Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Uloric, which is also called febuxostat, be listed by Canada's publicly funded drug plans for the treatment of gout in patients who have documented hypersensitivity (reaction) to allopurinol.

Reasons for the Recommendation:
1. In three studies reviewed by CEDAC, a greater percentage of patients on Uloric had lowering of their serum uric acid (SUA) level to less than 6 mg/dL, compared with patients on allopurinol. However, the percentage of patients requiring treatment of gout flares (attacks) was about the same for Uloric and allopurinol in two of the studies, and was greater for Uloric compared with allopurinol in one study.
2. The cost of Uloric, 80 mg once daily ($1.59), is greater than that of allopurinol, 100 to 800 mg daily ($0.08 to $0.52).
3. Uloric and allopurinol work in a similar way; therefore, Uloric is not a useful alternative for patients who do not get enough benefit from allopurinol. However, Uloric and allopurinol have different chemical structures, and there are some data suggesting that Uloric may be an option for patients who have a hypersensitivity to allopurinol.

Of Note:
1. Although Uloric lowered SUA levels in a greater percentage of patients compared with allopurinol, the Committee was concerned that the fixed doses of allopurinol used in the studies (no dosage adjustments or doses greater than 300 mg per day were allowed) may have made Uloric appear more effective, compared with allopurinol, than it really is.
2. Drug-induced Hypersensitivity Syndrome (DIHS) involves major skin symptoms, fever, multiple body organ effects, swelling of the lymph nodes, and changes in the blood, such as increases in eosinophils (a type of white blood cell involved in allergic reactions) and atypical (unusual) lymphocytes (a type of white blood cell usually involved in fighting infection). The symptoms usually begin two to eight weeks after the start of treatment with the drug causing the reaction (most common drugs causing the reaction: some epilepsy

medications, sulpha drugs, allopurinol, antibiotics, and some medications used to treat human immunodeficiency virus). Different patients may have very different symptoms, and not all of the symptoms in the list above are seen in all patients. At least three of the symptoms listed above, including at least one symptom involving a part of the body other than the skin, should be seen in a patient in order to make the diagnosis of DIHS. Most patients have fever. Other than the skin, the most commonly involved organ is the liver (high liver function tests or inflammation of the liver), but many other organs can be involved as well (kidney, lung, blood system, lymphoid system, heart, digestive system). Most patients with DIHS have skin symptoms. The most common skin symptom is a rash, but other symptoms (e.g., scaling, peeling, and/or blistering) are also seen.

Background:
Uloric belongs to a class of drugs called xanthine oxidase inhibitors. It works to lower the uric acid in the blood by inhibiting xanthine oxidase, a naturally occurring enzyme that is involved in uric acid formation. The normal uric acid level should be lower than 360 µmol/L (6.0 mg/dL). Uloric is approved by Health Canada to lower uric acid levels in adult patients with gout.

It is available as 80 mg tablets and the Health Canada-approved dose is 80 mg once daily.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Uloric and a review of economic information prepared by the manufacturer of Uloric. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials
CEDAC reviewed three studies of patients with gout (diagnosed using the American College of Rheumatology criteria) and hyperuricemia (high uric acid in the blood, defined as a SUA level of 8 mg/dL or greater):

- APEX, with 1,072 patients, was a six-month study that took place in more than one clinic, with patients receiving one of five treatments. The study compared Uloric 80 mg per day, 120 mg per day, and 240 mg per day with placebo (a tablet containing no active medication) and allopurinol (either 300 mg per day or 100 mg per day, depending on kidney function).
- FACT, with 762 patients, was a one-year study that took place in more than one clinic, and patients received one of the following: Uloric 80 mg per day, Uloric 120 mg per day, or allopurinol 300 mg per day.
- CONFIRMS, with 2,268 patients, was a six-month study that took place in more than one clinic, and patients received one of the following: Uloric 80 mg per day, Uloric 120 mg per day, or allopurinol (either 300 mg per day or 200 mg per day, depending on kidney function).

The purpose of all three studies was to see whether Uloric was not worse than allopurinol, and if this was the case, then the data would be analyzed to see whether Uloric was better than allopurinol. The CDR systematic review (an exhaustive review or summary of literature relevant

to the underlying research question) included only the Uloric data for the Health Canada-approved dose of 80 mg per day.

Most of the patients in the studies were males between the ages of 45 and 65 years and had had gout for at least 10 years. All three studies included a period of time during which any uric acid-lowering treatments were stopped, to allow their effects on the body to wane. For APEX and FACT, this period of time was two weeks, and for CONFIRMS, it was four weeks. None of the studies included patients with severe kidney disease, and the FACT study did not allow any patients with kidney disease to take part in the study. All three studies used additional treatments for gout, such as naproxen or colchicine, for a minimum of eight weeks.

