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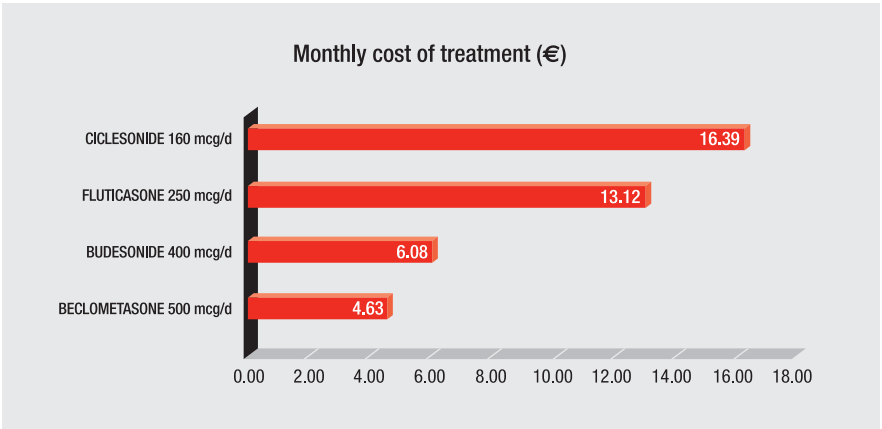
Ciclesonide▲ (Alvesco®) in asthma

...and one more inhaled glucocorticoid



Similar efficacy to other inhaled glucocorticoids in mild to moderate asthma

- Ciclesonide is an inhaled corticosteroid indicated in the management of persistent asthma in adults and adolescents (≥12 years).
- The short-term efficacy is similar to other available inhaled corticosteroids in the management of mild and moderate asthma patients.
- There are no long-term data available either for severe asthma or use at high doses.
- The theoretical single daily dose advantage is undermined by only one available 160 µg dose presentation which limits individual dose adjustments.

Therapeutic indications[1]

Ciclesonide is an inhaled corticosteroid indicated for the maintenance treatment of asthma and as prophylactic therapy in adult and adolescent patients aged 12 years and older.

Mechanism of action and pharmacokinetics[1]

Once inhaled orally this glucocorticoid is converted enzymatically in the lungs into the active metabolite. The oral bioavailability of ciclesonide and its active metabolite is insignificant (<1%). Lung sedimentation in healthy persons is 52% and lung esterases hydrolyse ciclesonide to its active metabolite. Elimination is via faeces (67%).

Posology and method of administration[1]

Administration: solution for inhalation in a pressurized container. Recommended dose: 160 µg daily in a single dose, preferably at night. In some patients, a reduction of the dose to 80 µg once daily could be the effective maintanence dose, although currently the 80 µg and 40 µg presentations are not marketed.

Clinical efficacy

Of a total of 11 controlled clinical trials that compared ciclesonide to another inhaled corticosteroid (budesonise or fluticasone) in patients ≥12 years, three were discarded due to their deficient methodological quality. No study comparing ciclesonide to budesonide has been published.

All the studies were non-inferiority trials except for one superiority clinical trial[2]. The primary endpoints were the change in spirometric values in the daily peak expiratory flow (PEF) records and/or asthma symptom control. The non-inferiority limits in the majority of studies were -0.200L for FEV_1 and FVC_1, and -25 L/min for PEF. The duration of the studies was 12 weeks. Exacerbations were registered in only 5 studies, although there was considerable variability in the definition of criteria[2-6].

In the majority of the studies patients were affected with mild to moderate asthma. The average age of the participants ranged between 29 and 46 years except for one study in which the average age was 14 years.

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.

Ciclesonide vs budesonide

In 4 of the 5 randomised clinical trials (RCT) published[3,4,6-8], in four of which the daily dose of ciclesonide employed was 320 µg, which is higher than the recommeded dose in the Summary of Product Characteristics.

Change in spirometric values (FEV_1, FVC, PEF) and daily record of PEF: ciclesonide was not inferior to budesonide in 4[3,4,6,8] of the 5 studies and, in only one of them[7], ciclesonide showed superiority to an underdosed budesonide, though the differences observed in the improvement of these values could not be considered clinically relevant.

