15,27]

Indacaterol versus Salmeterol (INLIGHT-2) [28]

INLIGHT-2, a 26-week, randomized, double-blind, placebo controlled, multicenter, parallel group study by Kornmann et al. assessed the efficacy and safety of indacaterol 150 mcg OD compared with placebo or salmeterol as an active control.[28] The patients enrolled in the study were males and females aged ≥ 40 years with a clinical diagnosis of moderate-to-severe COPD and a smoking history of ≥ 20 pack-years. Patients were randomized to 6 months double-blind treatment with indacaterol (150 mcg OD), salmeterol (50 mcg BID), or placebo. Of the 1,002 patients enrolled, 838 (84%) completed the study. The primary efficacy endpoint was trough FEV_1 after 12 weeks. Indacaterol increased trough FEV_1 at week 12 by 170 mL over placebo ($p < 0.001$) and by 60 mL over salmeterol ($p < 0.001$). Both active treatments improved health status (via the SGRQ) and dyspnea (via the transition dyspnea index, or TDI) compared with placebo, with differences between them favoring indacaterol. Safety profiles were similar across the treatment groups and both indacaterol and salmeterol were well tolerated.[28]

Indacaterol versus Tiotropium (INHANCE) [26]

In INHANCE, a Phase III, 26-week, multicenter, randomized, double-blind, double dummy, placebo-controlled, adaptive, seamless, parallel-group study, Donohue et al. assessed the efficacy, safety and tolerability of two doses of indacaterol (selected from 75, 150, 300 and 600 mcg OD) in patients with COPD using blinded formoterol (12 mcg BID) and open label tiotropium (18 mcg OD) as active controls.[26] Stage 1 was designed to provide data on the risk-benefit of the four different doses of indacaterol in order to select two doses to carry forward into Stage 2. Tiotropium (18 mcg OD) was selected to compare the safety and efficacy of indacaterol during stage 2 as it is the cur-

rent gold standard treatment for COPD.[26]

For the primary endpoint of trough FEV_1 at 12 weeks, indacaterol 150 mcg and 300 mcg were statistically and clinically significantly superior to placebo ($p < 0.001$), and showed superiority to tiotropium 18 mcg OD at 12 weeks and non-inferiority to tiotropium 18 mcg OD up to 26 weeks after treatment initiation.[27]

Table 2 provides the summary of the most recent clinical trials, including the study by Kerwin et al., which resulted in the approval of the 75 mcg dose.[29]

Safety/Adverse Events

Safety was evaluated in 2516 patients receiving indacaterol at doses of 75 mcg or greater for at least 12 weeks in six confirmatory randomized, double-blind, placebo and active-controlled clinical trials.[15,21,26-29] Of the patients studied in trials, 48% of patients treated with any dose of indacaterol reported an adverse reaction compared with 43% of patients treated with placebo (**Table 3**). The proportion of patients who discontinued treatment due to an adverse reaction was 5% for both indacaterol- and placebo-treated patients. The most common adverse reactions that lead to discontinuation of indacaterol were COPD (10.2% at the 150 mcg dose) and dyspnea (2.2% at the 150 mcg dose). In these trials, 449 patients were exposed to the FDA approved dose of 75 mcg for up to 3 months. An average of 24% of patients experienced a cough on at least 20% of visits following inhalation of the approved 75 mcg dose of indacaterol compared to 7% of patients receiving placebo. The cough usually occurred within 15 seconds following inhalation, lasted for no more than 15 seconds, and was not associated with bronchospasm, exacerbations, deteriorations of disease, or loss of efficacy.[15,21,26-29]

As with other inhaled $beta_2$-adrenergic drugs, indacaterol should not be used more often than prescribed, at higher doses than recommended, or in conjunction with other medications containing long-acting $beta_2$-agonists.[15] Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs along with a paradoxical bronchospasm that may be life threatening and requires discontinuation of the drug.[15]

