APPEAL BY IPSEN LTD AGAINST THE FAD BY NICE ON THE USE OF FEBUXOSTAT FOR THE MANAGEMENT OF HYPERURICAEMIA IN PATIENTS WITH GOUT

EXECUTIVE SUMMARY

Ipsen wishes to appeal the Final Appraisal Determination (FAD) regarding the use of febuxostat for the management of hyperuricaemia in patients with gout. The appeal is brought under Ground 1 (Procedural Unfairness) and Ground 2 (Perversity), permitted under the National Institute for Health and Clinical Excellence (NICE) appeal procedures.

The points of appeal under Ground 1 (Procedural Unfairness) concern:

1. The Institute has acted unfairly by failing to act in accordance with the provisions of its appraisal procedures concerning selection of comparators.

2. The Institute has acted unfairly given that there is no clinical evidence to support NICE in its decision to reject 300 mg fixed-dose allopurinol (the acknowledged standard of care) in favour of titrated dosing.

3. The Institute has acted unfairly by effectively redefining the scope of the appraisal by focusing the review on gout flares rather than "management of hyperuricaemia" as outlined in the scope.

4. We believe the decision to exclude febuxostat from certain patient subgroups that cannot be prescribed allopurinol is unethical, given the lack of alternative treatment options in the United Kingdom (UK). The Social Value Judgements Guide, "non-maleficence involves an obligation not to inflict harm (either physical or psychological) and is associated with the maxim 'first, do no harm,'" needs to be fully taken into account when deciding to withhold an existing effective treatment to avoid and reverse disabling gout symptoms in patient without any safe treatment alternatives to allopurinol in clinical practice.

The points of appeal under Ground 2 (Perversity) concern:

5. The decision by the NICE Appraisal Committee to disregard the wider health-related quality of life (HRQoL) impacts of gout, through symptoms that are strongly associated with raised sUA levels, is a perverse one in light of the evidence submitted.

6. The decision by the NICE Appraisal Committee and the Evidence Review Group (ERG) not to fully accept the sUA level as an appropriate clinical endpoint for the pivotal trials of febuxostat is a perverse one in light of the submitted evidence and current recognized clinical guidelines and recommendations developed by the British Society of Rheumatology (BSR)[1] and the European League Against Rheumatism (EULAR).[2]

7. The NICE Appraisal Committee and the ERG have ignored the clear evidence of clinical effect in specific patient subgroups where allopurinol does not provide an adequate control of sUA, or where allopurinol is not an appropriate therapy. This decision denies these subgroups an effective and safe treatment to patients with progressive severe gout and high unmet need, in the clear absence of other approved treatments. This is perverse given the evidence of clinical effect of febuxostat in these patient groups.

Requested Actions

Ipsen requests that the Appeal Panel refer this appraisal back to the Appraisal Committee for further consideration with the following directions:

a. Reconsider the choice of comparator to reflect the current standard of care within the National Health Service (NHS) (i.e., fixed-dose allopurinol 300 mg/day) as required by NICE single technology assessment (STA) process and the appraisal objectives outlined in the scope.

[1] Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology 2007;1of 3.

[2] Zhang W, Doherty M, Bardin T, Pascual E, Baskova V, Conaghan P, et al. EULAR evidence-based recommendations for gout. Part II Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312-24.

b. Reconsider the level of impact on QALY of sUA as surrogate marker for long-term effects to ensure the appraisal focuses on management of hyperuricaemia (as outlined in the scope) and not just gout flares.

c. Reconsider the public health consequences of the decision to withhold an existing effective and safe treatment from a patient population with a progressive disabling disease.

d. Reconsider the Guidance by revising paragraph 1.1 and removing current paragraph 1.2 (definition of intolerance). Paragraph 1.3 then becomes 1.2 as follows:

    1.1 Febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout for people who are intolerant of allopurinol, for whom allopurinol is contraindicated, or for whom allopurinol is not effective in providing adequate control (sUA level reduced to below the level recommended by the British Society of Rheumatology).

