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Drug Assessment Report
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Febuxostat

(▼Adenuric®) in chronic hyperuricaemia with urate deposits. What is painful for the patient are gout flares

Abstract

- Febuxostat has shown a greater reduction in the levels of uric acid than fixed-dose (300 mg/d) allopurinol. With no titration of this dose, it is possible that the compared efficacy of febuxostat is overestimated.
- This drug has not proven more effective than allopurinol in reducing the frequency of gout attacks.
- The long-term safety profile is unknown, in particular with regard to cardiac-related events and other affectations of the liver, blood and thyroid gland. Cases of severe hypersensitivity including Stevens Johnson syndrome, acute anaphylaxis and shock, and liver failure have been notified.
- The cost of treatment with febuxostat is much higher than allopurinol.

Indications[1]

Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Mechanism of action and pharmacokinetics[1]

Reduces the concentration of uric acid by inhibiting xantine oxidase. The absorption is 84% and four metabolites have been identified. The drug is excreted in faeces (45%) and urine (49%).

Posology and form of adminstration[1,2]

The recommended oral dose is 80 mg daily, independent of meal times. If serum uric acid levels are >6 mg/dL (357 µmol/L) after 2-4 weeks, then 120 mg daily can be considered.

On initiating treatment, prophylaxis of gout crisis with NSAIDs or colchicine for a minimum of 6 months is recommended.

In case of gout attack, treatment with febuxostat should not be initiated until the episode has resolved.

If a gout flare occurs during treatment with febuxostat, there is no need to discontinue treatment, and the episode is treated simultaneously.

Clinical efficacy

The efficacy of febuxostat in patients with hyperuricaemia (> 8 mg/dL) and gout was evaluated in three trials, in which allopurinol was found to be superior both in the reduction of uric acid and in the proportion of patients that obtained serum levels <6 mg/dL (primary endpoint).

The three trials included prophylaxis for gout with naproxen (250 mg/12h) or colchicine (0.6 mg daily) for the first 8 or 9 weeks of treatment. None of the trials included patients with severe renal failure and the FACT study excluded patients with renal failure. The percentage of patients abandoning treatment was greater in the febuxostat group.

During prophylaxis, the incidence of gout was greater with febuxostat compared to allopurinol. In the FACT trial both febuxostat doses tested (120 and 80 mg daily) resulted in a higher incidence of gout attacks than allopurinol. The withdrawal of propylaxis was accompanied by an increase in the incidence of gout flares (greater with febuxostat 120 mg), which suggests that the prophylaxis period should be increased to more than 8 weeks.

In a Cochrane review[9] which included these trials, it was observed that any dose reduced uric acid levels. During the initial phases of treatment, the incidence of gout flares with febuxostat was higher than with allopurinol. This increment was not observed in long-term extension trials versus allopurinol.

'Serious doubts on cardiovascular safety, higher incidence of gout flares than allopurinol, and at 10 times the cost'

Safety

Adverse reactions[1]

The most frequent adverse reactions (≥1/100 to <1/10) were acute episodes of gout flares, liver function alterations, diarrhoea, nausea, headache, skin eruptions and oedema. In trials comparing febuxostat to allopurinol at fixed doses, there was a higher incidence of cardiovascular events and death that did not reach statistical significance. Severe hypersensitivity reactions have been notified including Steven Johnson syndrome, acute anaphylaxis and shock and liver failure.

Contraindications[1]

Hypersensitivity to the active sustance or any of its excipients.

Warnings and precautions[1]

· Do not employ in patients with heart disease, or congestive heart failure, or in those with very high urate production.

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

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.

CLINICAL EFFICACY OF FEBUXOSTAT

STUDY	N	FEBUXOSTAT GROUP	CONTROL	DURATION	PROPORTION OF PATIENTS WITH URIC ACID IN SERUM <6 mg/dl
FACT[3]	760	80 mg daily 120 mg daily	Alopurinol 300 mg daily	52 weeks	F 80 mg: 53% F 120 mg: 62% A 300 mg: 21%
APEX[4]	1,072	80 mg daily 120 mg daily 240 mg daily	Placebo Alopurinol (300 daily or 100 mg daily depending on renal function	28 weeks	F 80 mg: 48% F 120 mg: 65% A 300/100 mg: 22%
CONFIRMS[5]	2,268	40 mg daily 80 mg daily	Alopurinol 300 daily ór 200 mg daily in cases of mild-moderate renal impairment	24 weeks	F 80 mg: 67.1% A 300/200 mg: 42.1%

· Liver function tests are recommended before initiating treatment and they should be repeated periodically according to the clinicians criteria.
· Precaution is advised in patients with alterations of the thyroid gland and those who employ machinery.