Asthma-related Death

Long-acting $beta_2$-adrenergic agonists, such as indacaterol, are associated with increased risk of asthma-related death.[15] In a 28-week, placebo-controlled U.S. study comparing the safety of another long-acting $beta_2$-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, an increase in asthma-related deaths was observed in patients receiving salmeterol (13 patients out of 13,176 patients treated with salmeterol vs. 3 patients out of 13,179 patients treated with placebo; RR: 4.37; 95% CI: 1.25 - 15.34).[30] The increased risk of asthma-related death is considered a class effect of the LABAs, including indacaterol. The safety and efficacy of indacaterol in patients with asthma has not been established. Indacaterol is not indicated for the treatment of asthma, as serious asthma-related events, including death, were reported in clinical studies with indacaterol.[28,31] The size of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.[31]

Table 3 | Number and frequency of adverse drug reactions greater than 2% in COPD patients exposed to indacaterol 75 mcg for up to 3 months [15]

	Indacaterol 75 mcg QD (N=449)	Placebo (N=445)
	N (%)	N (%)
Respiratory/Thoracic		
Cough	29 (6.5)	20 (4.5)
Oropharyngeal pain	10 (2.2)	3 (0.7)
Infections and infestations		
Nasopharyngitis	24 (5.3)	12 (2.7)
Nervous System		
Headache	23 (5.1)	11 (2.5)
Gastrointestinal		
Nausea	11 (2.4)	4 (0.9)

QD = once daily.

Dosing, Administration, and Cost

Indacaterol is available as Arcapta Neohaler ®. The recommended dose for the treatment of airflow obstruction in patients with COPD is 75 mcg OD via the Neohaler inhaler. Indacaterol capsules are only for oral inhalation and must not be swallowed as the intended effects on the lungs will not be realized. Indacaterol should be administered once daily at the same time in the morning or evening as improvements in trough FEV_1 values are not affected by the timing of indacaterol administration.[32] If a dose is missed, the next dose should be taken as soon as it is remembered; however, indacaterol should not be used more than one time in 24 hours. Indacaterol must always be stored in the blister-pack, and only removed immediately prior to use with the Neohaler inhaler. The price-range of a 30-day supply of indacaterol 75 mcg, including the Neohaler, is $195.00-205.00 without insurance.[33,34]

Summary

As the progression of COPD worsens and the burden of multiple medications increases, compliance becomes a greater issue in symptom management. Aside from this, the current twice-daily dosing of LABAs has been shown to cause fluctuations in airway patency leading to poor breathing mechanics, potentially affecting the successful management of the disease. A possible solution to these issues is the development of once-daily dosing provided by an extended duration of action. Indacaterol, the first once-daily LABA with a 24 hour duration of action approved for the long-term maintenance of airflow obstruction in patients with COPD has shown to be non-inferior in efficacy to tiotropium, the current gold standard treatment, while maintaining superiority to twice-daily salmeterol. In regards to safety, indacaterol has shown to be non-inferior to tiotropium and superior to salmeterol. Overall, indacaterol is well tolerated with most common adverse reactions including cough, nasopharyngitis, headache, nausea, and oropharyngeal pain occurring within the first three months of treatment. Compared to the other LABAs, indacaterol provides an equally safe and more effective method to improve patient symptoms and compliance in managing the multiple medications required in the treatment of moderate to severe COPD.

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RANOLAZINE: A NEW TREATMENT FOR CHRONIC ANGINA

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Approximately 9.8 million Americans experience angina pectoris annually, with 500,000 new cases occurring every year.[1] In 2005, CDC data suggested that women have a lower prevalence of angina and/or coronary heart disease (3.4%) compared to men (5.5%).[2] Recent studies show a higher female prevalence of age-adjusted angina pectoris among Americans aged 40-74 years old.[1] The estimated financial burden for Americans with coronary heart disease in 2006 was approximately $142.5 billion.[3]

Currently available treatment options for angina include: beta blockers; calcium channel blockers; or nitrates. On January 27, 2006, Ranolazine, sold under the trade name Ranexa® by Gilead Sciences, was approved by the FDA for monotherapy or add-on therapy for the treatment of chronic angina. The objective of this article is to review the pharmacology, pharmacokinetics, clinical trials, drug interactions and contraindications, adverse effects, safety, and cost of ranolazine.

