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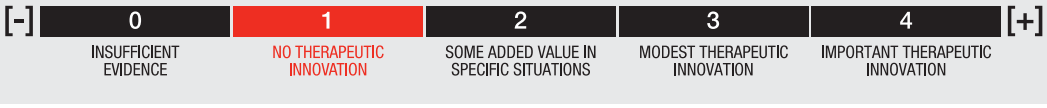
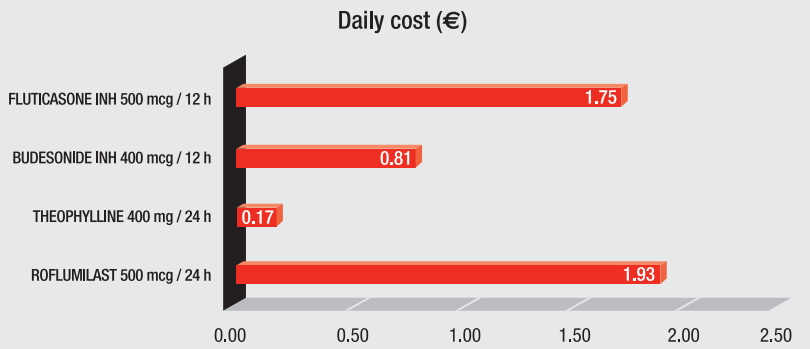
Roflumilast (▲Daxas®, ▲Libertek®) in severe COPD

Doubts on safety and questionable efficacy





There are other more effective and safer bronchodilators available for these patients

Therapeutic indications[1]

Roflumilast is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

Mechanism of action and pharmacokinetics[1]

The drug acts by inhibiting phosphodiesterase 4. Bioavailability = 80%. It is highly metabolized and one of the metabolites, roflumilast N-oxide, is the main agent responsible for the drug's action. Plasma protein binding is over 95%, and 20% is eliminated in faeces, while 70% in urine in inactive metabolite form.

Posology and method of administration[1]

500 mcg once daily, at the same hour with or without food.

Clinical efficacy

It has been evaluated in different studies over the last 15 years[3]. During this period, not only have the indications been modified substantially, but also the studies' design, the outcomes, and the target population. *There is no trial evaluating active comparators.*

The inclusion criteria in the trials *versus placebo* were different. The EMA[2] considered that only two trials with 3096 patients, adjusted to the population characteristics adequately with regard to the indications, while another four trials[6,7] provide support to these two. In the two main trials, the concomimitant use of long-acting inhaled anticholinergic agents or inhaled corticoids as maintenance therapy was prohibited. The primary[1] endpoints of the trials were changes in pre-bronchodilation FEV_1 from the beginning of treatment and exacerbations of COPD.

- This drug is taken orally and is authorized in a small group of patients.
- It has only been compared to placebo in patients who were not correctly treated.
- There are doubts on its clinical efficacy in the trials.
- There is concern regarding safety issues: suicide, weight loss, and absence of data on use over more than one year.

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.

Roflumilast improved FEV_1 in the two main trials and the 4 supporting trials, with a difference compared to placebo of 48 mL (35-62 mL). The differences were lower than those considered clinically relevant[3] and those observed with other active substances[2].

An improvement was seen in moderate or severe exacerbations in the two main trials (average rate of exacerbation per patient and year, 1.14 vs 1.37; RAR=0.23 and RRR=17%). In the four supporting trials there were no significant differences in the rate of exacerbations compared to placebo. It should be taken into account that:
· The size of the effect is lower than what is considered clinically relevant[2].
· On carrying out the evaluation by protocol, the results were not coherent, and the reduction in the rate of exacerbations was no longer statistically significant[2].
· When examining the evolution of exacerbations over time, there is a reduction compared to placebo from the fourth week up to the 28th week (8 months) which disappears after the 36th week.

Safety and precautions

Adverse reactions[1,2]

In the clinical trials the most frequent side effects were: weight loss, loss of appetite, insomnia, headache, diarrhoea, nausea, abdominal pain. There was also an increase in psychiatric related disorders (anxiety, depression, insomnia) compared to placebo, including 5 cases of suicide in the group under roflumilast compared to none in the placebo group. In studies of one year duration, weight loss was frequently observed OR = 4.6 (3.4-6.3)[4]. Weight loss was associated with worse prognosis in COPD patients. There are no published safety data beyond one year.