    1.2 People currently receiving febuxostat and who do not meet the criteria in 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Original draft FAD text is repeated below:

Guidance

1.1
Febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol (as defined in section 1.2) or for whom allopurinol is contraindicated.

1.2
For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation.

1.3
People currently receiving febuxostat should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

1. INTRODUCTION

Ipsen UK provides formal notification to appeal the FAD following consideration of the NICE Appraisal Committee's draft determination with respect to febuxostat for management of hyperuricaemia in patients with gout. Ipsen requests an oral hearing before NICE's Appeal Panel for the determination of this appeal.

The appeal is brought under the following grounds:

- Ground 1 (Procedural Unfairness): The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.
- Ground 2 (Perversity): The Institute has prepared guidance that is perverse in the light of the evidence submitted.

The points of appeal raised under each of these grounds are set out in Section 2 of this Notice of Appeal.

2. GROUNDS FOR APPEAL

Ipsen's appeal is brought on grounds of procedural unfairness and perversity. The points of appeal under these grounds are set out below.

Appeal Point 1. (Procedural Unfairness):

The Institute has acted unfairly by failing to act in accordance with the provisions of its appraisal procedures[3] concerning selection of comparators.

The NICE STA guidelines stipulate that the STA should compare the new technology to the "current standard treatment in the NHS in England and Wales". Both the ERG and the Committee acknowledged that fixed-dose allopurinol 300 mg per day is the current standard treatment in the NHS and "that dose titration of allopurinol is rarely carried out in routine practice".[4] This conclusion is supported by two large observational studies that have shown that 300 mg or less of allopurinol is used in the large majority of gout patients (89%) in the

[3] NHS. National Institute for Health and Clinical Excellence Guide to the Single Technology Assessment (STA) Process. September 2006. Available at http://www.nice.org.uk/nicemedia/pdf/STA_Process_Guide.pdf#null

[4] FAD paragraph 3.8

UK.[5, 6] Most cases of gout treated with allopurinol (98%) use doses of 300 mg or less per day.[5] Yet the FAD guidance (and the underlying rationale) is premised on a titrated dosing of allopurinol up to 900 mg per day, dosing that is clearly not reflective of current clinical practice.

Furthermore, the scope makes no reference to the titrated dosing of allopurinol (up to 900 mg per day). It is therefore unfair for NICE to rely on such a comparison. Nor is it reasonable to expect Ipsen to anticipate in its submissions that NICE would focus its comparative analysis on a treatment other than the "current standard treatment in England and Wales" (i.e., fixed-dose allopurinol 300 mg per day).

Accordingly, allopurinol 300 mg, nontitrated, should be identified as the most appropriate comparator for the appraisal of febuxostat.

Appeal Point 2. (Procedural Unfairness):

The Institute has acted unfairly given that there is no clinical evidence to support NICE in its decision to reject fixed-dose 300 mg (the acknowledged standard of care) in favour of titrated dosing.

More specifically, there is no randomized trial evidence available in the published domain that demonstrates any differences in sUA or gout symptom-based treatment effects for titrated or nontitrated allopurinol prescribing. A systematic literature review conducted for Ipsen as part of the review process found no randomized controlled clinical trials of allopurinol evaluating efficacy or safety in doses above 300 mg. The allopurinol SPC (approved 1964) states that no modern evaluation of the safety of allopurinol has been conducted. The lack of evidence regarding titrated doses of allopurinol has been acknowledged by both the BSR guidelines and the EULAR guidelines (i.e., "formal comparison with a fixed-dose strategy has not been undertaken").

We therefore believe that the rejection of allopurinol 300 mg as a primary comparator remains unfair and unclear, and we ask the NICE Appraisal Committee to provide the evidence base and justification as to why a trial-based

[5] Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Mailer V, Gilbert T, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis. 2007 Nov 2 [Epub ahead of print].

[6] IMS. A health economic assessment of febuxostat in the management of gout. Version No.1.0 19/10/2007. IMSWorld Publications Ltd. Data on file. 2007.

comparison of febuxostat to allopurinol 300 mg has not been accepted as an appropriate assessment against standard clinical practice in the UK.