PHARMACOLOGY

Ranolazine inhibits the late sodium currents causing a decrease in intracellular sodium and calcium overload in ischemic cardiac muscle.[4] The reduction in intracellular Na^+ contributes to a subsequent reduction in the magnitude of ischemia-induced Ca^{2+} overload, and improves myocardial function as well as myocardial perfusion.[5] Therefore, the reduced Ca^{2+} overload produced by ranolazine decreases stiffness in the left ventricle. Researchers believe that diastolic tension should be decreased along with a reduction in myocardial oxygen consumption and compression of the vascular space.[6] When studied in canines, the blockade of late sodium currents is believed to be responsible for the antiarrhythmic action in the atria. When combined with the antiarrythmic dronederone, ranolazine acts synergistically to terminate and prevent the reinduction of atrial fibrillation (AF) by inhibiting sodium channels via two independent mechanisms.

PHARMACOKINETICS

Ranolazine is predominately metabolized by cytochrome P450 (CYP) 3A enzymes, minimally by CYP2D6, and is a substrate of P-glycoproteins (PGP). Ranolazine is metabolized by at least 12 drug elimination pathways, forming numerous metabolites, with three related to the parent compound. Active metabolites having exposure (AUC) of at least 10% relative to the parent compound include: the desmethyl metabolite (RS-88390), the *N*-dealkylated metabolite (RS-94287), and the *O*-dearylated metabolite (RS-8860).[7] The terminal half-life of ranolazine is approximately 7 hours and steady-state for the parent drug is usually achieved within 3 days after twice daily (BID) dosing.

Half-lives of the active metabolites range from 6-22 hours, with time to steady-state for the longest-acting metabolite estimated at 5 times longer than the parent drug. Ranolazine can be taken without regards to meals[8] (**Table 1**).

Compared to placebo, patients' ≥ 75 years old taking ranolazine had a higher incidence of adverse events and drug discontinuations. Due to greater chances of impaired renal and hepatic function in the elderly population, it is recommended that prescribers start therapy with ranolazine at a lower dose. Compared to patients with no renal impairment, maximum concentration (Cmax) was increased between 40%-50% in patients with all stages of renal impairment. Use of ranolazine should be avoided in patients with severe renal impairment and used with caution in patients with mild to moderate renal impairment.[8] Currently, there is no specific dosage adjustments recommended by the manufacturer for patients with renal or hepatic impairment. In cirrhotic patients, the Cmax of ranolazine was increased 30% in patients with mild (Child-Pugh Class A) hepatic impairment, but increased 80% in patients with moderate (Child-Pugh Class B) hepatic impairment compared to patients without hepatic impairment.[8] Ranolazine is contraindicated in patients with liver cirrhosis.

Clinical Trials

Four major trials comprise clinical evidence used to evaluate the effectiveness of ranolazine in chronic angina. These trials include: The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial[9]; The Effects of Ranolazine on Recurrent Cardiovascular Events in Patients With Non–ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI 36)[10]; Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial[11]; and the Efficacy of Ranolazine in Chronic Angina (ERICA) trial[12] (**Table 2**).

CARISA Trial

CARISA was a randomized, parallel, double-blinded, placebo-controlled trial for symptomatic patients who suffer from chronic angina and patients were randomly assigned to receive placebo or ranolazine.[9] The trial began in July 1999 and ended in August 2001, with long-term follow-up reported through October 2002. There were 823 patients randomized throughout 15 countries at 118 investigational sites. Enrolled patients were required to have experienced exertional angina for at least 3 months duration and had been previously treated with standard doses of atenolol 50 mg/day, amlodipine 5 mg/day, or diltiazem 180 mg/day. The primary end point compared the effects of ranolazine vs. placebo on treadmill exercise duration at 12 hours after dosing. Secondary endpoints included: change in exercise duration, time to onset of angina, time to onset of ischemia, nitroglycerin use, and number of angina attacks. At baseline, patients were experiencing an average of 4.5 angina attacks/week. Ranolazine reduced the mean angina attacks/week from 3.3 for placebo to 2.5 for ranolazine 750 mg ($p = 0.006$) and 2.1 for 1000 mg ($p < 0.001$). Ranolazine also significantly reduced nitroglycerin use with a similar dose response. Unlike the comparators, ranolazine showed no clinically meaningful changes in standing or end-exercise blood pressure or heart rate. The results of the trial showed that BID doses of ranolazine increased exercise capacity and provided additional anti-anginal relief to patients already taking atenolol, amlodipine, or diltiazem.[9]

