The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**febuxostat (Adenuric®)** is accepted for restricted use within NHS Scotland.

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

**SMC restriction:** when treatment with allopurinol is inadequate, not tolerated or contraindicated.

Febuxostat is superior to allopurinol 300mg daily in reducing serum uric acid to <6mg/dL, (360micromol/L) in patients with hyperuricaemia and gout. (NB The maximum licensed daily dose of allopurinol is 900mg.)

The economic case was demonstrated for second line use of febuxostat in patients who had an inadequate response to allopurinol, or when allopurinol is contraindicated or not tolerated.

Overleaf is the detailed advice on this product.

**Chairman**

Scottish Medicines Consortium
Gout is characterised by the deposition of urate crystals causing acute monoarthritis and crystal deposits (tophi) in the skin. Treatment of chronic gout requires long-term reduction in serum uric acid (sUA) below the saturation level. Xanthine oxidase is a catalyst in the metabolism of purines, converting hypoxanthine to xanthine and xanthine to uric acid. Febuxostat is a 2-arylthiazole derivative that selectively inhibits xanthine oxidase, thereby decreasing uric acid.

The main evidence for the licence is from two pivotal phase III studies with similar patient populations and identical primary outcomes.

A 52-week, double-blind, randomised study investigated 760 adult patients with hyperuricaemia, (sUA ≥8mg/dL, [480micromol/L]), and gout (according to American College of Rheumatology criteria). Ineligibility criteria included an estimated creatinine clearance rate (CCR) <50ml/minute/1.73m² body-surface area (because of the possibility of receiving allopurinol 300mg) and consumption of >14 alcoholic drinks per week. After a 2-week washout period patients were randomised equally to treatment with once daily doses of febuxostat 80mg, febuxostat 120mg or allopurinol 300mg. Prophylaxis against gout flares with naproxen or colchicine was provided for the first eight weeks. Subsequent flares of gout were treated at the investigators’ discretion. Mean baseline sUA was 9.8 to 9.9mg/dL (583 to 589micromol/L). Thirty-five per cent of patients had mild to moderate renal impairment (though estimated CCR ≥50ml/minute/1.73m² body-surface area). The discontinuation rate was significantly higher in the 80mg and 120mg febuxostat groups than in the allopurinol group, 34%, 39% and 26%, respectively.

The primary outcome was sUA <6mg/dL, (360micromol/L) at each of the last three monthly measurements in the intention to treat (ITT) population, (all randomised patients who received ≥1 dose of study drug and had a serum urate level ≥8mg/dL at baseline). This was achieved by 53%, 62% and 21% of patients receiving febuxostat 80mg, febuxostat 120mg and allopurinol 300mg, respectively. The difference was statistically significant for each febuxostat group versus the allopurinol group. At all ranges of initial urate levels tested, the primary endpoint was reached by significantly higher proportions of febuxostat-treated patients than allopurinol-treated patients. By week 2 the proportion of patients with sUA <6 mg/dL, (360micromol/L) was

### Indication

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

### Dosing Information

80mg orally once daily. If serum uric acid is >6mg/dL (357micromol/L) after 2 to 4 weeks, 120mg once daily may be considered

### Product availability date

3 March 2010

### Summary of evidence on comparative efficacy

Gout is characterised by the deposition of urate crystals causing acute monoarthritis and crystal deposits (tophi) in the skin. Treatment of chronic gout requires long-term reduction in serum uric acid (sUA) below the saturation level. Xanthine oxidase is a catalyst in the metabolism of purines, converting hypoxanthine to xanthine and xanthine to uric acid. Febuxostat is a 2-arylthiazole derivative that selectively inhibits xanthine oxidase, thereby decreasing uric acid.

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The primary outcome was sUA <6mg/dL, (360micromol/L) at each of the last three monthly measurements in the intention to treat (ITT) population, (all randomised patients who received ≥1 dose of study drug and had a serum urate level ≥8mg/dL at baseline). This was achieved by 53%, 62% and 21% of patients receiving febuxostat 80mg, febuxostat 120mg and allopurinol 300mg, respectively. The difference was statistically significant for each febuxostat group versus the allopurinol group. At all ranges of initial urate levels tested, the primary endpoint was reached by significantly higher proportions of febuxostat-treated patients than allopurinol-treated patients. By week 2 the proportion of patients with sUA <6 mg/dL, (360micromol/L) was
significantly higher in those receiving febuxostat compared with allopurinol and these differences were sustained at all subsequent visits. The mean percentage reduction from baseline sUA concentration at the final visit was also greater in both febuxostat groups than in the allopurinol group. During weeks 9 through 52, similar proportions of patients in each group required treatment for gout flare: 64%, 70% and 64% in the febuxostat 80mg, febuxostat 120mg and allopurinol groups, respectively. During the initial 8-week prophylaxis period, a significantly greater proportion of patients in the febuxostat 120mg group required treatment for gout flares than in the other two groups. Withdrawal of prophylaxis was initially accompanied by a markedly increased incidence of gout flares in all groups which gradually decreased thereafter. By weeks 49 through 52, the incidence was 8%, 6% and 11% in the febuxostat 80mg, febuxostat 120mg and allopurinol groups, respectively. In the 156 patients with tophi at baseline, there were no significant differences after 52 weeks among treatment groups in the percentage reduction in tophus area or in the reduction in the number of tophi. In a post hoc analysis of sUA <5mg/dL (300micromol/L) at the final visit, the proportions of patients who achieved this lower target were 47%, 66% and 13% in the febuxostat 80mg, febuxostat 120mg and allopurinol groups, respectively.