Appeal Point 3. (Procedural Unfairness):

The Institute has acted unfairly by effectively redefining the scope of the appraisal by focusing the review on gout flares rather than "management of hyperuricaemia" as outlined in the scope.

The NICE Appraisal Committee appears to be focused heavily on the short-term efficacy of febuxostat on flare rates and has disregarded the well-accepted long-term benefits of hyperuricaemia management of gout (through the disregard to sUA based QALY calculations). This effectively redefines the scope of the NICE appraisal to the "management of flares in gout" rather than the "management of hyperuricaemia in adults with gout". The scope further indicates that gout flares is but one of several outcomes that should be considered in the appraisal.

The restricted assessment based on the avoidance of flares only suggests and assumes that acute short-duration flares are the most important disease indicator of gout and should therefore solely account for HRQoL. The appropriate control of sUA provides many benefits beyond the control of acute gout flares, based on the control of more chronic sUA-related conditions, such as tophi, joint erosions, polyarthritic syndrome, and renal complications.

By focusing on the reduction in flares only, the review is inconsistent with appraisal objectives laid out in the scope because it ignores the benefits of febuxostat in addressing the wider treatment objectives and HRQoL impacts faced by patients, many of whom are unable to gain sufficient control on allopurinol at doses regularly prescribed in the UK.

Ipsen believes that this decision has been unfair in changing the overall scope and focus of the assessment to one of the "management of flares in gout" rather than the "Treatment of chronic hyperuricaemia".

Appeal Point 4. (Procedural Unfairness):

It is unclear in the process how the Social Value Judgements Guide[7]

> ***"Non-maleficence involves an obligation not to inflict harm (either physical or psychological) and is associated with the maxim 'first, do no harm'"***

has been taken into account when deciding to withhold an existing effective treatment of gout patient without any safe treatment alternatives to allopurinol in clinical practice.

There are key categories of patients (including but not limited to gout patients with renal impairment, severe gout with tophi, patients with high sUA levels, patients intolerant of fixed-dose allopurinol) that cannot be sufficiently treated by allopurinol at the dose currently used by the vast majority of general practitioners and specialists. There is a paucity of effective and safe treatment options for these patients.

Ipsen believes that febuxostat is a valid treatment option both for the overall gout population but also for specific patient groups that are unlikely to be suitable for treatment with allopurinol. This belief is consistent with the comments offered by the BSR, which stated:

"Rather than not recommend febuxostat at all, a case could be made for considering this new drug for those patients who had failed on, or cannot receive available treatment options".

Not recommending use of febuxostat would preclude all these patients with very high unmet need from accessing febuxostat as an effective treatment alternative. The gout population living in the UK will suffer from a disability that is avoidable.

Appeal Point 5. (Perversity):

The decision by the NICE Appraisal Committee to disregard the wider HRQoL impacts of gout, through symptoms that are strongly associated with raised sUA levels, is a perverse one in light of the evidence submitted

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[7] National Institute for Health and Clinical Excellence. Social Value Judgements Principles for the development of NICE guidance. Second edition, July 18, 2008. Available at http://www.nice.org.uk/media. Accessed July 24, 2008

As part of their consideration and review of the febuxostat submission, NICE and the ERG focused on an exploratory analyses using a restricted utility calculation based on the impact of sUA on the risk of flares only. This suggests and assumes that the risk of flares should therefore solely account for utility.

This approach does not take into account a full and adequate reflection of the utility impacts of the overall condition (including both acute and chronic impacts). There is no plausible reason to make such an extreme assumption that the incremental quality-adjusted life year (QALY) is only dependent on the rate of gout flares and as such is fully independent of the chronic effect of elevated sUA levels through other chronic symptoms of gout (e.g., debilitating progression to tophi, joint erosions, limitation of motion, chronic pain, polyarthritic syndrome, renal complications). The other chronic symptoms can clearly be linked to the presence of raised sUA levels (independent of the flare effects), which the Committee states with the exploratory analyses (comment 4.10 in the CDA response).