A post-hoc analysis of the CARISA trial examined the effect of ranolazine on glycosylated haemoglobin (A1c) in patients with diabetes and chronic angina. In the study, 23% of patients (n = 189) had diabetes mellitus. Patients receiving ranolazine 750 mg BID had an absolute reduction in A1c of 0.5% ($p = 0.008$) and a reduction of 0.72% with ranolazine 1000 mg BID ($p = 0.0002$) compared with the placebo group.[10] This effect was even more evident in patients who treated their diabetes with insulin. In patients using insulin, a 0.84% ($p = 0.016$) and a 1.1% ($p = 0.008$) absolute reduction in A1c was noted with ranolazine 750 and 1000 mg BID, respectively, compared to placebo.[13]

MERLIN-TIMI 36 Trial

The purpose of the MERLIN-TIMI 36 trial was to evaluate the efficacy and safety of ranolazine as a new add-on treatment for the reduction of cardiovascular death, myocardial infarction, or recurrent ischemia in patients with ACS receiving standard therapy. [11] Ranolazine had not been studied in patients with ACS

Table 1 | Pharmacokinetic Information for Ranolazine [8]

Property	Ranolazine
Cmax	2569 ng/ml*
Tmax	2-5 hours
Terminal 1/2 life	7 hours
Elimination Pathways	Magor:CYP3A, Minor: CYP2D6, PGP
Bioavailability	76%
Elimination	75% urine, 25% feces

*Based on an oral dose of 1000 mg BID
Cmax: maximum concentration; CYP: cytochrome P450 enzyme; ng/mL: nanograms per milliliter; PGP: p-glycoprotein; Tmax: time to maximum concentration.

or for secondary prevention of major cardiovascular events in patients with established CAD. The MERLIN-TIMI 36 trial was a randomized, double-blind, placebo -controlled, multinational clinical trial that treated patients with ranolazine within 48 hours of ischemic symptoms. The primary end point was a composite of cardiovascular death, myocardial infarction, and recurrent ischemia. The major safety end points included death from any cause and symptomatic documented arrhythmias. Concomitant medications that were administered included: clopidogrel or ticlodipine (64.3%); β-blockers (89.2%); calcium channel blockers (30.1%), including diltiazem (4.8%) and verapamil (2.9%); ACE-inhibitors or angiotensin II receptor blockers (78.2%); and statins (82.4%). Patients were followed for up to 24 months, with a median follow-up

