febuxostat 120mg film-coated tablet (Adenuric®)  SMC No. (1153/16)
A. Menarini Farmaceutica Internazionale SRL

06 May 2016

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 Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**Febuxostat film-coated tablet (Adenuric®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumour Lysis Syndrome (TLS).

**SMC restriction:** prevention of hyperuricaemia in adult patients at intermediate risk of TLS in whom allopurinol is either unsuitable or contraindicated, such as:
- Those intolerant of allopurinol
- Those in whom allopurinol is contraindicated, e.g. patients with renal impairment

In a phase III, randomised, double-blind study in adults with haematologic malignancies at intermediate to high risk of TLS, febuxostat was significantly superior to a xanthine oxidase inhibitor at reducing serum uric acid levels.

Overleaf is the detailed advice on this product.

**Chairman,**
Scottish Medicines Consortium
**Indication**
The prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumour Lysis Syndrome (TLS).

**Dosing Information**
One tablet (120mg) taken orally once daily, with or without food. Febuxostat should be started two days before the beginning of cytotoxic therapy and continued for a minimum of seven days; however, treatment may be prolonged up to nine days according to chemotherapy duration as per clinical judgment.

**Product availability date**
08 April 2015

**Summary of evidence on comparative efficacy**

Tumour lysis syndrome (TLS) results from the rapid breakdown of large numbers of tumour cells and is characterised by hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. Malignancies can be stratified as low risk (<1%), intermediate risk (1% to 5%) or high risk (>5%) for the development of TLS. Serum uric acid (sUA) plays a key role in the development of the condition, and current strategies for the management of hyperuricaemia associated with TLS involve clinical monitoring and adequate hydration (at all risk levels) and pharmacological measures to reduce sUA (allopurinol prophylaxis for intermediate risk TLS; rasburicase prophylaxis for high risk TLS or for treating established TLS).²³ Febuxostat is a potent, non-purine, selective inhibitor of xanthine oxidase (an enzyme which catalyses the metabolism of xanthine to uric acid), and thereby exerts its therapeutic effect by decreasing sUA.²³

The submitting company has requested that SMC considers febuxostat when positioned for the prevention of hyperuricaemia in adult patients at intermediate risk of TLS in whom allopurinol is either unsuitable or contraindicated, such as:
- Those intolerant of allopurinol
- Those in whom allopurinol is contraindicated, e.g. patients with renal impairment

Clinical evidence derives from one phase III, randomised, multicentre, double-blind study (FLORENCE) of febuxostat versus allopurinol for the prevention of TLS in adults with haematologic malignancies at intermediate to high risk of TLS.²⁴ The study recruited adults with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3, a life expectancy of at least one month and an sUA level <10mg/dL (<600micromol/L) at randomisation. Patients were scheduled to receive their first cytotoxic chemotherapy cycle (regardless of the line of treatment) because of haematologic malignancies at intermediate to high risk of TLS (as per TLS panel consensus)⁵, and were candidates for allopurinol or had no access to rasburicase. Most patients recruited to the study had an intermediate risk of TLS (82%).

Patients were randomised equally to treatment with febuxostat 120mg daily (n=173) or allopurinol (n=173) 200mg, 300mg or 600mg daily (dose chosen by the investigator) for seven
to nine days according to the duration of chemotherapy. The majority of patients allocated to treatment with allopurinol received a dose of 300mg/day (83%). Treatment was initiated two days prior to induction chemotherapy and patients received adequate or increased hydration of up to 3 litres/m²/day as per TLS prophylaxis recommendations. Randomisation was stratified by TLS risk and baseline sUA level.

The co-primary efficacy outcome was the area under the concentration-time curve of sUA over days one to eight (AUC sUA₁–₈) and change in serum creatinine level from baseline to day eight. sUA is considered a clinically well-established surrogate endpoint for TLS and renal impairment. The mean (±standard deviation [SD]) AUC sUA₁–₈ was significantly lower for febuxostat (514 ±226mg × hour/dL) compared with allopurinol (708 ±234mg × hour/dL), p<0.0001. The mean sUA level was significantly lower for febuxostat from day two of treatment and evident at each time point throughout the treatment period to day eight, with a mean difference of at least 1mg/dL (60micromol/L) between treatments at each time point. The mean (±SD) percentage change in serum creatinine from baseline to day eight was −0.8% ±27% for febuxostat and −4.9% ±17% for allopurinol, with no significant difference between treatments at day eight (p=0.0903) or at any time point throughout the study. This was as a result of renal function remaining, on average, stable over time in both treatment groups. Superiority of febuxostat over allopurinol was therefore not demonstrated for this outcome and hence the co-primary endpoint was not formally met.

