

INDACATEROL: A NEW APPROVED MOLECULE TO TREAT COPD

Jaithlia Rajiv*, Dev Suresh Kr., Gupta Akash, Tanwar Ravindra, Chouhan Chetan
Lachoo Memorial College of Sciences and Technology, Jodhpur, Rajasthan

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*Corresponding author

Rajiv Jaithlia, student, Email: rajivjaithlia@gmail.com

ABSTRACT

Indacaterol approved as once-daily bronchodilator for chronic obstructive pulmonary disease (COPD). Indacaterol is a new molecular entity in the β_2 -adrenergic agonist class taken only once a day unlike the currently available β_2 -adrenergic agonist that helps relax muscles around lung airways to prevent COPD symptoms, such as wheezing and breathlessness. It is approved only for the treatment of chronic obstructive pulmonary disease (COPD) (long-term data in patients with asthma are thus far lacking). It is delivered as an aerosol formulation through a dry powder inhaler. The most commonly reported side effects/adverse effects in patients taking Indacaterol (> 2% and more common than placebo) are runny nose, cough, sore throat, headache, and nausea. The main benefit, it is Long Acting β_2 -adrenergic agonist (LABA), once in a day dosing is sufficient.

KEYWORDS: Indacaterol, COPD, β_2 -adrenergic agonist, Onbrez, Arcapta Neohaler.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the co-occurrence of chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs, causing shortness of breath. In clinical practice, COPD is defined by its characteristically low airflow on lung function tests. In contrast to asthma, this limitation is poorly reversible and usually gets progressively worse over time.¹⁻⁴

COPD is caused by noxious particles or gas, most commonly from tobacco smoking, which triggers an abnormal inflammatory response in the lung. The inflammatory response in the larger airways is known as chronic bronchitis, which is diagnosed clinically when people regularly cough up sputum. In the alveoli, the inflammatory response causes destruction of the tissues of the lung, a process known as emphysema. The natural course of COPD is characterized by occasional sudden worsenings of symptoms called acute exacerbations, most of which are caused by infections or air pollution.¹⁻⁴

In rare cases, nonsmokers who lack a protein called alpha-1 antitrypsin can develop emphysema.

Risk factors for COPD are

- Smoking.
- Exposure to certain gases or fumes in the workplace
- Exposure to heavy amounts of secondhand smoke and pollution
- Frequent use of cooking fire without proper ventilation¹⁻⁴

Symptoms

- Cough, with or without mucus
- Fatigue
- Many respiratory infections
- Shortness of breath (**dyspnea**) that gets worse with mild activity
- Trouble catching one's breath
- Wheezing¹⁻⁴

Treatment

Treatment can make you more comfortable, but there is no cure. Quitting smoking is the best way to avoid developing COPD.

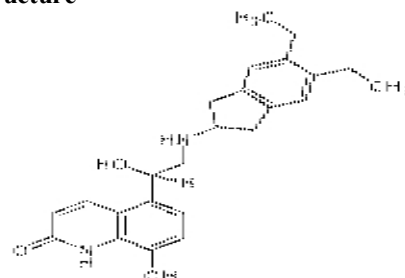
- Bronchodilators
- Inhaled steroids
- Anti-inflammatory
- Oxygen therapy, Assistance during breathing from a machine
- Lung transplant for severe cases¹⁻⁴

Indacaterol is a new molecular entity in the β_2 -adrenergic agonist class that helps relax muscles around lung airways to prevent COPD

symptoms, such as wheezing and breathlessness. The Global Initiative for Asthma (GINA) guidelines recognizes the role of long-acting beta2 agonists (LABAs) for the optimal treatment of moderate-to-severe persistent asthma. Currently available inhaled LABAs have durations of action of approximately 12 hours at recommended doses, necessitating twice daily dosing to provide optimal clinical efficacy. Hence Indacaterol is developed which is a novel once daily β_2 -adrenergic agonist.⁵⁻¹¹

DRUG DESCRIPTION^{5,6}

Molecular Structure



IUPAC Name

(R)-5-[2-[(5,6-Diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one

Pharmacology

Indacaterol (IND) is a novel, long-acting inhaled β_2 -agonist. The claimed indication for this product is: long term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease. The recommended dose is the inhalation of the content of one 150 microgram capsule once a day, using indacaterol inhaler⁸⁻¹².

