Ipsen – Response to Appraisal Consultation Document

From: [redacted]
Sent: 18 June 2008 08:07
To: Natalie Bemrose
Subject: Febuxostat- Comments from IPSEN on NICE ACD and key points raised by the ERG

Attachments: FINAL DOCUMENT SEND TO NICE 18th June 2008.pdf; Appendix NNT 17th June 2008.pdf; Appendix C02-021.17th June 2008.pdf; Appendix TMX-01-005 17th June 2008.pdf

Dear Natalie

Please find attached Ipsen's response document on ACD and key points raised by ERG on Single Technology Appraisal of Febuxostat.

The response addresses 4 key questions listed in the letter received from NICE on 19th May 2008 and Ipsen's response to points raised by ERG.

Please note, the appendices provided are confidential information (for information only) from Ipsen and it should not be published by NICE.

Should you require any further information, please do not hesitate to contact me.

Best regards

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FEBUXOSTAT FOR THE MANAGEMENT OF HYPERURICAEMIA IN PATIENTS WITH GOUT

A formal manufacturer response document to the NICE confidential ACD and the key issues raised by the ERG evidence review as referenced in the ACD document

The following manufacturer response document provides formal feedback from the manufacturer (IPSEN) on the ACD for febuxostat in the treatment of gout.

A summary of the key feedback points is provided in an initial section to this response document, based on the general headings provided by NICE:

1. Do you consider that all the relevant evidence has been taken into account?

2. Do you consider that the summaries of the clinical and cost-effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

4. Are there any equality related issues that need special consideration that are not covered in the ACD?

This is followed by a more detailed main section to the response document, structured as a step-by-step response to address the specific points raised in the ERG review of evidence on clinical and cost-effectiveness. The focus is specific to those ERG points which are direct referenced in the ACD in support of the proposed ACD recommendation of *'not recommending febuxostat for the management of chronic hyperuricemia in people with gout'*

Section 1: ACD Response Summary

Gout is a chronic, progressive and disabling disease. When patients with gout do not receive proper care, the intermittent arthropathy progresses to persistent and severe joint disease and to physical disability. In the kidney, gout can cause nephrolithiasis (kidney stones), interstitial kidney disease, and monosodium urate crystal intrarenal obstructive uropathy. Renal impairment is common among gout patients, and limits the effective treatment of patients due to dose limitations. Continuous high sUA levels leaves the patients exposed to a much greater risk of acute gout flares, and prolonged lack of sUA control can lead to the manifestation of chronic gout symptoms, including tophi and joint damage.

The British Society for Rheumatology (BSR) Guideline for the Management of Gout (Jordan et al., 2007) identifies an unmet need for gout treatment due to the limited efficacy of allopurinol *"… In recent years, however, it has become apparent that <50% of patients receiving allopurinol 300mg daily in comparative drug trials were achieving optimum reductions in plasma urate concentrations."* Consequently, the only options available in the UK today are to either increase the dose of allopurinol to high doses that have not been documented safe or clinically effective, or to use sulphinpyrazone, a drug that is generally regarded as inferior than allopurinol and which itself has several limitations related to renal impairment (Jordan et al., 2007; Zhang et al., 2006); Other options are to use the drugs benzbromarone and probenecid, but these can only be used on a name to name basis as they are not approved on the UK market for general prescribing due to clear safety considerations. Therefore, current treatment of gout is dominated in the UK by allopurinol at doses of up to 300mg/day, reflecting the above mentioned limitations of alternatives in clinical practice.

Febuxostat is a xanthine oxidase inhibitor and a therapy for gout that aims to reduce serum urate (sUA) levels and thereby reduces symptoms and reverts progression of gout from built up monosodium urat (MSU) crystals which causes flares, tophi, and renal impairment. Head-to-head randomized controlled trials (RCT) have shown that febuxostat has a significantly superior effect compared to allopurinol 300mg/day in lowering sUA levels both in the short-term and long-term perspective, and provide strong indications of febuxostat preventing gout flares and resolve tophi ("cure gout") in the long-term.

The sections below responds to and comments the questions the committee enclosed with the ACD and ERG report.

1. Do you consider that all the relevant evidence has been taken into account?

IPSEN does not consider that all the relevant evidence has been taken into account in the preliminary recommendations, or that the available evidence has been fully utilised in the recommendations.

