

CEDAC FINAL RECOMMENDATION

FEBUXOSTAT **(Uloric – Takeda Canada Inc.)** **Indication: Gout**

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that febuxostat be listed for patients with symptomatic gout who have documented hypersensitivity to allopurinol.

Reasons for the Recommendation:

1. In three double-blind randomized controlled trials (RCTs), included in the systematic review considered by CEDAC, febuxostat achieved a statistically significantly greater proportion of patients with a serum uric acid (SUA) level of less than 6 mg/dL compared with allopurinol. However, the proportion of patients requiring treatment of gout flares was not statistically significantly different between febuxostat and allopurinol in two of the trials, and was statistically significantly greater for febuxostat compared with allopurinol in one trial.
2. The cost of febuxostat, 80 mg once daily (\$1.59), is greater than allopurinol, 100 mg to 800 mg daily (\$0.08 to \$0.52).
3. Febuxostat and allopurinol have a similar mechanism of action; thus, febuxostat was not considered to be a useful alternative for patients inadequately treated with allopurinol. However, febuxostat and allopurinol have different chemical structures, and there is limited evidence to suggest that febuxostat may be an option for patients who have a hypersensitivity to allopurinol.

Of Note:

1. Despite the statistically significant between-treatment differences in SUA levels, favouring febuxostat, the Committee was concerned that the fixed doses of allopurinol used in the trials (no titration or doses greater than 300 mg per day) may have overestimated the comparative efficacy of febuxostat.
2. Drug-induced Hypersensitivity Syndrome (DIHS) is characterized by a major skin manifestation, fever, multi-organ involvement, lymphadenopathy, and hematological abnormalities (eosinophilia, atypical lymphocytes). The onset of symptoms usually occurs two to eight weeks after therapy initiation of the causative drug (most commonly associated drugs: aromatic anticonvulsants, sulphonamides, allopurinol, antibiotics, and antiretroviral drugs). A large variability in the clinical presentation is seen among different patients, and

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not all of the characteristics listed above are seen in all patients. At least three of the characteristics listed above should be present, including involvement of at least one extracutaneous organ system, for the diagnosis of DIHS. Fever is seen in a majority of patients. The extracutaneous organ most frequently involved in DIHS is the liver (abnormal liver function tests, hepatitis), but a multitude of other organs can be involved as well (kidney, lung, blood system, lymphoid system, heart, gastrointestinal tract). A skin manifestation is seen in a majority of patients with DIHS. The most common skin manifestation is an exanthematous eruption, but other manifestations (e.g., urticarial plaques, exfoliative and pustular eruptions) are also seen.

Background:

Febuxostat has a Health Canada indication to lower SUA levels in patients with gout. Febuxostat is a xanthine oxidase inhibitor. It is available as 80 mg tablets and the Health Canada-approved dose is 80 mg once daily.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of febuxostat, a critique of the manufacturer's pharmacoeconomic evaluation and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included three double-blind RCTs of patients with gout (diagnosed using the American College of Rheumatology criteria) and hyperuricemia (defined as a SUA level of ≥ 8 mg/dL):

- APEX (N = 1,072) was a six-month multicentre trial with five treatment groups. The trial compared febuxostat 80 mg per day, 120 mg per day, and 240 mg per day with placebo and allopurinol (either 300 mg per day or 100 mg per day, dependent on renal function).
- FACT (N = 762) was a one-year multicentre trial with three treatment groups. The trial compared febuxostat 80 mg per day and 120 mg per day with allopurinol 300 mg per day.
- CONFIRMS (N = 2,268) was a six-month multicentre trial with three treatment groups. The trial compared febuxostat 80 mg per day and 120 mg per day with allopurinol (either 300 mg per day or 200 mg per day, dependent on renal function).

All three trials were designed to test the non-inferiority of febuxostat and included preplanned superiority testing, to be conducted if non-inferiority was demonstrated. The CDR systematic review included only the febuxostat data for the Health Canada-approved dose (80 mg per day).

Most of the patients in the trials were male between the ages of 45 and 65 years and had had gout for at least 10 years. All three trials included a washout period of two (APEX and FACT) or four (CONFIRMS) weeks, during which prior urate-lowering treatments were discontinued. None of the trials included patients with severe renal impairment, and the FACT study excluded patients with renal impairment. All three trials included preventive treatment with either naproxen or colchicine for a minimum of eight weeks.

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Limitations of the trials included fixed allopurinol dosing, which did not allow for titration or doses greater than 300 mg per day, and differential withdrawal between treatment groups.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: quality of life, patient-reported gout flares, change in SUA levels, study discontinuation due to adverse events and flares, serious adverse events, and rash.

The primary outcomes for each of the trials were as follows:

- APEX: the proportion of patients whose last three monthly SUA levels were < 6.0 mg/dL
- FACT: the proportion of patients whose last three monthly SUA levels were < 6.0 mg/dL
- CONFIRMS: the proportion of patients with a SUA level of < 6.0 mg/dL at final visit.