A 28-week, double-blind, randomised study recruited a very similar patient population to the first study but also included patients with more severe renal impairment. After a 2-week washout period, 1,072 patients were randomised, stratified by renal function, in a 2:2:1:2:1 ratio to once-daily febuxostat 80mg, febuxostat 120mg, febuxostat 240mg (unlicensed dose), allopurinol 300mg (100mg in renal impairment), or placebo. Mean baseline sUA was 9.8mg/dL and 4% had impaired renal function (serum creatinine level >1.5 to ≤2.0 mg/dL). Premature withdrawal rates were significantly higher in the febuxostat 80mg and 240mg groups (35% and 36%, respectively) than in the febuxostat 120mg (26%) or allopurinol (21%) groups.

The primary outcome of sUA <6mg/dL, (360micromol/L) at each of the last three monthly measurements in the ITT population was achieved in a significantly greater proportion of patients receiving febuxostat at any dose than patients receiving allopurinol or placebo. Responses were 48%, 65%, 69%, 22% and 0% in patients receiving febuxostat 80mg, febuxostat 120mg, febuxostat 240mg, allopurinol and placebo, respectively. Among patients with baseline sUA level ≥10.0mg/dL, 36%, 52%, and 66% achieved the primary endpoint while receiving febuxostat 80mg, 120mg, and 240mg, respectively. In contrast, few (10%) of these patients achieved last three sUA levels <6mg/dL while receiving allopurinol. The proportions of patients with impaired renal function (serum creatinine >1.5 to ≤2.0mg/dL) attaining last three monthly sUA levels <6mg/dL were 44%, 46%, 60%, 0% and 0% in patients receiving febuxostat 80mg, febuxostat 120mg, febuxostat 240mg, allopurinol 100mg and placebo, respectively.

At the week 28 visit the proportions of patients who achieved sUA <6mg/dL were 76%, 87%, 94%, 41% and 1% for those receiving febuxostat 80mg, febuxostat 120mg, febuxostat 240mg, allopurinol and placebo, respectively. At this visit, all febuxostat doses produced significantly greater decreases in sUA levels from baseline (-48% for 80mg, -55% for 120mg, and -68% for 240mg) compared with allopurinol (-34%) and placebo (-4%). Between weeks 8 and 28, there were no significant differences between treatment groups in the proportions of patients requiring treatment for gout flares. During the first eight weeks of the study, when gout flare prophylaxis was provided, significantly higher proportions of patients receiving febuxostat 120mg (97/269 [36%]) and 240mg (69/134 [46%]) required treatment for gout flares compared with those receiving febuxostat 80mg (73/262 [28%]), allopurinol (61/268 [23%]), or placebo (27/134 [20%]). There were no significant differences between treatment groups in reductions in median tophus size from baseline or in the number of tophi except for the comparison of febuxostat 120mg (-1.2) versus placebo (-0.3) at week 28.
A 6-month phase III, double-blind, randomised controlled study compared febuxostat 40mg (unlicensed dose), febuxostat 80mg and allopurinol 300mg (200mg in moderate renal impairment) in 2,269 patients with gout and sUA ≥8mg/dL. The primary endpoint, (proportion of patients in each treatment group with sUA <6mg/dL at the final visit), was achieved in 45%, 67%, and 42%, patients receiving febuxostat 40mg, febuxostat 80mg, and allopurinol, respectively. Febuxostat 40mg was non-inferior to allopurinol, but febuxostat 80mg was superior to both. Achievement of target sUA in patients with renal impairment was also superior with febuxostat 80mg (72%) compared with febuxostat 40mg (50%) or allopurinol (42%).

Summary of evidence on comparative safety

Long term safety data are limited. In the pivotal studies over 1,000 patients received a recommended dose of febuxostat. The incidence of adverse events (AEs) was similar among treatment groups and most AEs were mild to moderate in severity. In both studies the incidence of serious AEs was also similar among treatment groups. The most commonly reported treatment-related AEs, according to investigator assessment, were liver function abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%) and rash (1.5 %). In the open label extension studies these AEs and in addition, hypertension, were all commonly reported.

A greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared with the allopurinol group in the pivotal (1.3 versus 0.3 events per 100 patient years) and long-term extension studies (1.4 versus 0.7 events per 100 patient years), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure. Consequently, treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. The marketing authorisation holder has committed to perform a post-marketing comparative cardiovascular safety study of febuxostat and allopurinol.

Summary of clinical effectiveness issues

Febuxostat is superior to allopurinol 300mg daily in reducing sUA <6mg/dL, (360micromol/L) in patients with hyperuricaemia and gout. Its efficacy compared with higher doses of allopurinol is unknown. Although the use of allopurinol in a 300mg daily dose seems to reflect clinical practice this is substantially below the maximum licensed dose (900mg daily) and clinical experts have advised that there is evidence of sub-optimal dosing with allopurinol in practice.

The pivotal studies do not demonstrate evidence of improved clinical outcome with febuxostat. Allopurinol and febuxostat were equally effective at preventing recurrence of gout at 9 to 52 weeks, but higher-dose febuxostat increased the number of initial treatment-related gout flares in the first 8 weeks of treatment in people also taking naproxen or colchicine. However this result is difficult to interpret due to the inadequate duration of flare prophylaxis in the studies, eight weeks compared with the licence recommendation of at least six months. Also the pivotal studies may have been too short to detect a difference in clinical outcomes between treatments. Febuxostat produced higher rates of premature withdrawal than allopurinol. Possible contributory factors include the short duration of flare prophylaxis and the initiation of the 120mg
A dose of febuxostat without titration. The Summary of Product Characteristics for febuxostat recommends starting treatment with 80mg daily and only increasing to 120mg daily if the target <6mg/dL (357micromol/L) is not reached after two to four weeks.

Two open label long term extension studies demonstrated that febuxostat produced sustained reduction of sUA <6mg/dL that was associated with progressive and almost complete elimination of gout flares. However, there was a high discontinuation rate in both studies.

The sUA target in the clinical studies was <6mg/dL (360micromol/L), however the British Society of Rheumatology has recently recommended a target of <5mg/dL, (300micromol/L). A post hoc analysis of sUA levels at the final visit found that febuxostat was superior to allopurinol in achieving this more stringent target.

Liver function abnormalities were the most commonly reported treatment-related AEs (3.5%) in the pivotal studies despite patients with higher alcohol consumption (≥14 alcoholic beverages per week) being excluded. Liver function testing is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement.

Febuxostat is not recommended for use in patients with ischaemic heart disease or congestive heart failure; these are common co-morbidities in patients with gout and may limit its use.

Allopurinol is the only urate-lowering treatment commonly used in the UK; the European Medicines Agency (EMA) stated that it may be difficult to use or may not be an option in patients with renal impairment or those who have experienced previous rashes or hypersensitivity reactions. However, they noted that experience of treatment with febuxostat is also limited in these subgroups. Febuxostat is not recommended in patients with creatinine clearance <30mL/min. Unlike allopurinol, no dose adjustment is necessary for warfarin when administered with febuxostat.

### Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing the cost-effectiveness of various treatment sequences for patients with chronic gout, including febuxostat 80mg and 120mg per day doses as first or second line, and with sequences including allopurinol 300mg per day. All sequences ended with ‘no treatment’. The comparator was appropriate given that it reflects standard clinical practice in Scotland, although it is below the maximum licensed dose of allopurinol of up to 900mg/day. The model incorporated health states based on sUA control levels. Treatment response was defined as achieving a sUA level ≤6mg/dL (one of the 4 health states, the other states being 6-8mg/dL, 8-10mg/dL, and >10mg/dL). Model cycle length was 3 months. Patients who failed to respond within the first 3 month cycle to the first treatment tried were switched to the next treatment in the sequence, and finally to ‘no treatment’ at the end of each sequence. The model incorporated drop-outs as a reason to switch treatments, and estimated the incidence of gout flares. A 5 year time horizon was adopted in the base case.

The primary clinical data used for sUA outcomes and drop-outs in the first cycle were pooled 28 and 52 week phase III clinical trial data comparing febuxostat 80/120mg and allopurinol 300mg. Other febuxostat clinical data were used for sub-group analysis which covered a patient population who were intolerant or who had an inadequate response to allopurinol and were switched to febuxostat, and a mild/moderate renal impairment sub-group. Estimates of higher
long-term gout flare probabilities associated with higher sUA for the period from after the first
cycle to the end of the time horizon were based on an unpublished 24 month observational
study conducted in over 400 European patients. The observational study also collected EQ-5D
data which were used to estimate a disutility of -0.034 between each sUA health state without
flares (from a base mean utility of 0.75 for the ≤6mg/dL state), and a disutility of 0.0097 for each
acute gout flare. Drop-outs over a further 3 year time period were based on data from a phase
III extension trial for febuxostat. Cost estimates for acute gout flares (of £295 per flare) and
non-drug clinical management of gout were included in the model using resource use data
collected within the observational study.