Similar results were obtained from an exploratory analysis in a subgroup of patients at intermediate risk of TLS. The mean (±SD) AUC sUA₁–₈ was significantly lower for febuxostat (506 ±225mg × hour/dL) compared with allopurinol (710 ±223mg × hour/dL), p<0.0001, and the mean (±SD) percentage change in serum creatinine from baseline to day eight was −0.5% ±24% for febuxostat and −3.4% ±17% for allopurinol, with no significant difference between treatments (p=0.2136).

Treatment response (maintenance of sUA ≤7.5mg/dL [<450micromol/L]) and the incidence of laboratory TLS (presence of at least two laboratory abnormalities, including a 25% increase or levels above normal for serum uric acid, potassium or phosphate, or a 25% decrease or levels below normal for calcium) and clinical TLS (presence of laboratory TLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias, sudden death, seizures) were assessed as secondary outcomes from day three (start of chemotherapy) to day eight. Although there were no significant differences between the treatment groups for any of these secondary outcome analyses, there was a high response rate (98% [170/173] for febuxostat and 96% [166/173] for allopurinol), and a low incidence of laboratory TLS (8.1% [14/173] for febuxostat and 9.2% [16/173] for allopurinol) and clinical TLS (1.7% [3/173] for febuxostat and 1.2% [2/173] for allopurinol) in both treatment groups.

<table>
<thead>
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<th>Summary of evidence on comparative safety</th>
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In the FLORENCE study, drug-related treatment-emergent signs and symptoms (TESS) were reported in 6.4% (11/173) of patients in both treatment groups, in which zero patients in the febuxostat group and 1.2% (2/173) of patients in the allopurinol group experienced severe drug-related TESS. No serious drug-related TESS were reported. Pneumonia (in 2.0% [7/346] of patients) and febrile neutropenia (in 1.2% [4/346] of patients) were the most common serious TESS in the study, regardless of causality. One patient in the febuxostat group discontinued treatment as a result of TESS which was considered unrelated to study drug.²,₄
Anaemia (22% [39/173]), neutropenia (18% [31/173]), leukopenia (16% [27/173]) and thrombocytopenia (14% [25/173]) were the most common TESS in the febuxostat group. A higher incidence of the following TESS were reported in the febuxostat group versus the allopurinol group:

- Anaemia (22% vs. 14%)
- Mucosal inflammation (6.4% vs. 1.7%)
- Pyrexia (14% vs. 10%)
- Headache (8.7% vs. 2.9%)

A higher incidence of neutropenia was reported in the allopurinol group (24%) versus the febuxostat group (18%).

The European Public Assessment Report (EPAR) noted that, given previous experience of febuxostat in the treatment of gout, FLORENCE did not highlight any additional safety concerns, with the exception of left bundle branch block, sinus tachycardia and haemorrhage. These adverse events are reflected in the Summary of Product Characteristics (SPC). The SPC also advises that treatment with febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure.

Six deaths occurred in the febuxostat group, one of which was due to myocardial ischaemia and acute cardiac failure. Following detailed analysis of each death, a relation to the study treatment could not be detected; however, a post-marketing comparative cardiovascular safety study is currently ongoing to clarify the cardiovascular risk profile of febuxostat versus allopurinol (FAST). Cardiac monitoring (as clinically appropriate) is advised as a precautionary measure during therapy with febuxostat.

**Summary of clinical effectiveness issues**

TLS is most often observed after initial treatment with chemotherapy for haematological malignancies as the normal homeostatic processes for handling the release of cellular contents from cell breakdown become overwhelmed. It is a critical complication with potentially severe consequences, including cardiac arrhythmias, seizures, acute kidney injury and death.

The submitting company has requested that SMC considers febuxostat when positioned for the prevention of hyperuricaemia in adult patients at intermediate risk of TLS in whom allopurinol is either unsuitable or contraindicated, such as:

- Those intolerant of allopurinol
- Those in whom allopurinol is contraindicated, e.g. patients with renal impairment

The British Committee for Standards in Haematology (BCSH) guidelines advise that it is generally safe to use only prophylactic hydration (and careful monitoring) in patients who are allergic to allopurinol. Although the marketing authorisation for allopurinol does not contraindicate its use in renal impairment, the BCSH guidelines also note that any patient with a haematological diagnosis who has renal impairment, or who is allergic to allopurinol, should be considered for rasburicase despite their risk assignment based on tumour features; however, those with low risk disease can often be managed using hydration alone. Rasburicase has an immediate treatment effect, reducing uric acid plasma levels within four hours of intravenous administration, enabling initiation of chemotherapy sooner than might be safe for allopurinol.