First, it is essential to re-iterate that the key objective in the treatment of gout is to establish and maintain a well controlled sUA level over both the short and longer-term. This goal of therapy is supported by the current BSR and EULAR guidelines and is based on the saturation points as supported clearly in these guidelines; 0.30 mmol/l (5.0mg/dL) and 0.36 mmol/l (6.0mg/dL), respectively. The basis to this treatment objective for gout is absolutely clear. In patients with gout, high sUA levels have been demonstrated to be directly linked to the presence of gout related symptoms, both in the short-term and when continued over the long-term. These symptoms and complications of gout can have severe impacts on a patient's quality of life. Also, the most severe impacts of gout are observed where the sUA level is poorly maintained and is often above the targeted level, or where it reduces rapidly. Therefore, an effective and improved treatment for gout is one which can safely lower sUA levels, and maintains these over the longer-term. In conclusion, the clinical relevance of the end-point used in clinical trials has been emphasized by EULAR and BSR.

Febuxostat has been the subject of two well designed very large phase III randomised clinical trials, comparing to both placebo and to the current standard of treatment in the UK for gout (allopurinol at doses of up to 300mg). These trials have confirmed that febuxostat has a clear superior efficacy to allopurinol, both in the short term control of sUA levels and also in the maintenance of this control over the longer term. Again, this is the key clinical assessment used in judging the effectiveness of treatment in gout, as supported in the guideline documents.

The superior efficacy of febuxostat is evident in a much wider range of patients than can be seen with the efficacy attributed to current standard treatments. In particular the efficacy of febuxostat for the control of sUA levels is carried through into a significant sub-group of gout patients, those patients with renal impairment where treatment options and dose flexibility are very limited.

We consider that the preliminary ACD recommendation is based on several flawed assumptions:

a) [*the comparator choice*] the assumption in the ACD that high dose allopurinol or other comparators: sulphinpyrazone, benzbromarone and probenecid (the last two products are not approved on the UK market) provide improved efficacy in patients that do not achieve a response or are intolerant to 300mg allopurinol, and are used actively in clinical practice;

b) [*the challenge to the use of a surrogate marker*] the assumption in the ACD that sUA can not be strongly linked to the clinical symptoms of gout and that this limits the benefits on quality adjusted life years on lowering serum urate levels in gout patients over long-term (a questioning of the use of sUA as a surrogate marker); and

c) *[the challenge to a long-term treatment effect]* the ACD document re-calculates the ICERs based on a 1-year time horizon and a restriction to flare impacts only, ignoring the inter-critical and longer term impacts of raised sUA levels.

Comparator choice

The level of evidence is poor for recommending use of another comparator than the gold standard allopurinol 300 mg non-titrated. High dose allopurinol is neither routinely used in clinical practice nor is there any evidence based support for its efficacy and safety. Allopurinol titration as allowed per SmPC is not currently used in practice (SmPC starting dose 100mg, to be increased based on safety and efficacy). A systematic literature review 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. Sulphinpyrazone is only used sparely, mainly by specialists in hospitals and not by general practitioners, and is generally regarded as inferior to allopurinol and is to be used with caution in patients with renal impairment, who represent a sensitive gout sub population (Aturan SPC; section 4.4); Benzbromarone and probenecid are not approved for

use on the UK market and therefore it cannot be plausible to consider those drugs as best clinical practice or standard clinical practice in the UK.

There is a high level of evidence (level B) that allopurinol 300mg, non-titrated, is the standard treatment in the UK and the appropriate comparator. Several observational studies have shown allopurinol 300 mg or less is used in the majority of the gout patients in the UK.

We therefore strongly believe that a trial based comparison of febuxostat to allopurinol 300mg non-titrated is an appropriate assessment against standard clinical practice in the UK.