Table 2 | Summary of Published Studies on the Effectiveness of Ranolazine

Study	Design	Dose	Results	Conclusion
CARISA[9]	-R, 3-group, P, DB, PC - 823 adults with SCA. -TE occurred 12 hrs & 4 hrs after dosing -Evaluation at week 2, 6, & 12 -PO: CID, TTA, TTOA, TTOI, NU, NAA	BID PL or 750 mg or 1000 mg of RN	ED ↑ by 115.6s in both RN groups vs. 91.7s in the PG (*P* = .01). The times to angina and to EI ↑ in the RN groups RN ↓ angina attacks & NU by 1/ week vs. P (*P*< 0.02).	BID doses of RN ↑ EC & provided additional AA relief to symptomatic patients with SCA taking standard doses of atenolol, amlodipine, or diltiazem
MERLIN-TIMI 36 [10]	-RD, DB, PC, MN CT -6560 patients Tx with RN(n = 3279) & PL (n = 3281), within 48 hours of ischemic symptoms -F/U for a median of 348 days. -PO: composite of CD, MI, & RI -MSEP: death from any cause and symptomatic arrhythmias	RN initiated IV then po RN SR 1000 mg BID	PO occurred in 696 patients (21.8%) in the RN group vs. 753 patients (23.5%) in the PL group [HzR], 0.92; 95% [CI], 0.83-1.02; p = 0.11). RI was ↓ in the RN group (430 [13.9%]) vs. the PL (494 [16.1%]; HzR, 0.87; 95% CI, 0.76-0.99; p = 0.03). No SS difference in symptomatic arrhythmias or total mortality	Adding RN to standard treatment for ACS did not ↓ MCE There was ↓ RI, and fewer ↑ in other antianginal AA Tx in patients treated with RN
MARISA [11]	Patients (n = 191) with angina-limited exercise discontinued AA medications and were R into a DB four-period CO study	SR RAN 500mg, 1,000mg, or 1,500mg, or PL BID for 1 week	EC ↑ with all doses of RN BID by 94s (500mg), 103s (1000mg), & 116s (1500mg) vs. 70s (PL); p < 0.005 1 year survival rate was 96.3 ± 1.7%.	RN MO was well tolerated and ↑ EC throughout its dosing interval at all doses RN had negligible effects on HR and BP
ERICA [12]	Patients (n=565) with coronary disease and 3 anginal attacks/week taking MRD of AM were R and DB to RA or PL for 6 weeks PO: frequency of angina episodes/week Efficacy was also assessed by NU/week and the (SAQ).	AM 10mg/day 1,000 mg RN BID x 6 weeks or PL	Compared with PL, RN significantly ↓ frequency of angina episodes (2.88 ±0.19 on RN vs. 3.31±0.22 on PL; p = 0.028) & NU (2.03±0.20 on RN vs. 2.68±0.22; p = 0.014) The median angina WER at baseline was 4.5/week. Subgroup analysis showed SS ↓of angina frequency and NU.	RN significantly ↓ frequency of angina and NU vs. PL

AA: Anti-Anginal; ACS: Acute Coronary Syndrome; AM: Amlodipine; BP: Blood Pressure; CD: Cardiovascular Death; CI: Confidence Interval; CID: Change in Exercise Duration; CO: Cross Over; CT: Clinical Trial; DB: Double-Blinded; EC: Exercise Capacity; EI: Electrocardiographic Ischemia; F/U: follow-up; HR: Heart Rate; hrs: hours; HzR: Hazard Ratio; IV: intravenous; MCE: Major Cardiovascular Events; MI: Myocardial Infarction; MN: Multinational; MO: Monotherapy; MRD: Max Recommended Dosage; MSEP: Major Safety End Points; NAA: Number of Angina Attacks; NU: Nitroglycerin Use; P: Parallel; PC: Placebo Controlled; PG: Placebo Group; PL: Placebo; PO: Primary Outcomes, RD: Randomized; RI: Recurrent Ischemia; RN: Ranolazine; s: seconds; SAQ: Seattle Angina Questionnaire; SCA: Symptomatic Chronic Angina; SR: Sustained Release; SS: Statistically Significant; TE: Treadmill Exercise; TTIO: Time to Onset of Ischemia; TTOA: Time to Onset of Angina; Tx: Treated; WER: Weekly Episode Rate.

Table 3 | Examples of Common CYP3A4 Inhibitors and Inducers [8]

Inhibitors	Inducers	PGP-Inhibitors
Nelfinavir	Carbamazepine	Cyclosporine
Clarithromycin	St. John's wort	Clarithromycin
Nefazodone	Phenobarbital	Diltiazem, Verapamil
Diltiazem, Verapamil	Phenytoin	Itraconazole, Ketoconazole
Fluconazole	Rifapentine	Ritonavir
Itraconazole, Ketoconazole	Rifampin	
Ritonavir	Rifabutin	

CYP: cytochrome P450 enzymes; PGP: p-glycoprotein.

of 348 days. The primary end point occurred in 696 patients (21.8%) in the ranolazine group vs. 753 patients (23.5%) in the placebo group (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.83-1.02; p = 0.11). Ranolazine reduced worsening angina by at least 1 Canadian Cardiovascular Society Class compared with placebo (135 [4.2%] vs. 175 [5.9%]; HR, 0.77; 95% CI, 0.62-0.97; p = 0.02). An increase in or addition of anti-anginal therapy was less frequent in the ranolazine group (316 [10.6%]) compared with the placebo group (391 [13.0%]; HR, 0.80; 95% CI, 0.69-0.93; p = 0.003). Death from any cause in the safety analysis did not differ in patients treated with ranolazine vs. patients treated with placebo (HR, 0.99; 95% CI, 0.80-1.22; p = 0.091). Additionally, the incidence of symptomatic, documented arrhythmias throughout the study was comparable in patients treated with ranolazine vs. placebo (p = 0.84). Lastly, the frequency of clinically significant arrhythmias observed during the first 7 days was lower in the ranolazine group (2330 patients [73.7%]) vs. the placebo group (2650 patients [83.1%], p < 0.001).[11]