The co-primary endpoint in the FLORENCE study was not formally met and the EPAR notes this was due to the study objectives not being optimally translated into statistically testable endpoints and hypotheses. Despite this, the superiority of febuxostat at controlling sUA levels was considered sufficient from a clinical perspective, and renal function was preserved. Exploratory analyses conducted in subpopulations of patients with different baseline
characteristics confirmed that the efficacy of febuxostat was maintained regardless of baseline hyperuricaemia (sUA level >7.5mg/dL [>450micromol/L]), creatinine level, type of haematological malignancy, ECOG performance status and grade of TLS risk.\textsuperscript{2}

For every mg/dL increase in sUA, the risk of developing TLS increases by a factor of 1.75 and the risk of renal events increases by a factor of 2.21.\textsuperscript{2} FLORENCE demonstrated that from day two onwards the mean sUA level was significantly lower with febuxostat, compared with allopurinol, and the EPAR considered this to be of clinical relevance for those patients in whom chemotherapy administration cannot be delayed. The EPAR concluded that febuxostat, compared with allopurinol, was expected to provide better control of sUA levels and subsequently reduce the risk of TLS-consequences in patients undergoing chemotherapy at intermediate and high risk of TLS.\textsuperscript{2} In a subgroup analysis of patients at intermediate risk of TLS, febuxostat was also significantly superior to allopurinol at controlling sUA. A high rate of treatment response and a low incidence of laboratory and clinical TLS were reported in both treatment groups; however, the differences between the groups were not significant for these secondary outcomes.

Only patients with certain types of haematological malignancies (chronic lymphocytic leukaemia, acute leukaemia and lymphoma) were included in the study and, therefore, it is unknown if the medicines used for the treatment of other malignancies would affect the efficacy of febuxostat.\textsuperscript{2} No drug interaction studies of febuxostat with cytotoxic chemotherapy have been conducted, and although febuxostat was administered to patients undergoing several chemotherapy regimens in the FLORENCE study, drug-drug and drug-disease interactions were not investigated.\textsuperscript{3}

The study provided evidence of the clinical efficacy of febuxostat versus allopurinol for the prevention of hyperuricaemia in adults with haematological malignancies at intermediate (and high) risk of TLS. No clinical data were presented to compare febuxostat with hydration alone or with rasburicase.

**Summary of comparative health economic evidence**

The company submitted a cost-minimisation analysis comparing febuxostat with rasburicase for the prevention of hyperuricaemia in patients at intermediate risk of TLS in whom allopurinol is either unsuitable or contraindicated. The comparator was justified by the company in consultation with Scottish clinical experts and with reference to local cancer network guidelines on the prevention and treatment of TLS.

A one year time horizon was used and the results were presented in the form of cost per chemotherapy cycle and cost per year. Patients were assumed to receive initial treatment with either febuxostat or rasburicase, with non-responders in both arms receiving intensification of rasburicase treatment and subsequently responding to treatment.

For the febuxostat arm, the clinical data were taken from the FLORENCE study. The response rate included in the economic analysis was 98% (95% CI: 96% to 100%) and the discontinuation rate was 0.6%. For the rasburicase arm, the response rate included was 99.5% and the discontinuation rate was 0.6%, based on assumption only. No comparative clinical data or formal indirect comparison comparing febuxostat with rasburicase was provided. A key
assumption in the analysis is that the lower response rate with febuxostat does not impact on patient outcomes.

The analysis included the drug acquisition and administration costs of febuxostat and rasburicase. No other resource use was included. The medicine costs of initial treatment were based on 120mg of febuxostat once daily for 9 days and 0.2mg/kg of rasburicase. Based on an average weight of 75.8kg, the company estimated that 2 x 7.5mg of rasburicase would be required and it was assumed that patients would be treated for one day. Non-responders in both arms were assumed to receive intensification of daily rasburicase at 0.2mg/kg for 6 days. Administration costs were included in the rasburicase arm where it was assumed that 1 hour of nurse time would be required to administer treatment.

In the base case analysis, the company estimated a cost per cycle for febuxostat of £105 versus £803 for rasburicase, resulting in a saving of £698 per patient per cycle. The cost per year for febuxostat ranged between £290 (based on 2.76 cycles of chemotherapy treatment) and £385 (based on 3.66 cycles). For rasburicase the cost per year was £2,214 up to £2,941, resulting in estimated annual savings with febuxostat of between £1,924 and £2,556. However, TLS usually only occurs in the first cycle of chemotherapy, so prophylaxis may not be appropriate in subsequent cycles.

Limited sensitivity analysis was provided where the dose of rasburicase was varied in two scenario analyses. Note that the efficacy of rasburicase was also reduced marginally in these analyses from 99.5% response rate to 99.1%. Assuming patients received a single dose of 7.5mg per cycle reduced the cost of rasburicase to £456, reducing overall savings with febuxostat to £353. Assuming patients receive a single dose of 3mg reduced the cost of rasburicase to £336, reducing overall savings with febuxostat to £231.