Although gout flares ("acute" flare effect) clearly impacts HRQoL, this effect is limited when expressed in utilities due to the fact that the duration of a flare is limited in time. In the submitted economic evaluation, the chronic impact of elevated sUA on HRQoL during the intercritical gout period was also considered, independent of the acute flare effect. Both acute and chronic effects were assessed using the EQ-5D generic instrument within a study including patients of various sUA levels.

The IMS study[8] measured quality of life (QoL) directly with the EQ-5D in a gout population of 417 patients in the UK, France, and Germany and provides a high level of evidence (level B). Only patients with clinical gout were included; therefore, individuals with asymptomatic hyperuricaemia were excluded from the analysis. This research study found that:

1. Gout flares were associated with a significant reduction in HRQoL.

2. Elevated sUA levels were significantly associated with an increase risk of flares.

[8] IMS. A health economic assessment of febuxostat in the management of gout. Version No.1.0 19/10/2007. IMSWorld Publications Ltd. Data on file. 2007.

3. Elevated sUA levels were significantly associated with reductions in HRQoL during the intercritical gout period (i.e., the period in between acute gout flare events).

The IMS study was conducted in accordance with NICE guidelines[9] concerning methods for collecting data on utility estimates directly from the patient population using the EQ-5D. These data were subsequently used in the cost-effectiveness model to provide estimates of utilities by sUA levels. There was a clear distinction between the acute effect (i.e., combining the increased risk of flares in patients with elevated sUA with the reduction in HRQoL during a flare) and the chronic effect (i.e., during intercritical gout, elevated sUA is associated with a lower HRQoL) of elevated sUA. This distinction directly links the surrogate endpoint sUA and the gout patient's perception of symptoms and QoL.

Considering the high level of evidence provided in the IMS study, the Committee's concern about uncertainty of the relationship between absolute serum uric acid concentration and gout symptoms is out of proportion (FAD section 4.11-4.13). If the committee sustain the opinion of the wide range of uncertainty, the committee may also consider that the uncertainty may include a larger overall incremental QALY gain than 0.032 that would be in favour of febuxostat.

Appeal Point 6. (Perversity):

NICE and the ERG have inappropriately questioned the use of the sUA level as an appropriate surrogate clinical endpoint.

The decision by NICE and the ERG not to fully accept the sUA level as an appropriate clinical endpoint for the pivotal trials of febuxostat is a perverse one in light of the submitted evidence and also current clinical guidelines.

Firstly, the urate lowering effect of treatment is a well-recognized and a strongly supported surrogate marker for gout and is in full accordance with the EULAR guidelines recommendation, which states the following regarding the goal of urate lowering therapy: "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 (≤ 360 µmol/l)".

[9] NHS. National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. April 2004. Section 5.5.3. Available at http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf

The BSR guidelines (p.9 of 17) similarly state "Recommendation: The plasma urate should be lowered to, and maintained below, 300 µmol/l (using a uricase assay) by treatment. The goal of this is to prevent acute gout, tophus formation and tissue damage".

Therefore, key clinical treatment decisions for patients with gout are based on the target of reducing sUA levels to below the levels as stated in the current clinical guidelines. This target is to both reduce the risk of developing new symptoms and to help reduce the impact of existing physical symptoms of gout (debilitating progression to tophi, joint erosions, polyarthritic syndrome, renal complications).

The impact of sUA level on HRQoL ("chronic" gout effect), irrespective of the number of experienced flares ("chronic" gout effect), is seen through the chronic consequences of higher sUA levels (e.g., tophi, joint erosions, polyarthritic syndrome and renal complications).

As stated in Appeal Point 5 above, we presented strong EQ-5D-based evidence linking sUA levels to utility scores.

By not fully accepting the use of sUA as a surrogate clinical outcome, NICE and the ERG are going against the established framework for clinically managing gout as described in the EULAR and BSR guidelines and are focusing exclusively on the HRQoL impacts from gout flares only. This decision removes the chronic utility gain of maintaining a lower serum level, with the ERG making an extreme assumption that a gout patient's QoL is totally driven by flare events. This position is perverse in light of the available EQ-5D data presented in the submission.