Use in special situations[1]

Mild to moderate renal failure: no dose adjustments are required. There is no evaluation available in cases of severe renal failure. **Mild to moderate liver failure:** the recommended dose is 80 mg. In cases of severe liver failure there are no available data. **Elderly:** no dose adjustments are required. **Children, pregnancy and lactation:** no information.

Interactions[1]

Mercaptopurine/azathioprine: its concomitant use is not recommended. **Theophylline:** plasma levels should be monitored.

EMA Risk Management Plan[1]

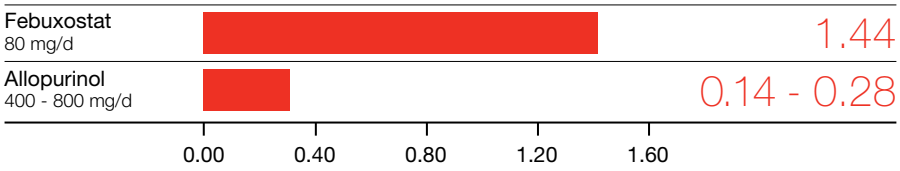
Includes the need for a phase IV clinical trial to determine the cardiovascular risk of febuxostat compared to allopurinol.[2]

Place in therapeutics

In patients with persistent hyperuricaemia and gout, hypouricaemic treatment is given as reduced serum levels of uric acid under 6 mg/dL have shown to prevent the formation of crystals or even dissolve existing crystals or reduce tophus size. Some patients achieve this with changes in lifestyle, but the majority need indefinite treatment with hypouricaemic agents.[10]

The elective choice is allopurinol, given its efficacy, safety profile and cost-effectiveness. Although in common clinical practice 300 mg daily doses are employed, the dose can be adjusted to a maximum of 800-900 mg daily (dose divided and taken twice daily). Although rare, one of the potential limitations of allopurinol is the hypersensitivity syndrome. From a clinical perspective the available and effective alternative pharmacological agents are very scarce. Management with allopurinol can be difficult or even impossible (for example, patients with renal failure or those who suffer from rash, or an hypersensitive reaction).

DAILY COST OF TREATMENT (€)



The experience with febuxostat is very limited in these subgroups as well as in patients with high urate levels due to tumoral processes.[2] In the case of patients who do not respond or tolerate allopurinol, the available alternative choice is benzbromarone, an uricosuric drug of restricted use given its liver toxicity.[11]

Febuxostat has achieved a greater proportion of patients with uric acid levels < 6 mg/dL compared to allopurinol 300 mg daily. However, it has not been compared to allopurinol at different doses. The nature and strength of the combination between the reduction of uric acid and the prevention of gout symptoms is not clear. It has not proven more effective than allopurinol in the reduction of gout flares.

The data on long term safety are unknown, in particular knowledge of the effects on the heart, liver, blood, and thyroid gland remain limited. Cases of severe hypersensitivity including Stevens Johnson syndrome, acute anaphylaxis and shock, and liver failure have been notified.

Febuxostat cannot be considered a first-line option for the management of patients with gout and chronic hyperuricaemia. There is no clear evidence of the benefits of febuxostat compared to allopurinol, at fixed doses, in the improvement of clinical results, such as control of the incidence of gout flares, the reduction of size and number of tophi, and the prevention of organ and joint damage as a result of the deposits of urate crystals in the long term.

On the other hand, there is limited evidence that suggest that it could be an option for patients with hypersensitivity to allopurinol and there still remains serious doubts on the drug´s cardiovascular safety profile.

Presentations

Adenuric® (Menarini Internacional Luxembourg S.A.) 80 and 120 mg, 28 tablets (40.26 €)

References and full report

Available at, www.dtb.navarra.es

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