The following limitations were noted:

- No clinical evidence was provided to show comparable efficacy between febuxostat and rasburicase, which is necessary for a cost-minimisation analysis. The submitting company states that febuxostat is less effective than rasburicase and as such the analysis includes a lower response rate with febuxostat. In addition, there are no clinical data on the efficacy of febuxostat in patients who are unsuitable for allopurinol and the response rate of rasburicase used in the model is based on assumption only.

- If febuxostat is less effective than rasburicase then a cost-minimisation analysis may not be the appropriate form of analysis. The company noted that the lower response rate associated with febuxostat was not considered to have an impact on patient outcomes and as a result there is an implicit assumption in the analysis that no patient will develop TLS. The company was asked to provide further justification for the approach used and to explore the potential impact on patient outcomes but chose not to provide any further analysis. It may be that due to the potential savings relative to rasburicase it is unlikely that the QALY loss would be significant enough to result in febuxostat not being cost-effective.

- The cost of rasburicase used in the analysis is based on the licensed dose given for one day. However, in practice the off-label dose of rasburicase is likely to be used. As noted above, using a single dose of 3mg reduced the cost of rasburicase to £336 and reduced overall savings with febuxostat to £231 per cycle. Assuming no wastage and based on
Despite the limitations outlined above, the economic case has been demonstrated.

**Summary of patient and public involvement**

A Patient Group submission was not made.

**Additional information: guidelines and protocols**

In 2015, the British Committee for Standards in Haematology produced guidelines for the management of TLS in haematological malignancies. Prophylaxis with rasburicase and increased hydration is recommended in patients at high or very high risk of TLS. Patients at intermediate risk should be offered up to seven days of prophylactic allopurinol (200 to 400mg/m²/day) in addition to increased hydration. Allopurinol may also be considered in some low risk patients based on fluid monitoring and laboratory results. In patients who are allergic to allopurinol or have renal impairment, and who are not high risk, rasburicase may be considered (0.2mg/kg for five to seven days [licensed dose], or a single fixed dose of 3mg [off-label dose]), although prophylactic hydration in conjunction with careful monitoring is acknowledged to be generally safe. The use of sodium bicarbonate to alkalise the urine is not recommended. The guideline further notes that any course of TLS prophylaxis is unlikely to be useful in a cancer consolidation therapy scenario.

An international expert consensus TLS guideline document was published in 2010. The consensus panel developed an evidence-driven TLS risk stratification tool and presented corresponding recommendations for prophylaxis:

- Low risk patients should normally be monitored and receive no increased hydration or hyperuricaemia prophylaxis. Allopurinol should be added if there are metabolic changes or advanced, bulky or highly proliferative disease
- Intermediate risk patients should be monitored, receive increased hydration and allopurinol at 100 to 300mg daily.
- High risk patients should be monitored, receive increased hydration (unless renal insufficiency and oliguria are present) and single dose rasburicase at 0.1 to 0.2mg/kg, repeated only if clinically necessary. Rasburicase should be replaced with allopurinol in patients with a prior history of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

These recommendations were adapted from a previous evidence-led consensus guideline produced in 2008. The publication emphasises the use of aggressive hydration and diuresis in TLS prevention. Allopurinol 100 to 400mg/m² daily is recommended as a prophylactic option in patients at intermediate risk although reduced clearance of high dose methotrexate and hypersensitivity reactions have been associated with its use. Allopurinol is noted as being contraindicated in combination with cyclophosphamide and other cytotoxic agents due to increased bone marrow suppression. Rasburicase at a dose of 0.1 to 0.2mg/kg daily for up to seven days is recommended for patients at high risk of TLS, who have pre-existing hyperuricaemia (≥450 micromole/litre) or who develop hyperuricaemia despite prophylactic
treatment with allopurinol. Rasburicase is contraindicated in patients with known G6DP deficiency.

These guidelines predate the availability of febuxostat for the indication under review.

### Additional information: comparators

Hydration ± rasburicase.

### Cost of relevant comparators

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<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
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<tbody>
<tr>
<td>Febuxostat</td>
<td>120mg orally once daily for seven to nine days</td>
<td>6 to 8</td>
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<tr>
<td>Rasburicase</td>
<td>By intravenous infusion, 0.2mg/kg/day for five to seven days † or single fixed dose of 3mg (off-label) ‡</td>
<td>2,894 to 4,052</td>
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<td>139</td>
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### Additional information: budget impact

The submitting company estimated there would be 127 patients eligible for treatment with febuxostat in year 1 and 152 patients in year 5. The estimated uptake rate was 100% in all years and a discontinuation rate of 0.60% was applied each year, resulting in 126 patients estimated to be treated in year 1 and 151 patients in year 5.

The gross impact on the medicines budget was estimated to be £3k in all years. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £53k in year 1 and a saving of £64k in year 5. The net budget impact assumes displacement of the 3mg off-label single dose of rasburicase.
References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 18 April 2016.

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.