Surrogate marker

The urate lowering effect of treatment is a well recognized surrogate marker for gout and is in accordance with the EULAR guidelines recommendation 7, which states the following regarding the goal of urate lowering therapy (ULT): *"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)."* The BSR guidelines (p.9 of 17) 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. "*

The high level of evidence (level B) from the IMS study measured QoL directly with EQ-5D in a gout population of 417 patients in the UK, France, and Germany. Only patients with clinical gout were included, therefore asymptomatic hyperuricaemia individuals were excluded from the study. This research study found that (1) gout flares are associated with a significant reduction in HRQoL, (2) elevated sUA levels were significantly associated with an increase in flare frequency, and (3) during inter-critical gout (period between gout attacks) elevated sUA levels were significantly associated with reductions in health-related quality of life during the inter-critical gout period (i.e. the period in between acute flare events). This is done in accordance with NICE recommendations of methods to collect data to provide utility estimates with EQ-5D direct from the patient population (NICE, 2004 section 5.53). These data were subsequently used in the cost-effectiveness model to provide estimates of

utilities by sUA levels which directly links the surrogate endpoint sUA and the gout patients' perception of symptoms and quality of life.

The key outcome for NICE decision making is the QALY; all cost-utility analyses use some method of linking clinical outcomes to QALYs, via utility weights. In this case, a direct association was made between the primary trial end-point (sUA) and the final outcome (utility) using methodologies favoured by NICE (EQ-5D data collected within a study including patients of various sUA levels). This measure may therefore be considered to represent the total impact of high sUA on quality of life, including (1) the acute impact of gout flares of which the frequency is positively correlated with higher sUA level, and (2) the chronic effect of gout of which the debilitating progression to tophi, joint erosions, polyarthritic syndrome, renal complications, etc. increases with a higher sUA level.

It was therefore not necessary to define the relationship between hyperuricaemia and the clinical manifestations of gout, since an indirect (via acute effect of gout flares) and direct (via chronic effect of gout) relationship between sUA and utility was applied.

Longer-term treatment effect

In evaluating a new drug it is understandable to take a conservative standpoint as only limited data is often available. However, in the consideration of febuxostat several elements of evidence are well documented, including its continued efficacy beyond the 1-year phase III data, with high levels of treatment adherence over allopurinol and also stable treatment efficacy in patients who have failed on allopurinol. We kindly request that the committee reconsider the following evidence and their recommendation.

- The strong gold level evidence (level A) from two large double-blind randomized controlled head-to-head trials showing the clear superior effect of febuxostat to lower serum urate (sUA) levels compared to allopurinol, non titrated 300 mg/day. This superior effect is demonstrated whatever the baseline sUA and is even more pronounced patients with highly elevated sUA. Moreover, subgroup have shown the superiority in efficacy is maintained regardless of baseline sUA levels and has shown that febuxostat is well tolerated in patients with mild-to-moderate renal impairment. Tophi are a severe and disabling manifestation of gout and a clinical relevant endpoint for the patient. A subgroup analysis of patients

with tophi showed a greater reduction of tophi with febuxostat than with allopurinol within 28 weeks of treatment and a complete dissolution of tophi in a significant proportion of patients when treated long-term with febuxostat, with their sUA maintained below 0.36 mmol/l (6.0 mg/dL).

- This urate lowering effect prevents clinical symptoms of gout, in particular when the target sUA is achieved and maintained over a long-term time frame of more than one year (level B). Gout is a chronic and, if not treated appropriately, a progressive and disabling disease. Urate crystal resolution takes time and needs to be evaluated over a longer term of more than 1 year to achieve hard clinical endpoints of tophi resolution and decreased rate of gout flares. The data from the long-term efficacy studies provides supportive evidence for this.

2. Do you consider that the summaries of the clinical and cost-effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

<u>Clinical effectiveness</u>

We agree with the summary of clinical effectiveness that both the pooled analysis and the meta-analysis (section 3.4, 3.5) suggests that:

- "Febuxostat 80 mg/day and 120 mg/day was significantly more effective ($p \leq 0.05$) than fixed-dose allopurinol (300 or 100 mg/day) at lowering serum uric acid concentrations either to target therapeutic levels of below 0.36 mmol/l (6.0mg/dL), from baseline levels at the last three visits or the final visit"….

- "Post-hoc subgroup analysis of the pooled data showed that febuxostat was more effective ($p \leq 0.05$) than allopurinol in lowering serum uric acid concentration to below 0.36 mmol/l (6.0mg/dL) in three subgroups of patients defined according to baseline serum acid concentrations of below 9 mg/100 ml, between 9 and 10 mg/100 ml and above 10 mg/100 ml. The proportion of patients receiving febuxostat who achieved a target serum uric acid concentration of below 0.30 mmol/l (5.0mg/dL was higher ($p \leq 0.05$) than among those receiving fixed-dose allopurinol."