The accuracy of the results may be affected by the fixed allopurinol dosing, which did not allow for dosage changes or for doses greater than 300 mg per day. Accuracy could also be affected by the fact that different proportions of patients stopped participating in the study depending upon which treatment they received.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: quality of life, patient-reported gout flares, change in SUA levels, stopping participation in the study because of side effects and flares, serious side effects, and rash.

The main purpose of each study was to measure the following:

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

For each of the above studies, if the percentage of patients reaching a SUA level of less than 6.0 mg/dL in the Uloric group was not more than 10% lower (worse) than the percentage of patients reaching a SUA level of 6 mg/dL in the allopurinol group, then Uloric would be considered not worse than allopurinol. Patient groups supplying input to CDR did not mention SUA levels as being an important outcome.

Measuring pain due to gout flares was not stated as a purpose of any of the included studies, although it was recognized as an important outcome by patient groups supplying input to CDR.

Results

Efficacy or Effectiveness

- Both APEX and FACT had about the same percentage of patients who needed to have treatment for gout flare between Uloric and allopurinol, both from week zero to week eight, and from week nine to the end of the study. However, the CONFIRMS study found that a greater percentage of patients on Uloric compared with allopurinol required treatment of gout flare, both from week zero to week eight (20.1% versus 15.2%) and from week nine to end of study (12.8% versus 8.4%).

- In all three studies, patients on Uloric had greater reductions in SUA and were more likely to achieve a SUA of less than 6.0 mg/dL compared with allopurinol.
- Two studies (APEX and FACT) measured quality of life. Neither Uloric 80 mg nor allopurinol 300 mg seemed to improve quality of life, and there did not seem to be any difference between the treatments in the quality of life scores.
- Gout pain, which patient groups mentioned as being an important outcome, was not an outcome that any of the studies specifically planned to look at. However, pain was measured as part of the quality of life scales used in the APEX and FACT studies. In all cases, improvements in pain appeared to be slightly better for allopurinol compared with Uloric, but it is not known if these small differences were important.

Harms (Safety and Tolerability)

- The percentage of patients who stopped taking part in the study ranged from 20% to 35% for Uloric 80 mg groups, compared with 18% to 26% for allopurinol groups; a greater percentage of patients stopped taking part in the study in the Uloric groups compared with allopurinol groups in two of the three studies.
- In APEX, a higher percentage of patients taking Uloric 80 mg (4.9%) compared with allopurinol (0.4%) stopped taking the treatment because of gout flare. However, in FACT and CONFIRMS, the percentage of patients who stopped taking the treatment because of gout flare was about the same, regardless of which treatment they were on.
- The percentage of patients who had a side effect of rash was similar between Uloric 80 mg and allopurinol in all three studies. Similarly, the proportion of patients that stopped treatment because of a rash from the treatment was about the same for Uloric 80 mg and allopurinol, in all three of the studies.
- The percentage of patients with a side effect was about the same for Uloric 80 mg and allopurinol in all three of the studies.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Uloric (80 mg daily) with that of allopurinol (300 mg daily) to evaluate the health benefit for the treatment of hyperuricemia in patients with gout. The manufacturer's economic evaluation was based on the assumption that high SUA levels result in gout flares and poorer quality of life. This was not supported by the studies reviewed by CEDAC, which showed that although SUA levels for those receiving Uloric were lower compared with allopurinol, quality of life (as measured by the SF-36) was similar for both the treatments. In addition, results from the studies may make Uloric appear more effective, compared with allopurinol, than it really is, because the doses of allopurinol were fixed (no dosage adjustments or doses greater than 300 mg per day were allowed).

At 80 mg once daily, the cost of Uloric ($1.59) is greater than that of 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 attacks of gout is a very important problem for patients.
- Patients saw Uloric as an alternative medication to prevent gout when existing treatments could not be used.

Other Discussion Points:

- The Committee considered that it is not known for certain that high SUA levels cause gout flares and that in medical practice, treatment is based upon gout flares and symptoms, rather than SUA levels. Specifically, it was noted that gout flares in medical practice may result in increasing the dose of allopurinol to more than 300 mg per day.
- In a small study of 13 patients with previous severe allopurinol reactions, 12 patients were noted to have been able to take Uloric without having a severe reaction (the average length of time they took Uloric was 10 months), while one patient developed cutaneous leukocytoclastic vasculitis (a disease involving inflammation of the blood vessels of the skin) after four days of taking Uloric.

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
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans, based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.