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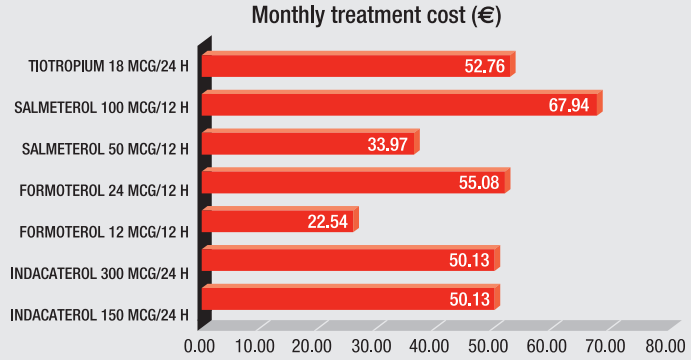
01/2011

Indacaterol▲ (Onbrez breezhaler®) Maintenance bronchodilator therapy in patients with COPD

Uncertainty regarding safety



- Indacaterol is a long-acting beta 2 agonist that is administered once daily and authorized for patients with chronic obstructive pulmonary disease (COPD).
- It has not been clinically proven that this agent is more effective than tiotropium or the other long-acting beta 2 agonists, salmeterol or formeterol.
- Clinical trials available are short lasting, less than a year, with few patients and important exclusion criteria. Thus, the safety profile of the agent is not conclusive.
- The rapid onset of its action could result in inadequate use of the drug as rescue therapy.

Therapeutic indications[1]

Maintenance bronchodilator therapy for airflow obstruction in adult patients with COPD.

Mechanism of action and pharmacokinetics[1]

This agent is a partial, long-acting beta 2 agonist that produces relaxation of bronchial smooth muscle. After inhalation, the median time to reach maximum serum levels is 15 minutes, with an absolute bioavailability of 43%. The most abundant metabolite in serum is a hydroxylate derivative produced mainly through the CYP3A4 isoenzyme. The elimination half-life oscillates between 40 and 52 hours.

Posology and administration[1]

The recommended dose consists of an **inhalation**, through a specific inhalation device, of the contents of a 150 mcg capsule once a day. The dose may be increased up to 300 mcg daily (maximum authorized dose).

There are no clinical differences with the existing bronchodilators available for COPD

Clinical efficacy

In three clinical trials comparing placebo there was one branch with active treatment: one trial involving formoterol[2] (12 months duration), another salmeterol[3] (6 months duration) and a third, tiotropium[4] (6-month duration open trial). Comparisons between indacaterol and salmeterol or tiotropium were secondary endpoints, while the objective of the comparison with formeterol was exploratory.

Among others, patients excluded from the trials included those with exacerbations or infections in the previous 6 weeks, diabetes, asthma, relevant laboratory abnormalities or prolonged QT intervals.

The primary endpoint was not a patient-oriented endpoint, but rather related to lung

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

function, the forced expiratory volume in one second (FEV_1) after 12 weeks. The minimum clinically important difference was 120 mL. The main secondary patient-oriented endpoints included days of poor control, variation in health status (St George's Respiratory questionnaire), variation in dyspnoea (Transitional Dyspnoea Index) and COPD exacerbations.

In all trials the difference in FEV_1 was not clinically significant. There were no differences in secondary endpoints of clinical efficacy (reduction in exacerbations, quality of life, dyspnoea or days of inadequate control) measured at the end of the trials. There are no long term comparative trials (more than one year).

A comparison of the onset of action of indacaterol with salbutamol (short-acting beta 2 agonist) and with salmeterol / fluticasone has been studied in one trial[13]. The FEV_1 was measured 5 minutes after a single dose, although no other outcome of clinical relevance was measured. Indacaterol presented an onset of action similar to salbutamol but was much quicker than the combined salmeterol / fluticasone. It is not clear though whether this rapid action of indacaterol is of any clinical benefit.

Safety and precautions

Adverse reactions[1]

The most frequent adverse reactions (1-10%) reported in clinical trials, with 2,154 patients treated for at least one year, include: nasopharyngitis, sinusitis, respiratory tract infections, diabetes mellitus and hyperglycaemia, headache, cardiac ischaemia, cough, pharyngolaryngeal pain, rinorrhea, respiratory tract congestion, muscle spasms, tremor and peripheral oedema.