Appeal Point 7. (Perversity):

The NICE Appraisal Committee and the ERG have ignored the clear evidence of clinical effect in specific patient subgroups where allopurinol does not provide an adequate control of sUA, or where allopurinol is not an appropriate therapy. This decision denies these subgroups an effective and safe treatment in a progressive severe disease of gout in the clear absence of other approved treatments.

It is clear from the clinical guidelines that there are key categories of patients (including but not limited to gout patients with renal impairment, severe gout with tophi, patients with high sUA levels, patients intolerant of allopurinol) that cannot be sufficiently treated by allopurinol at the dose currently used by the vast

majority of UK general practitioners and specialists, and there is a paucity of effective and safe treatment options for these patients.

The following subgroups have been specifically excluded by the FAD from access to febuxostat, when there are no other viable treatment alternatives and a clear unmet need. These exclusions, in light of no viable evidence-based alternative therapy, is a perverse decision given the clear unmet need and the clinical evidence as described in the submission and the ACD response.

Subgroup: Patients who remain uncontrolled with a dose of allopurinol up to 300 mg/day

A subgroup analysis for patients who have uncontrolled sUA levels whilst on allopurinol up to a standard dose of 300 mg demonstrated that febuxostat was an effective and safe treatment in this patient group (as detailed in section 3.5 of the ACD response).

Data from a randomized extension study show that a higher proportion of patients on febuxostat maintain treatment after the first year and achieve a sUA below 360 µmol/L (6.0 mg/dL) compared to allopurinol. More patients on allopurinol (57%) switched to febuxostat due to insufficient effect or intolerance than patients on febuxostat (18% on 80 mg and 8% on 120 mg) switched to allopurinol.

When switched from allopurinol to febuxostat, 67% of patients reached sUA levels ≤ 360 µmol/L (6.0 mg/dL), whereas only 9% of patients who switched from febuxostat to allopurinol did so.

These data demonstrate that febuxostat has a clear clinical efficacy in patients who have previously been unsuccessfully treated with standard fixed-dose allopurinol.

These patients deserve to have access to an effective and safe treatment option, for sUA control, in the absence of other viable alternatives. A decision to not consider febuxostat in this case is a perverse interpretation of the clinical evidence.

Subgroup: Patients with an sUA level of higher than 600 µmol/L (10 mg/dL) where a significant reduction in sUA levels is required

A significant proportion of patients with high sUA levels over the 360 µmol/L (6 mg/dL) levels targeted by the clinical guidelines have levels at or above 600 µmol/L (10 mg/dL). In the two febuxostat pivotal clinical trials, 30% and 40% of the patients, respectively, had baseline sUA levels that were at least 600 µmol/L (≥ 10 mg/dL). These data were reported in section 5.4.6 of the submission document.

In both trials, febuxostat was associated with a significantly higher proportion of patients achieving a final sUA level below the clinical guideline target of 360 µmol/L (6 mg/dL): 60% versus 21% in the APEX trial and 47% versus 8% in the FACT trial, in favour of febuxostat over allopurinol.

This evidence demonstrates that patients with raised sUA levels have a worse outcome on allopurinol than febuxostat and that use of febuxostat would result in a far greater proportion of patients being controlled.

A decision to not consider febuxostat as a direct alternative to allopurinol in this patient subgroup is a perverse interpretation of the clinical evidence.

Subgroup: Patients with renal impairment where an alternative and effective licensed treatment is required

Patients with renal impairment are more likely to have adverse reactions to allopurinol and should be prescribed lower doses of allopurinol.[10, 11] The key dosing issue is that allopurinol and its metabolites are excreted by the kidney, and impaired renal function may lead to retention of the drug and/or its metabolites, with consequent prolongation of plasma half-lives. Upward dose adjustments of allopurinol are not indicated in patients with renal failure due the potential for adverse health outcomes in this population. The UK Summary of Product Characteristics for allopurinol clearly states that in patients with renal impairment, a low-level daily dose of less than 100 mg, or less frequent dosing at 100 mg per dose, should be considered. An alternative for dialysis patients is a dosage of 300 mg to 400 mg taken immediately after each dialysis session (where dialysis is given 2 to 3 times per week).