The data from the pivotal randomised clinical trial comparing febuxostat and allopurinol have clearly evidenced the fact that febuxostat has superior efficacy in term of the key clinical outcome marker championed by the EULAR and BSR guidelines, the sUA level. Critically, this superior treatment effect is seen using both the 0.36 mmol/l (6.0 mg/dL) and 0.30 mmol/l (5.0 mg/dL) target levels. Also, unlike allopurinol, there is clear clinical evidence that this effect is maintained over the longer term, certainly well beyond the initial year of treatment, and that its efficacy is present in patients who have failed on a prior therapy for gout.

It should be emphasized that the magnitude of the observed difference between febuxostat and allopurinol is very high. Indeed, data from RCTS have been computed by IPSEN as relative risk of success and number of patients needed to treat (NNT). With this way of expressing results, the efficiency of febuxostat vs allopurinol is dramatically superior (see annex). Therefore, the magnitude of effect shown by febuxostat makes it a clinical entity that outperforms the current treatment.

The following re-iterates the points on which we have a clear disagreement to the ACD document and ERG conclusions that underpin the committee's recommendations.

- We do not agree with the statement that the benefit of febuxostat in Phase III study has not been demonstrated (3.7). As cited above, the randomized double-blind studies of up to one year have clearly shown superiority in the generally accepted surrogate endpoint of sUA levels. Long-term extension studies over several years indicate that the clinical efficacy of febuxostat in lowering sUA levels is reflected in hard clinical endpoints, e.g. 97 % of patients do not require a treatment for a flare at Month 16-24 and 54 % of the patients with tophi at baseline have complete tophi resolution (Adenuric SmPC). It should be noted that no long-term data documenting the clinical efficacy of allopurinol is available. Gout attacks are the most clinically relevant endpoint for the patients and tophi, when present, are a severe and disabling manifestation of gout.

- We do not agree with the statement that the benefit of febuxostat in Phase III study is not generalisable in the UK gout population that are perceived to have a milder disease. The clinical trials reflect a population with mild to severe gout with an sUA > 0.48 mmol/l (8.0 mg/dL), a mean sUA at

initiation of treatment of 0.59 mmol/L (9.8 mg/dL), 20-26% of the gout patients have tophi and 35% have mild-to-moderate renal impairment. There is no data available in the literature documenting the severity of the UK gout population. However, even if the gout population in the UK were seen to have a milder manifestation of gout, subgroup analyses have shown febuxostat has superior effect against allopurinol regardless of baseline sUA level, renal impairment or presence of tophi (see discussion comment 3.4). We believe this evidences the generalisability of the treatment effect advantage of febuxostat over allopurinol across the potential patient group variations in the UK.

- A subgroup analysis conducted for patients with renal impairment showed that febuxostat is effective and safe in this patient group (See discussion to section 3.5). The sUA control treatment effect of febuxostat can be clearly seen in patients with renal impairment, which is a patient group more difficult to treat with allopurinol due to the limitations of possible dose increasing. These patients deserve to have access to an effective and safe treatment option in the absence of other viable alternatives.

- A subgroup analysis for non-responders to allopurinol showed that febuxostat is effective and safe in this patient group (See discussion to section 3.5). 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 0.36 mmol/l (6.0mg/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 ≤0.36 mmol/l (6.0mg/dL) whereas only 9% of patients switched from febuxostat to allopurinol did so.

Cost-effectiveness

Utility Assessment

We do not agree with the magnitude of uncertainty that the ERG states about (a) the ‘chronic utility gain’ associated with lower serum uric acid concentrations and (b) the decreased (acute) utility associated with gout flares. It should be noted here that those 2 parameters are considered independently in the model:

- **The impact of experiencing a flare on HRQoL ("acute" flare effect).** It is clear that experiencing a flare has an impact on HRQoL, although the impact of 1 flare, which is not a chronic condition, is quite limited when expressed in utilities due to the fact that the duration of a flare is limited in time. In the economic model, the impact of experiencing a flare on HRQoL is considered entirely independent of the chronic impact of higher sUA levels on HRQoL (chronic impact is explained in bullet 2 hereunder). However, this "acute" flare effect on utilities is indirectly influenced by sUA level: the higher the sUA level, the higher the frequency of flares, and consequently the lower the utilities in patients with higher sUA.
- **The impact of sUA level on HRQoL, irrespective of the number of experienced flares ("chronic" gout effect).** This parameter does not take into account the acute effect of experiencing a flare. sUA is a surrogate parameter, since the impact on HRQoL is not caused by the sUA level as such, but by the "chronic" consequences of higher sUA levels (excluding the abovementioned acute effect of gout flares), like tophi, joint erosions, polyarthritic syndrome, renal complications, etc.