Each treatment sequence considered was assessed for cost-effectiveness, with the outcome
that the sequence with 80/120mg/day febuxostat second line to allopurinol 300mg was the most
cost-effective sequence with an incremental cost per quality adjusted life year (QALY) of £3,578
compared to first line allopurinol alone (an additional £530 and 0.15 QALYs per patient). This
was related to the superior sUA control for febuxostat and associated lower long run flare
probability and drop-out rate. This sequence also ‘dominated’ first line use of febuxostat
followed by allopurinol. A limitation for the second line febuxostat assessment was that this was
not from a direct patient population who had received allopurinol first line. The sub-group
analysis performed for the patient population who had an inadequate response to allopurinol
demonstrated a higher cost per QALY of £5,529.

An incremental cost/QALY of £4,957 (an additional £900 and 0.18 QALYs per patient) was
estimated for a sequence of first line febuxostat versus no treatment (i.e. representing a proxy
for patients who are contraindicated to allopurinol). However, a potential weakness was that
there were no direct data in patients who are contraindicated to allopurinol.

A weakness in the model relates to the time horizon. The appropriate time horizon for the
analysis is lifetime, so the choice of a 5 year timeline was pragmatic to limit extrapolation of
outcomes beyond the clinical trial evidence, and reflects a moderately high treatment drop-out
rate. This is important as the model assumes sUA level remains constant at the end of the
treatment sequence, which may not be realistic for longer term time horizons. Therefore, long-
term cost-effectiveness is uncertain.

There are other weaknesses in the economic model including a lack of data to estimate the
impact of potential dose titration above 300mg/day for allopurinol, uncertainty over the impact
of prophylaxis on short term flare rates, and uncertainty over the quality of life impact (and
disutility) associated with sUA level. However, sensitivity analysis indicated that the results
were most sensitive to the disutility associated with sUA. When it was reduced to only 25% of
the base case value, the cost per QALY of second line febuxostat compared to allopurinol alone
was above £14,000. This was close to £25,000 per QALY gained in the sub-group who had an
inadequate response to allopurinol. Sensitivity analysis indicated the cost per QALY was less
sensitive to all other parameters investigated, and also did not vary much for the renal
impairment sub-group.

Overall, despite some uncertainties the economic case was demonstrated for the second line
use of febuxostat when patient response to allopurinol is inadequate or where allopurinol is
contraindicated or not tolerated.
Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In 2007 the British Society for Rheumatology and British Health Professionals in Rheumatology published a Guideline for the Management of Gout. It states that initial long-term treatment of recurrent uncomplicated gout normally should be with allopurinol starting in a dose of 50 to 100mg/day and increasing by 50 to 100mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (sUA <300micromol/L) is reached (maximum dose 900mg).

In May 2006, the European League against Rheumatism (EULAR) published evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. It states that the therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation; this is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (360micromol/L). Allopurinol is an appropriate long term urate lowering drug; it should be started at a low dose (eg, 100mg daily) and increased by 100mg every 2 to 4 weeks if required; the dose must be adjusted in patients with renal impairment.

Additional information: comparators

Allopurinol is the main comparator. The only other medicine licensed for this indication, sulfinpyrazone, is seldom used in Scotland.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost Per Year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febuxostat</td>
<td>80 to 120mg orally daily</td>
<td>317</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>200 to 600mg orally daily</td>
<td>94 to 282</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>100 to 900mg orally daily</td>
<td>15 to 51</td>
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</tbody>
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Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27.05.10.
The medicines budget impact for febuxostat was estimated by the manufacturer for two patient populations: those who are intolerant or contraindicated to allopurinol, and as second line use in patients who had an inadequate response to allopurinol 300mg first line. For patients with an inadequate response to allopurinol 300mg, the budget impact was estimated at £504k in year 1 (1,407 patients), rising to £4.5m by year 5 (14,280 patients). In patients intolerant or contraindicated to allopurinol the estimated budget impact was £57k in year 1 based on 10% uptake (180 patients), rising to £581k by year 5 based on 100% uptake (1,831 patients).
References

The undernoted references were supplied with the submission.


Becker MA, Schumacher HR, MacDonald PA et al Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol 2009; 36: 1273–82


This assessment is based on data submitted by the applicant company up to and including 16 July 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.