A subgroup analysis conducted for patients with renal impairment showed that febuxostat is effective and safe in this patient group (as reported in section 3.5 of the ACD response). Febuxostat 80 mg/day had a 45% response rate compared

[10] Underwood M. Diagnosis and management of gout. BMJ 2006; 332:1315-9.
[11] Anderson BE, Adams DR. Allopurinol hypersensitivity syndrome. J Drugs Dermatol 2002;1:60-2.

to 9% for allopurinol 300 mg/day, in patients with a baseline serum creatinine level of < 1.5 mg/dL. The superiority of febuxostat over allopurinol (300/100 mg) in decreasing sUA levels to ≤ 360 µmol/L (6.0 mg/dL) has been sufficiently demonstrated in this patient subpopulation, particularly considering the lack of effective treatment alternatives.

The only other potential treatment, sulphinpyrazone, is used sparingly by specialists in hospitals and is not used by general practitioners. Sulphinpyrazone is generally regarded as inferior to allopurinol and is to be used with caution in patients with renal impairment.

The SPC approved for febuxostat indicates that no dosage adjustment is necessary in patients with mild or moderate renal impairment.

These patients deserve to have access to an effective and safe treatment option in the absence of other viable alternatives. A decision to not consider febuxostat in this patient subgroup is a perverse interpretation of the clinical evidence.

Subgroup: Patients with existing tophi where a significant reduction in sUA levels is required to fully dissolve large pools of crystal urate.

Tophi are a severe and disabling manifestation of gout that can be resolved with adequate urate lowering therapy. Serum uric acid levels should be maintained well below the saturation level for a sufficient period of time to produce a decrease in tophi size. This was demonstrated by Perez-Ruiz and colleagues,[12] who reported a relationship between the time to decrease tophi volume and sUA levels reached. In contrast to allopurinol, febuxostat produces a more rapid reduction in sUA levels and therefore a more rapid dissolution of pools of urate crystals within the tophi. The lower the sUA level, the quicker the tophi volume reduction. It is noteworthy that Perez-Ruiz and colleagues observed a mean time from onset of uric acid lowering therapy to disappearance of the target tophus for the entire series of 20.8 ± 10.2 months (range 6-64 months). The results of the long-term extension studies with febuxostat confirmed the need of a long-term maintenance of sUA levels below 360 µmol/L (6.0 mg/dL) for resolving tophi. Fifty-four percent of the primary tophi resolved completely (100% reduction of tophi size) in patients treated for at least 24 months with febuxostat.

[12] Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, and Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002; 47(4): 356-60.

CONCLUDING REMARKS/REQUESTED ACTION

In summary, for the reasons set out above, Ipsen believes that the Appraisal Committee should be required to explain the basis for departing from the STA procedures by ignoring current clinical practice (i.e., fixed-dose allopurinol) in England and Wales, for redefining the scope of the appraisal (i.e., focusing only on gout flares instead of global management of hyperuricaemia in gout, and for denying febuxostat to patients for whom there are no well-accepted evidence-based treatment alternatives.

Ipsen requests that the Appeal Panel refer this appraisal back to the Appraisal Committee for further consideration with the following recommendations:

a. Reconsider the choice of comparator as allopurinol 300 mg.

b. Reconsider the level of impact on QALY of sUA, and its use as a surrogate marker for long-term effects.

c. Reconsider the public health consequences of the decision to withhold an existing effective and safe treatment to a patient population with a progressive disabling disease. There are a number of specific patient subgroups for whom febuxostat would represent the only effective treatment alternative outside of standard treatment for gout.

d. Reconsider the Guidance by revising paragraph 1.1 and removing paragraph 1.2. (definition of intolerance). Paragraph 1.3 then becomes 1.2 as follows:

    1.1 Febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout for people who are intolerant of allopurinol, for whom allopurinol is contraindicated or for whom allopurinol is not effective in providing adequate control (sUA level reduced to below the level recommended by the British Society of Rheumatology).

    1.2 People who are currently receiving febuxostat and who do not meet the criteria in 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.