We do not agree with the statement that a linear relationship between sUA level and the frequency of gout flares was applied in the cost-effectiveness model. The discussion in 3.14 explains in detail how the estimates of monthly number of flares were obtained by a non-linear relationship, as recommended by the ERG (and opposite to the statement that a linear relationship was applied).

A two-phase approach, using logistic regression of the odds of experiencing flare(s) in the first phase, was applied. In the second phase, the monthly number of flares in the subgroup of patients experiencing flares, was estimated through linear regression with the $\log_{10}$-transformed number of flares as dependent variable. Multiplication of the proportion of patients with flares (logistic regression) with the monthly number of flares in patients who experienced flare(s) ($\log_{10}$ transformation) resulted in an estimate of the monthly number of flares by sUA level as applied in the economic evaluation. Thus none of these estimates were based on a linear relationship. The relationship between the probability of experiencing flare(s) and sUA levels have been confirmed in two peer reviewed publications (Shoji et al. 2004; Sarawate et al. 2006). A sensitivity analysis using the published estimates obtained similar and even a lower ICER with one of the published data.

Moreover, we do not agree with the extreme assumption that the incremental QALY is independent of sUA levels and is only dependent on the rate of gout flares; which the committee states with the exploratory analyses in comment 4.10.

- The magnitude of the incremental utility is subject to some uncertainty, but given the strong indications of tophi resolution in long-term studies on one hand (curative effect), and the prevention of progression of disease towards tophi, joint erosions, polyarthritic syndrome, renal complications, etc in patients in early stages of disease, the link between QALY and sUA levels should be well established and accepted. The model is moderately sensitive to the utilities and rates assigned to gout flares. The base case ICER of febuxostat versus allopurinol over 2 years is £15,565/QALYG.

- The link between sUA levels and utility to reflect variation in HRQoL (and subsequently QALY) that was obtained in the IMS study have been confirmed in two recent reports of the two extension studies (FOCUS and EXCEL) conducted with febuxostat (Discussion 3.15).

- An observational study by IMS of 417 gout patients in the UK, France and Germany collected data on quality of life (QoL) with EQ-5D together with sUA levels, flare frequency data and cost data. This is done in accordance with NICE recommendations of methods to collect data to provide utility estimates with EQ-5D direct from the patient population (NICE, 2004 section 5.53). These data were used in the cost-effectiveness model to provide estimates of utilities by (1) gout flares (acute effect) and (2) sUA levels (chronic effect) which directly links the surrogate endpoint sUA and the gout patients' perception of symptoms and quality of life.

There is also further data to support the direct link between sUA and HRQoL:

- The open label extension study FOCUS (TMX-01-005) showed statistically significant ($p<0.05$) improvements from baseline in several of the SF-36 domains, the Physical Component Summary (PCS), Health Transition and the Gout Assessment Questionnaire (GAQ) domains (Appendix TMX-01-005).

- Similar data have been obtained on QoL in the EXCEL study (C02-021): subjects on all treatment groups experienced improvements in all SF-36

scales from baseline to the final visit. These improvements were statistically significant in the Scales of Role-Physical, Bodily Pain, Vitality, Reported Health Transition, Physical Component Summary, and MOS Health Distress. Because only subjects whose sUA levels were controlled remained in study, the QoL results are representative of only subjects who responded to treatment (Appendix C02-021).

- It can be concluded from the QoL evaluation conducted in the long-term extension studies that maintaining sUA level below 0.36 mmol/l (6.0mg/dL) for a long period of time decreases progressively the symptomatic burden of gout, and this has been associated with an improvement of the SF-36 domains associated with physical function, particularly on Role-Physical, Bodily Pain and Vitality domains.