Contraindications and precautions[1]

Contraindications: hypersensitivity to roflumilast or any of its excipients (contains lactose). Moderate to severe liver failure (Child-Pugh class B or C).

Precautions: do not employ this drug as rescue treatment in cases of acute bronchospasm. In patients with lower than normal body weight, weight control should be carried out at every visit. Treatment should be discontinued in cases of relevant clinical weight loss and of no other explanation.

Do not employ this drug in patients with severe immunological disease, acute severe infections, cancer patients, or those treated with immunosupressant drugs (except systemic corticosteriods taken in short periods of time).

The experience in patients with latent infections such as tuberculosis, viral infections due to herpes and herpes zoster is limited.

Do not employ in cases of a personal history of depression associated with suicidal ideas or behaviour, in patients with congestive heart failure (NYHA grade III and IV), or in patients under treatment with theophilin.

Evaluate carefully the benefits and risks when patients refer psychiatric symptoms or in the case of concommitant therapy with other drugs which could produce psychiatric disorders. Inform patients to be aware of any change in behaviour or mood and on any suicidal ideation or behaviour.

Interactions[1]

The concomitant administration of roflumilast and CYP3A4 inhibitors (erythromycin and ketoconazole), CYP1A2 inhibitors (fluvoxamine), and dual inhibitors CYP3A4/CYP1A2 (enoxacin and cimetidine) can increase exposure to the drug and cause persistent intolerance, and therefore the need for treatment should be reassessed. The use of potent P450 cytochrome inducers (phenobarbital, carbamazepine, phenytoin, rifampicin) can reduce its therapeutic efficacy.

Special situations [1]

Renal failure: no dose adjustments are required. **Liver failure:** precaution should be taken in patients with mild liver failure (Child-Pugh class A). It should not be employed in cases of moderate to severe liver failure (class B or C). **Pregnancy:** not recommended during pregnancy or in women in child bearing age who are not taking contraceptives. **Breastfeeding:** do not use.

Risk Management Plan of the European Medicines Agency (EMA)[2]

Avoid off-label use in patients with asthma, patients diagnosed with COPD with no frequent exacerbations, or those not associated with chronic bronchitis, or a FEV1 over 50%, or patients with alpha 1 anti trypsine deficiency.

Patients with important risks identified: weight decrease, psychiatric disorders, (insomnia, depression, nervousness, anxiety).

Important potential risks: malign tumours, infections, mesenteric vasculitis, ischemic colitis, cardiac safety, risk of triggering suicide, serious diarrhoea, gynecomastia, persistent intolerability in high-exposure populations.

Place in therapeutics

Pharmacological management of COPD is aimed at reducing symptoms and/or complications. It should be progressive, adjusted to the severity of the obstruction and the symptoms, and the response of the patient. In those patients with severe COPD and frequent exacerbations, a combination of various long-acting inhalers including inhaled corticoids are recommended[9,10]. As a second line therapy, in uncontrolled patients or those who do not tolerate inhalers, theophylline can be employed, although it shows a lower bronchodilator effect and more adverse effects than inhaled drugs.

Roflumilast is indicated exclusively in patients with severe COPD with chronic bronchitis and frequent exacerbations. EMA risk management plan states that roflumilast use be restricted to its authorized indication.

There is no trial evaluating the drug versus an active comparator. The data from clinical trials compare it to placebo and present many pitfalls. In some, the selected population is not the same as that of the approved indication; in others, patients were not allowed to take the recommended treatments for COPD during the trial. In all cases, the size of the effect was lower than that accepted as clinically relevant and its efficacy in the reduction of exacerbations disappears after the eight month. Some data on safety issues such as the increase in suicides, and weight loss are still a matter of concern.

For all these reasons, we do not know whether roflumilast is effective and safe in correctly treated patients with severe COPD, chronic bronchitis and frequent exacerbations.

Presentations

Daxas® and Libertek® (Nycomed GmbH) 500 mcg 30 tablets (57.84 €)

References

A complete report on roflumilast can be consulted at http://www.dtb.navarra.es

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