In the clinical trials 17-20% of the patients presented sporadic cough which usually occurred after inhalation. This effect lasted for 5 seconds (10 seconds in smokers). This could deter the patient from using this agent resulting in poor adherence to treatment and possibly worsening the patients quality of life[8].

Its rapid onset of action, similar to salbutamol[13], can lead it to be erroneously administered as rescue therapy. Supervision should be made to avoid this potential medication error. There is no available evidence of safety after 56 weeks of treatment.

Contraindications and precautions[1]

Contraindications: known hypersensitivity to indacaterol or any of its excipients (contains lactose).

Precautions: this treatment should not be employed in asthma given the lack of long-term outcome data. It can cause life threatening paradoxical bronchospasm. Neither is indacaterol indicated as rescue treatment in acute episodes of bronchospasm. Daily doses should not be increased beyond the maximum dose, 300 mcg.

Precaution should be taken when employed in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmia, hypertension) convulsive disorders or thyrotoxicosis, and in patients that present unusual responses to beta 2 agents. Indacaterol can produce cardiovascular effects including increases in pulse rate, blood pressure and alterations in the electrocardiogram.

Significant hypokalaemia can be induced which in turn can produce adverse cardiovascular effects. In patients with severe COPD, hypokalaemia can be potentiated by hypoxia and/or concomitant therapy, increasing the susceptibility to cardiac arrhythmia. Close monitoring of glycaemia is important in diabetes patients. No studies have been carried out on diabetes patients with inadequate control.

Interactions[1]

This agent should not be employed in conjunction with long acting beta 2 agonists (alone or as part of combined treatment). Special caution should be taken when employing agents which potentiate hypokalaemic effects, such as teophylline, corticosteroids, and non-potassium sparing diuretics. Beta-blockers can weaken or antagonize the effect of beta 2 agonists. Therefore they should not be used concomitantly unless compelling reasons justify it (preferably use cardioselective beta adrenergic blockers). When co-administered with CYP3A4 and P-glycoprotein, inhibitors raise the systemic exposure by up to two fold.

Special situations[1]

Renal impairment: no dose adjustment is required. **Hepatic impairment:** no dose adjustment is required in mild and moderate liver dysfunction. There are no data available for use in patients with severe hepatic impairment. **Children and adolescents:** there are no data available in these age groups. **Pregnancy:** indacaterol can be employed only when the expected benefits outweigh the potential risks. **Lactation:** it is not recommended.

Place in therapeutics

Pharmacological management of COPD is aimed to reduce symptoms and/or complications. It should be progressive, adjusted to the severity of the obstruction and symptoms as well as the response of the patient to treatment. Inhaled bronchodilators (long-acting beta 2 agonists and long-acting anticholinergic agents) form the basis of symptomatic management of COPD patients and of permanent symptoms[15]. Long-acting beta 2 agents (salmeterol and formeterol) have shown a reduction in hospitalizations and COPD exacerbations when compared to placebo. However, there are no significant differences in health benefits with regard to the use of long-acting anticholinergic agents (tiotropium)[14,16].

Indacaterol is the first long-acting beta 2 agonist that requires a single daily dose. When compared to other long-acting beta 2 agonists, indacaterol has shown similar efficacy. There were no differences when compared to tiotropium in a short open clinical trial.

Its safety profile is not well established given the low number of patients, shorte follow-up periods, of less than a year, and important exclusion criteria. The identified risks (proarrhythmic and cardiovascular effects, hyperglycaemia, hypokalaemia, complications in asthma patients or bronchospasm) are similar to beta 2 agonists, but the real incidence remains unknown.

In the short term, indacaterol presents a greater incidence of adverse effects, mainly cough, upper respiratory tract infections and muscle spasms. This agent presents a rapid onset of action, similar to salbutamol, which could lead to its inadequate use as rescue treatment, which physicians should take into account when prescribing.

There is no evidence that indacaterol is better than other long acting beta 2 agonists available on the market. It has no indication for management of asthma patients and for now there are no data to support its use in conjunction with steroids in patients with COPD.

Presentations

Onbrez breezhaler® (Novartis Pharmaceuticals S.A.) 150 mcg inhalation powder, 30 capsules (50.13 €), Onbrez breezhaler® 300 mcg inhalation powder, 30 capsules (50.13 €).

References

The complete report on indacaterol can be consulted at: http://www.dtb.navarra.es

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