Control of symptoms and rescue medication: no significant differences were observed in the control of symptoms and the need for rescue treatment except for one study[4] where the percentage of days free of symptoms was 43.6% and 25.8% for ciclesonide and budesonide respectively. There was also a reduction in the use of rescue treatment in favour of ciclesonide but not in the percentage of days without rescue treatment (57.5% vs 53.6%).

Exacerbations: only 3 studies[3,4,6] registered exacerbations. There were no significant differences between both treatments.

Ciclesonide vs fluticasone

There are 3 RCTs available[2,5,9].

Change in spirometric values (FEV_1, FVC, PEF) and daily record of PEF: ciclesonide was not inferior to fluticasone in the mentioned spirometric values[5,9]. In the only superiority trial[2], no statistically significant differences were found when comparing both medications.

Asthma symptom control and rescue medication: in the superiority trial[2] the primary endpoint was control of asthma (days free of symptoms and with no rescue treatment) and no significant differences were observed between ciclesonide and fluticasone (97% vs 98%). Nor were there significant differences in the other RCTs with regard to control of symptoms and the need for rescue medication on comparing both drugs.

Exacerbations: only 2 studies[2,5] registered this variable. The number of exacerbations was small (1-2) and no significant differences were found between both drugs.

Safety

Adverse reactions[1]

Uncommon (0.1%-1%): bad taste, application site reactions (burning, inflammation and irritation) application site dryness, hoarseness, cough, paradoxical bronchospasm, exanthema and eczema.

Risk of systemic side effects at high doses and prolonged treatments: Cushing syndrome, hypercorticism, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, and glaucoma

Contraindicacions[1]

Patients with hypersensitivity to ciclesonide or any of its excipients.

Warnings and precautions[1]

Do not employ in severe bronchospasm or acute episodes which require other intensive measures. Do not employ as rescue treatment.

Precaution in patients with active or latent pulmonary tuberculosis, fungal, viral or bacterial infections, severe liver failure, risk of adrenal gland failure after modifications in oral corticosteroid treatment to inhaled ciclesonide. Caution is advised in these cases when reducing doses of corticosteroids. Risk of adrenal suppression in stressful situations. Paradoxical bronchospasm.

Use in special situations[1]

Children under 12, pregnancy and lactation: it is not recommended given the lack of sufficient evidence regarding efficacy and/or safety. **Elderly:** age does not influence the systemic exposure of the active metabolite. **Liver failure:** can affect the elimination of the active metabolite. **Renal failure:** no dose adjustments required.

Interactions[1]

Avoid the concomitant administration of CYP3A4 inhibitors (ketoconazole, itraconazole and tironavir or nelfinavir), except when the benefits compensate the increased risk of adverse systemic reactions associated with corticosteroids.

Risk Management Plan of the European Medicines Agency (EMA)

The EMA considered that there is no sufficient evidence available to support the use of ciclesonide at high doses in patients with severe asthma. This led to the proposal of carrying out a well designed long term study to obtain sufficient information on the efficacy and safety of ciclesonide at 320 and 640 µg daily doses in patients with severe asthma[11].

Place in therapeutics

Inhaled corticoids are the elective management option in persistent asthma based on their efficacy in the reduction of symptoms and in the improvement in lung function and the reduction of exacerbations. Low dose corticoids, equivalent to 400 µg budesonide are effective in the majority of patients with mild to moderate asthma although high doses may be necessary in cases of severe asthma[12].

There is extensive evidence on efficacy and safety of beclomethasone, budesonide and flucitasone. However the studies on ciclesonide available up to now do not indicate superiority in terms of clinical relevance such as excerbations, hospital admissions, quality of life and long-tem safety (>12 weeks) when compared to the other inhaled corticoids. No long term studies are available that compare ciclesonide to other inhaled corticoids in patients with severe asthma and at high doses.

It should be taken into account that asthma is a dynamic disease, and currently ciclesonide is only available in its 160 µg presentation, which limits adequate individual dose adjustments which asthma patients often require. Therefore, and despite the single daily dose of ciclesonide, which does not necessarily mean an increase in treatment adherence, this agent cannot be considered the elective option in the management of asthma.

Presentations

Alvesco® (Nycomed GmbH) 160 mcg/puff; 60 puffs (32.78 €). Prescription medicine only.

References

A complete report on ciclesonide can found at http://www.dtb.navarra.es

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