Drug Monograph

Brand Name: Arcapta Neohaler™

Generic Name: Indacaterol

Manufacturer[1],[2]: Novartis

Drug Class[1],[2],[3],[4]: Beta2-Adrenergic Agonist, Long-Acting

Uses:

> **Labeled Uses**[1],[2],[3],[4]: Used for long-term maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and/or emphysema.

Mechanism of Action[1]:

> Acts locally in the lung to relax bronchial smooth muscle by selective action on beta2-receptors with little effect on heart rate.

Pharmacokinetics:

> **Absorption**[4]:

Tmax	15 minutes
Vd (Vz)	2,361-2,557 L
t1/2	40-56 h
Clearance	Serum: 18.8-23.3 L/h Renal: 0.46-1.2 L/h
Protein binding	94.1%-96.2%
Bioavailability (systemic inhalation)	43-45%

> **Metabolism**[1]: Indacaterol is hepatically metabolized and hydroxylated via CYP3A4, CYP2D6, and CYP1A1.

> **Elimination**[1],[4]: Indacaterol is primarily excreted in the feces (>90%). 54% is excreted as unchanged drug.

Efficacy:

Feldman G, Siler T, Prasad N, Jack D, Piggott S, Owen R, Higgins M, Kramer B. Efficacy and safety of indacaterol 150 mcg once-daily in COPD: a double-blind, randomized, 12-week study. BMC Pulmonary Medicine. 2010; 10:11

Study Design: Multicenter, double-blind, placebo-controlled, parallel group, Phase III study[5].

Description of Study: *Methods:* This study was conducted at 103 centers in US, New Zealand and Belgium. 416 patients with moderate-to-severe COPD were randomized to receive either indacaterol 150 μg (n= 211) or placebo (n=205). The study consisted of a 14-day run-in period and a 12-week treatment period. Efficacy was evaluated through trough FEV1 after 1 dose, 29 days, and 12 weeks of treatment, individual time point FEV1 and peak FEV1 on day 1 and at week 12, and standardized area under the curve (AUC) for FEV1 at various time points. Other efficacy outcomes included use of rescue medication, PEF, and the number of days of poor control. Safety was evaluated through the monitoring of adverse effects (AEs). Analysis was based on intent-to-treat (ITT) population. *Outcome Results:* 24-hour post-dose trough FEV1 at week 12 showed a mean difference of 130 ± 24 ml (SE) (p<0.001) between the indacaterol and placebo groups. Trough FEV1 showed a mean difference of 80 ± 19 ml and 140 ± 24 ml after the 1st dose and at day 29, respectively (p <0.001 for both). Indacaterol was associated with higher peak FEV1 than placebo on both day 1 and week 12. Indacaterol reduced the percentage of days of poor control versus placebo by 22.5% (p<0.001) and was also associated with significantly reduced use of rescue medication (p<0.001)[5].

Limitations: This study was funded by Novartis, the manufacturer of Indacaterol. Novartis was also responsible for the conception and design of the study, and analysis and interpretation of data. All of the authors were affiliated with Novartis, presenting a potential conflict of interest. Extensive exclusion criteria limited the number of patients enrolled and made the results difficult to extrapolate to the general COPD population. The SE was reported instead of SD in the results. The data recorded in the diaries were completely patient dependent with no way of verifying the accuracy of the information. Use of an active control would have been more appropriate to assess the effectiveness of Indacaterol against current FDA approved COPD therapy. The dose of Indacaterol used in this study was 150 μg, which is not the FDA approved dose; however, this is the dose currently recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Conclusion: This study showed that Indacaterol is superior to placebo for the treatment of moderate-to-severe COPD. For the 24-h post-dose trough, Indacaterol provided a bronchodilator efficacy superior to that of placebo with a mean difference of 130 ± 24 ml [SE] (p<0.001). Indacaterol is clinically useful and has advantages over using placebo for the treatment of moderate-to-severe COPD; however, it is difficult to extrapolate these results to the general population because of the extensive exclusion criteria and the relatively small sample size. Further studies with larger sample sizes and less exclusion criteria are needed to compare efficacy of indacaterol 75 mcg against current FDA approved medications for moderate-to-severe COPD.

Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: A 12-week study. Respiratory Medicine. 2011; 105: 719-726.

Study design: Multicenter, randomized, parallel-group, double-blind and double – dummy study[6].

