Pharmacotherapeutic report, summary
Febuxostat (Adenuric®) for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis)

Recommendation by Zorginstituut Nederland dated 27-10-2014, based on an evaluation by the WAR (Scientific Advisory Committee)

The WAR has approved a pharmacotherapeutic report for the medicine febuxostat (Adenuric®). In determining its therapeutic value, they compared febuxostat with allopurinol and benzbromarone. They reached the following conclusion.
- for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis), the therapeutic value of febuxostat is equivalent to that of allopurinol and greater than that of benzbromarone for patients who cannot (or can no longer) be treated with allopurinol or no longer respond to this treatment.

Medicine. Febuxostat (Adenuric®), film-coated tablets 80 and 120 mg for oral use

Registered indication. 'The treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis).'

Posology. 80 mg once daily orally, to be taken with or without food. If serum uric acid is > 6 mg/dl (0.35 mmol/l) after 2-4 weeks, 120 mg may be considered.

Mechanism of action. Febuxostat belongs to the group of compounds that inhibit uric acid production, the urostatics. Uric acid is a degradation product of the DNA components adenine and guanine and the end product of purine metabolism in humans. It is generated in the cascade of hypoxanthine $\rightarrow$ xanthine $\rightarrow$ uric acid. Both steps in this cascade are catalysed by xanthine oxidase. Febuxostat is a non-purine selective inhibitor of xanthine oxidase. As a result, the degradation of hypoxanthine and xanthine to uric acid is inhibited and the concentration of uric acid in the blood is gradually reduced, tophi shrink and the deposition of urate crystals is prevented. Uric acid concentration is reduced to normal values after 2-4 weeks. It may take months before the frequency of acute gout attacks is reduced. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or 8-pyrimidine metabolism.

Summary of the therapeutic value

Intended effects. Febuxostat has the same effect as allopurinol (up to 300 mg) for the treatment of adult patients with hyperuricaemia associated with urate deposition and gouty symptoms both with respect to the primary endpoint, reducing the serum uric acid concentration <0.36 mmol/l, and with respect to the frequency of gout attacks. These results were also found in the sub-populations of patients with renal impairment, while these patients either cannot be treated with allopurinol or the dose of allopurinol has to be reduced, which means the desired treatment effect cannot be realised with allopurinol. It is difficult to compare febuxostat with benzbromarone (an alternative for patients who were unsuccessful on allopurinol or who could not be treated with it, as only limited clinical studies are available.

Unintended effects. The most frequent unintended effects of both febuxostat and allopurinol are asymptomatic abnormal liver function tests, gastro-intestinal symptoms and skin rashes. One important difference between allopurinol and febuxostat is that hypersensitivity reactions, often presenting as a rash, are more frequent with allopurinol. This can be a forewarning of extremely severe hypersensitivity reactions: the "Allopurinol Hypersensitivity Syndrome' (AHS) with a mortality risk of 20-30% and the Stevens-Johnson syndrome. If allopurinol can no longer be used, then benzbromarone, until recently the only other medicine available, can be considered. Benzbromarone should be used with caution due

to possible occurrence of very severe hepatotoxicity. This is why benzbromarone has been taken off the market in many European countries and the USA, and in the Netherlands its indication has been limited to patients for whom allopurinol leads to insufficient results or unacceptable side effects. On the one hand febuxostat has a lower frequency of severe unintended effects than allopurinol and on the other hand its safety profile is more favourable than that of benzbromarone. It is true that PMS data show that severe skin reactions can also occur with febuxostat, but their incidence is lower and they are not life-threatening or fatal as with allopurinol. It seems that febuxostat can also be used for patients who have experienced severe hypersensitivity reactions to allopurinol.

Experience. Sufficient experience has been obtained with febuxostat (since 2008 on the market). Ample experience has been obtained with allopurinol and benzbromarone because these products have been on the market for longer than 10 years.

Applicability. An important difference in applicability of the medicines is the fact that extreme caution is required when using allopurinol in cases of renal impairment. Unlike allopurinol, no dose adjustment in febuxostat is required in cases of mild to moderate renal impairment. Benzbromarone may not be used in cases of liver impairment, liver diseases and urolithiasis. In general the applicability of febuxostat is greater than that of allopurinol and benzbromarone.

Ease of use. There are few differences between febuxostat, allopurinol and benzbromarone. All products are administered once daily orally. At high doses allopurinol is administered twice daily.

Final conclusion on therapeutic value. In long-term studies, the therapeutic value of febuxostat for treating adult patients with hyperuricaemia, urate deposition and gout complaints is comparable to that of allopurinol (up to 300 mg) in reducing the serum uric acid concentration and reducing gout attacks. Unlike allopurinol, febuxostat can also be used on patients with renal impairment. It is difficult to compare febuxostat and benzbromarone (an alternative for patients who were unsuccessful on allopurinol or who cannot be treated with it), because only limited clinical studies are available. Febuxostat is well-tolerated and severe unintended effects occur only rarely. Benzbromarone is related to the risk of severe hepatotoxicity, urinary tract stones and renal colic and is solely indicated for use on patients with hypersensitivity or a contraindication to allopurinol, or in whom allopurinol leads to insufficient results or unacceptable unintended effects.

In conclusion, febuxostat can be said to have an equal value in comparison to allopurinol in the treatment of adult patients with hyperuricaemia, urate deposition and gouty symptoms. Febuxostat has an added therapeutic value in comparison to benzbromarone for the treatment of chronic hyperuricaemia in patients who cannot (or can no longer) be treated with allopurinol or do not respond to this treatment.

For further information, please contact: warcg@zinl.nl

*The original text of this excerpt from a **WAR-Report** of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's WAR-Report.*
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.