The pharmacological effects of β_2 adrenoceptor agonists including indacaterol are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels result in relaxation of bronchial smooth muscle. Thus, indacaterol acts locally as a bronchodilator when inhaled. It is very unlikely that systemic exposure to indacaterol will lead to interactions with secondary receptor systems following inhalation at the recommended therapeutic dosages. However, interactions with several receptor systems expressed in lung tissues may be significant.⁸

The median time to reach peak serum concentrations of Indacaterol was approximately 15 min after single or repeated inhaled doses. The in vitro human serum and plasma protein binding was 94.1-

95.3% and 95.1-96.2%, respectively. In vitro investigations indicated that UGT1A1 is the only UGT isoform that metabolised indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of Indacaterol.^{8,9,10}

Drug interactions

- Ketoconazole (potent CYP3A4 inhibitor) and indacaterol at clinically relevant doses: 40% and 100% increase in Cmax and AUC, respectively.
- Erythromycin (moderate CYP3A4 inhibitor) and Indacaterol at clinically relevant doses: 20% and 40 (0-24h) -60 (0-infinite h) % increase in Cmax and AUC respectively.
- Verapamil (potent p-pg inhibitor) and indacaterol at clinically relevant doses: 50% and 35 % increase in Cmax and AUC, respectively⁸.

Contraindications

Without use of a long-term asthma control medication, indacaterol maleate is contraindicated in patients with asthma. Indacaterol maleate should not be started in patients with acutely deteriorating COPD, nor should it be used to relieve acute symptoms, which should be managed with concomitant short-acting β_2 -agonists⁹.

Clinical Use

- Once-daily bronchodilator to prevent COPD symptoms, such as wheezing and breathlessness. Dosage is 75 μ g inhaled once daily every day, which should increase compliance relative to twice-daily inhalers.
- It is not intended for acute relief of COPD exacerbations.
- Indacaterol maleate is not indicated for use in children. No adjustment of dosage is warranted in geriatric patients nor in patients with mild and moderate hepatic impairment⁹.

Adverse Effects/Toxicity

The most common adverse effects associated with Indacaterol at licensed doses was nasopharyngitis, cough, palpitations, dizziness, diarrhea, tremor, QTc prolongation, upper respiratory tract infection, and headache.

The most notable adverse effect which clearly may influence treatment compliance was "post-inhalation cough". This cough was, however, generally mild, transient in nature and duration, and did not lead to discontinuation of the study in any patients. No safety concerns for diabetes, hypokalaemia, hypertension or brochospasm related adverse effects were reported.^{11, 12, 13, 15}

Recommended Dose

Indacaterol is a long-acting β_2 -agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD. The recommended dosage of indacaterol is the once-daily inhalation of the content of one 75 μ g or 150 μ g capsule using the inhalation device.^{14, 16}

Note

"It will carry a boxed warning that the risk for asthma-related death may be increased."

Storage

The product should be stored at 25°C, and the capsules should remain in their blister packs until immediately before use¹⁷.

Marketed products

Arcapta Neohaler- Capsule Dosage Form

Capsule containing Indacaterol (75 mg.), places a capsule into the inhaler and breathes the powder in through the mouth.

Mfd. By- Novartis

Onbrez Breezhaler- Capsule Dosage Form

Capsule containing Indacaterol (150 mg.), places a capsule into the inhaler and breathes the powder in through the mouth.

Mfd. By- Novartis¹⁸

CONCLUSION

Indacaterol is a new molecular entity, long-acting beta2 agonists (LABAs) for the optimal treatment of moderate-to-severe persistent asthma. Currently available inhaled LABAs have durations of action of approximately 12 hours at recommended doses, hence Indacaterol is developed which is a novel once daily β_2 -adrenergic agonist.

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