Description of Study: *Methods:* This study was conducted in 142 centers across 8 countries. 1123 patients with moderate-to-severe COPD were randomized to receive either 150 µg of indacaterol once daily or 50 µg of salmeterol twice daily. The study comprised of a 14-day screening/run-in period and a 12-week treatment period. Efficacy was evaluated by use of the spirometry tests FEV1 and FVC at specified time points during the treatment period and by use of a patient diary. Safety was evaluated by monitoring and recording any AEs, laboratory data, vital signs, and electrocardiograms. *Outcome Results:* Indacaterol FEV1 AUC at week 12 was statistically superior (p< 0.001) to salmeterol (adjusted mean difference [95% CI] 57 [35,79] ml). Indacaterol 24-h trough FEV1 was also statistically superior(60 [37,83] ml, p<0.001). The mean (%) changes from baseline for indacaterol and salmeterol were 0.19 (16.6%) L and 0.13 (11.4%) L, respectively. Results of serial measurements of FEV1 over 24-h at week 12 showed that indacaterol measurements were statistically superior (p<0.001) over salmeterol at all time points. Week 12 FVC measurements over a 24-h period were also statistically superior to salmeterol at all time points. TDI total score for indacaterol was statistically superior (p<0.001) to salmeterol at week 12 with a mean difference of 0.63 (95% CI: 0.30, 0.97). The proportion of patients with a ≥1 point improvement from baseline in TDI total score: 69.4% for indacaterol and 62.7% for salmeterol. Use of rescue medications was lower in the indacaterol group with a mean difference of -0.18 (95% CI: -0.36, 0.00; p<0.05)[6].

Limitations: This study was funded by Novartis, the manufacturer of Indacaterol. All of the study's authors are affiliated with Novartis, presenting a potential conflict-of-

interest. Patients previously on salmeterol were not excluded from the study, possibly influencing the study's results. The data recorded in the diaries were completely patient dependent with no way of verifying the accuracy of the information. Compliance was not addressed but is of concern since patients are more likely to be compliant with once-daily dosing than twice daily dosing. The dose of Indacaterol used was not the FDA-recommended dose.

Conclusion: This study showed that 150 μg of Indacaterol once-daily is statistically superior to 50 μg of salmeterol BID for the treatment of moderate-to-severe COPD; however, the clinical significance of using indacaterol over salmeterol is unclear. Further studies are needed to assess the efficacy of the FDA approved dose of 75 μg Indacaterol against salmeterol for the treatment of moderate-to-severe COPD.

Dahl R, Chung K F, Buhl R, Magnussen H, Nonikov V, Jack D, Bleasdale P, Owen R, Higgins M, Kramer B. Efficacy of a new once-daily long acting inhaled B2-agoinst indacaterol versus twice-daily formoterol in COPD. Thorax. 2010; 65: 473-479.

Study Design: Randomized, double-blind, double-dummy, parallel group study[7]

Description of Study: *Methods:* 1732 patients with moderate-to-severe COPD were randomized to receive once-daily indacaterol 300 μg or 600 μg, twice-daily formoterol 12 μg, or placebo for 52 weeks. A 2-week run-in was followed by 52 weeks of treatment. The primary efficacy endpoint was assessed through trough FEV1 measurements at week 12. Secondary endpoints were days of poor COPD control, SGRQ total score, time to first exacerbation, TDI scores, response percentage, exacerbation rates, and BODE index. Safety was assessed through analyzing incidence of AEs, clinically notable lab values, and through measuring QTc intervals. *Outcome Results:* Trough FEV1 at week 12 with both indacaterol doses was 170 ml higher than placebo ($p<0.001$) and 100 ml higher than formoterol ($p<0.001$). Symptomatic outcomes were improved with all active treatments compared to placebo. TDI scores were higher with indacaterol than with formoterol at week 12 but not at week 52[7]. AEs were similar between groups.

Limitations: Novartis funded this study and was responsible for the study design, and analysis and interpretation of data. Most of the authors had ties with Novartis, introducing a potential conflict-of-interest. The study does not mention from where the patients were recruited; the study only mentions that data was collected from outpatient clinics and physicians' offices. There was no mention if blinding was maintained. 129 patients were excluded before unblinding because of non-conformance with good clinical practice. Patients with stable disease were recruited in the study which is not representative of the general population and makes it difficult to

extrapolate to the general population. The doses of indacaterol in this study are 4-8 times greater than the current FDA recommended dose (75 µg).

Conclusion: Based on the results of this study, 300 mcg and 600 mcg of indacaterol appear to have a greater bronchodilator effect than formoterol; however, the comparison of these two drugs was not the main focus of the study. The main focus of this study was to compare the efficacy of both doses of indacaterol against placebo. Further studies are needed to assess the effectiveness of indacaterol 75 mcg versus formoterol in patients who are more representative of the general COPD population.

Contraindications[1,2]:

Monotherapy in the treatment of asthma: Monotherapy treatment of asthma with Indacaterol is an absolute contraindication. Long-acting beta2-agonists (LABAs) must be used with a long term asthma controller medication.