For each of the above trials, the non-inferiority margin was a 10% between-treatment difference in the primary outcome. The patient groups supplying input to CDR did not mention SUA levels as being an important outcome.

Pain due to gout flares was not specified as an outcome in any of the included trials, despite being identified as an important outcome by patient groups supplying input to CDR.

Results

Efficacy or Effectiveness

- Both APEX and FACT reported no statistically significant difference in the proportion of patients requiring treatment for gout flare between febuxostat and allopurinol, both from week zero to week eight, and from week nine to end of study. In contrast, the CONFIRMS study reported a statistically significantly greater proportion of patients requiring treatment of gout flare for febuxostat compared with allopurinol, both from week zero to week eight (20.1% versus 15.2%, $P = 0.04$) and from week nine to end of study (12.8% versus 8.4%, $P = 0.02$).
- All three trials reported statistically significant between-treatment differences favouring febuxostat compared with allopurinol at final visit, for both percent reduction in SUA level and proportion of patients achieving a SUA level of < 6.0 mg/dL.
- Two trials (APEX and FACT) included quality of life measures. Neither febuxostat 80 mg nor allopurinol 300 mg produced any consistent changes in quality of life, and there were no consistent between-treatment differences.
- Gout pain, which patient groups mentioned as an important outcome, was not specified as an outcome in any of the trials. Quality of life scales employed in APEX and FACT included assessments of pain. In all cases, improvements in pain were numerically greater for allopurinol compared with febuxostat; however, the statistical significance of these differences was not reported.

Harms (Safety and Tolerability)

- Total withdrawal ranged from 20% to 35% for febuxostat 80 mg groups, compared with 18% to 26% for allopurinol groups; total withdrawal was statistically significantly higher for febuxostat compared with allopurinol in two of three trials.

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- The frequency of treatment discontinuation due to gout flare was statistically significantly greater for febuxostat 80 mg (4.9%) compared with allopurinol (0.4%) in APEX, but was not statistically significantly different between treatments in FACT or CONFIRMS.
- The proportion of patients experiencing a rash adverse event was similar between febuxostat 80 mg and allopurinol in all three trials. Similarly, the proportion of patients discontinuing treatment due to a treatment-related rash was not statistically significantly different between febuxostat 80 mg and allopurinol, in any of the three trials.
- The proportion of patients experiencing an adverse event was not statistically significantly different between febuxostat 80 mg and allopurinol, in any of the three trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing febuxostat (80 mg daily) with allopurinol (300 mg daily) for the treatment of hyperuricemia in patients with gout. The model contained three health states: intercritical gout with median SUA level, gout flare at a given SUA level, and death. The expected SUA levels were assigned according to the results of the febuxostat clinical trials (APEX, FACT, and CONFIRMS). As such, the response is constant (i.e., after the first year, each group had the same mean SUA level for the duration of the model). The corresponding probability of a gout flare is assigned per year according to the SUA level as dictated by a published relationship, which was integrated into the model. Similarly, health resource utilization and health utility values (to calculate quality-adjusted life-years [QALYs]) are also assigned according to the mean SUA levels. The manufacturer reported that febuxostat compared with allopurinol resulted in a cost per QALY of \$18,395. The manufacturer's economic evaluation was limited by information to support the relationship between SUA levels and gout flares and quality of life. The manufacturer provided sensitivity analyses that suggest that the cost per QALY estimates are sensitive to changes in utility estimates, with incremental cost-utility ratios ranging from \$9,862 to \$64,652. Further, the relationship was not supported by the clinical trial results, which showed that despite significant reductions in SUA levels for those receiving febuxostat, compared with allopurinol, quality of life (as measured by the SF-36 health survey) was largely similar across the treatments. In addition, results from the RCTs may be biased against allopurinol, as the dose of allopurinol was fixed (no titration or doses greater than 300 mg per day were permitted).

At 80 mg once daily, the cost of febuxostat (\$1.59) is greater than allopurinol (100 mg to 800 mg; \$0.08 to \$0.52).

Patient Input Information:

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Pain associated with acute gout flares is of particular concern to patients.
- Patients see febuxostat as an alternative preventive agent when existing therapies are not appropriate for use.

Other Discussion Points:

- The Committee considered that the relationship between SUA levels and gout flares is uncertain and that in clinical practice treatment is based upon gout flares and symptoms, rather than SUA levels. Specifically, it was noted that gout flares in clinical practice may result in dose titration of allopurinol beyond 300 mg per day.

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- In a small (N = 13) retrospective study of patients with prior severe allopurinol reactions, 12 patients were noted to have tolerated febuxostat (mean exposure 10 months), while one patient developed cutaneous leukocytoclastic vasculitis after four days of febuxostat.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:

Dr. Anne Holbrook (Vice-Chair)

Conflicts of Interest:

None

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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