Currently ranolazine is being studied in animal models in combination with antiarrhythmic drugs to control atrial fibrillation. The Synergistic Effect of the Combination of Ranolazine and Dronedarone to Suppress Atrial Fibrillation[14] study was conducted to explore the potential role of ranolazine in atrial fibrillation.

This study examined the antiarrhythmic effects of ranolazine, dronedarone, and dual therapy of ranolazine plus dronedarone. The electrophysiological effects of AF were evaluated in canine isolated coronary-perfused atrials, left ventricular preparations, and pulmonary vein preparations. During combination therapy, there was little change in action potential in either chamber, but there was an induced use-dependent atrial-selective depression of the sodium channel–mediated parameters and substantial post-repolarization refractoriness. Dual therapy suppressed AF and prevented the induction of AF in 9 of 10 (90%) preparations consisting of coronary-perfused atrias, ventricles, and pulmonary veins. Monotherapy of dronedarone or ranolazine prevented the induction of AF in 17% and 29% of the preparations, respectively. In conclusion, low concentrations of ranolazine and dronedarone produce moderately weak electrophysiological effects and suppression of AF when used separately. Dual therapy creates a potent synergistic effect, resulting in atrial-selective depression of sodium channel–dependent parameters and effective suppression of AF.[14]

Dosing and Administration

Ranexa® is given orally as a 500 mg ER or 1000 mg ER tablet twice daily with or without food. Ranexa® can be used concomitantly with other common cardiovascular medications (calcium channel blockers, beta-blockers, nitrates, etc.) with minimal effects on blood pressure.

Contraindications & Drug Interactions

Concomitant use of ranolazine with CYP3A inducers, CYP3A inhibitors, or PGP inhibitors is contraindicated (Table 3). Ranolazine is also contraindicated for patients with liver cirrhosis. Patients with mild, mod-

Table 4 | Side Effects of Ranolazine vs. Current Treatments for Angina [16]

Medication	Dizziness (%)	Headache (%)	Hypotension (%)	Constipation (%)	Nausea (%)
Ranolazine	6.2	5.5	0.5-4	4.5	4.4
Amlodipine	1.1-3.4	7.8	<1	<1	2.9
Metoprolol	1.8	<1	1	1	1
Nitroglycerin	5	50-64	4	----	<1

erate, or severe hepatic impairment have approximately a 3-fold increase in QTc-prolongation.[8]

Safety and Side Effects

The most serious adverse event seen with ranolazine is dose-dependent QT-interval prolongation. Although QT prolongation has been shown in both the MERLIN-36 and CARISA trials, no patient discontinued these studies due to QT prolongation or Torsades de pointes.[9,11] Common side effects for Ranolazine include dizziness, headache, and constipation (**Table 4**).

Costs

The mean retail cost of Ranexa® 500mg and 1000mg for a 30 day supply is $235.26 and $385.31, respectfully. To minimize the cost of Ranexa®, Gilead Sciences is currently enrolling patients in their Patient Savings Program.[15] This program allows patients using most commercial insurances to pay the first $15 for their prescription, and save up to $60 with each refill (maximum of 12 prescriptions by 12/31/2012).

Summary

Ranolazine is the newest, extended release agent to treat angina. It is dispensed under the trade name Ranexa®, and is dosed twice daily as 500 or 1000mg tablets. Major side effects include QT Prolongation, dizziness, and headache. Future use of this medication may include dual therapy with anti-arrhythmic drugs for AF. Ranolazine may be used with current treatment options for angina, including: beta-blockers; nitrates; and calcium channel blockers.

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