Precautions[1,2]:

Asthma-related deaths [U.S. Boxed Warning]: LABAs increase the risk of asthma-related deaths. The safety and efficacy of indacaterol in treatment of asthma have not been established.

Cardiovascular disease: Use with caution in patients with cardiovascular disease; beta-agonists may cause elevation in blood pressure and heart rate and may produce changes in ECG.

COPD: Do not use Indacaterol for acute brochospastic episodes of COPD. Indacaterol should always be prescribed with an inhaled short-acting beta2-agonist and patients should be educated on appropriate use. Do not initiate in patients with significantly worsening or acutely deteriorating COPD. The indacaterol dose should not be increased beyond what is recommended.

Diabetes: Use with caution in patients with hyperthyroidism since Indacaterol may stimulate thyroid activity.

Hypokalemia: Use with caution in patients with hypokalemia since beta2-agonists may decrease serum potassium.

Seizure disorders: Use with caution in patients with seizure disorders since beta2-agonists may result in CNS stimulation/excitation.

Lactose: The Arcapta Neohaler™ contains lactose and allergic reactions are possible in patients with severe milk protein allergy.

Concomitant treatment issues: Do not use Indacaterol with other LABAs; deaths and significant cardiovascular effects have been reported.

Adverse Effects[1],[3]:

Occurring in >10% of patients
   Respiratory:
         Cough (post inhalation 7%-24%)

Occurring in >1% to <10% of patients
   Central Nervous System
         Headache (5%)

   Gastrointestinal
         Nausea (2%)

   Respiratory
         Nasopharyngitis (5%)
         Oropharyngeal pain (2%)

Drug Interactions[1],[2],[3]:

Alpha-/beta-blockers; Betahistine:
      May diminish the therapeutic effect of Beta2-Agonists.

Atomoxetine; Cannabinoids:
      May enhance the tachycardic effect.

Beta-Blockers (Beta1-Selective and nonselective):
      May diminish the bronchodilatory effect of Beta2-Agonists beta-blockers.

Caffeine:
      May enhance the adverse/toxic effect and may enhance the hypokalemic effect of Indacaterol.

Conivaptan:
      May increase the serum concentration of CYP3A4 substrates.

Corticosteroids; Loop diuretics; Thiazide diuretics:
      Indacaterol may enhance the hypokalemic effect of corticosteroids, loop diuretics, and thiazide diuretics.

Iobenguane I 123:
> Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123.

MAO Inhibitors:
> May enhance the adverse/toxic effect of Beta2-agonists.

Peginterferon Alfa-2b:
> May decrease the serum concentration of CYP2D6 substrates.

QTc-Prolonging Agents:
> Indacaterol may enhance the QTc-prolonging effect of QTc-prolonging agents.

Sympathomimetics:
> May enhance the adverse/toxic effect of other sympathomimetics.

Theophylline derivatives:
> May enhance the adverse/toxic effect and may enhance the hypokalemic effect of Indacaterol.

Tocilizumab:
> May decrease the serum concentration of CYP3A4 substrates.

Tricyclic antidepressants:
> May enhance the adverse/toxic effect of Beta2-Agonists.

Dosing/Administration[1]:

Adult Dosing
> One inhalation (75 mcg/inhalation) once daily.

Elderly
> One inhalation once daily.

Renal impairment
> No adjustment is required.

Hepatic impairment
> No data is available for patients with severe hepatic impairment.

Conclusion:

Arcapta™ (Indacaterol) is the first LABA FDA approved for once-daily dosing. The once-daily dosing along with its fast onset of action make this treatment more favorable than the current twice-daily dosing LABAs (Serevent™ and Foradil™). A disadvantage of this medication is that it is not FDA approved for the treatment of asthma, while Serevent™ and Foradil™ are. There are currently no trials comparing indacaterol 75 mcg to formoterol or salmeterol for COPD, nor data showing that indacaterol 75 mcg reduces COPD exacerbations. Higher doses of Indacaterol appear to be just as safe and effective as formoterol and salmeterol for the treatment of moderate-to-severe COPD; however, more studies are needed to evaluate the efficacy of the current FDA-approved dose of Indacaterol 75 mcg to other current FDA-approved medications for the treatment of COPD (Serevent™, Foradil™, and Spiriva™). This medication is an option for COPD patients who need a once-daily LABA. The price of Arcapta™ will be similar to Serevent™ and Foradil™[8].

References:

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6. Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: A 12-week study. Respiratory Medicine. 2011; 105: 719-726.
7. Dahl R, Chung K F, Buhl R, Magnussen H, Nonikov V, Jack D, Bleasdale P, Owen R, Higgins M, Kramer B. Efficacy of a new once-daily long acting inhaled B2-agoinst indacaterol versus twice-daily formoterol in COPD. Thorax. 2010; 65: 473-479.
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