- The model uses sUA level as the key driver of treatment decisions in the model, as is seen in clinical practice and recommended by the treatment clinical guidelines. The principle being that well controlled sUA levels will lead to a dissolution of crystals which in turn we know will lead to the improvement of gout-related symptoms, including but not limited to, the reduction and disappearance of gout attacks and the complete dissolution of tophi.

By removing the chronic utility gain of maintaining a lower serum level, the ERG makes an extreme assumption that the QoL in a gout patient is totally driven by flare events, and implies QoL is not impacted in between flare events by chronic gout conditions such as tophi, joint damage, chronic inflammation and renal impairment. The ERG disregards the benefit of preventing disabling long-term complications of gout that are causing most suffering for the individual and costs for the NHS.

A sensitivity analysis varying the ‘chronic’ utility increments from 0.02 to 0.05 varies the ICER between ICER (cost per QALY) £26,018 and ICER (cost per QALY) £10,786.

No Treatment and Sequential Treatment Comparators

The model was not designed to calculate the cost-effectiveness of no treatment. However, an exploratory analysis used data from the placebo arm in the APEX study estimates febuxostat versus no treatment at an acceptable cost-effectiveness with an ICER of £3,727/QALYG. This analysis does not account for the longer term progression of disease with no treatment (Gutman, 1973).

From a natural history perspective the randomised placebo arm of the APEX clinical trial, compared against febuxostat and allopurinol provides data that none of the placebo patients achieve a sUA level of ≤0.36 mmol/l (6.0mg/dL). These patients with gout are likely to progress and develop severe tophaceous gout.

The ACD also raises the issue of an economic model based on sequential treatment sequences for managing gout, in which patients who fail to gain a response move onto a next level of therapy (i.e. a model incorporating a 1st line, 2nd line and subsequent treatment or no treatment option). The original model was developed as a first-line treatment comparison versus allopurinol as this was felt to be the primary comparator. This is also in line with the EU marketing authorisation.

The original model was developed as a first-line treatment comparison versus allopurinol as this was felt to be the primary comparator. The placebo analysis above helps to look at the costs and benefits of febuxostat when no other treatment option is available (i.e. if they are contraindicated for allopurinol or if allopurinol has failed. We have data from EXCEL that shows a similar clinical effect for febuxostat in allopurinol failure patients.

The issue with developing a sequential treatment model is the lack of good quality data for treatment effect based on prior treatment, and the fact that the clinical trial data is predominantly a first-line treatment comparison. Although this has been raised as an issue in the initial ERG comments and the ACD it is not possible to utilise the current economic model to generate this type of comparison within the available timeframe of the NICE STA review.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

IPSEN does not consider the recommendations are sound as they are based on flawed assumptions, have not included considerations of high level of evidence

of efficacy and safety of febuxostat or considered the unmet need for an effective treatment of gout in large patient groups.

In addition, the committee needs to take into account the statements from the British Society for Rheumatology, the Royal College of Nursing Statement, the Clinical Expert Statement and the Patient expert that febuxostat provides a welcome addition to the limited arsenal of gout therapy to prevent and cure gout (as provided within the ERG report).

4. Are there any equality related issues that need special consideration that are not covered in the ACD?

It is clear 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 GPs and specialists and there is a paucity of effective and safe treatment options for these patients.

IPSEN believe that febuxostat is a clear treatment option both for the overall gout population but also for specific patient groups who are unlikely to be suitable for continued treatment with allopurinol. 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. Therefore we propose the appraisal committee to include febuxostat in their recommendation.

Section 2: ERG Response – Based on Specific Issues Raised in the ACD document

The following steps through some of the specific ACD/ERG comments on the manufacturer's submission, with each point replicated in the grey text box and referenced by the original ACD paragraph numbering system.

Each response is structured according to the issue, and where appropriate the response provides a specific conclusion or clear recommendation to NICE from the manufacturer.

ACD Paragraph 3.4

The pooled analysis suggested that febuxostat 80 mg/day and 120 mg/day was significantly more effective ($p \leq 0.05$) than fixed-dose allopurinol (300 or 100 mg/day) at lowering serum uric acid concentrations either to target therapeutic levels (of below 6.0 mg/100 ml) or from baseline levels at the last three visits or the final visit. No statistically significant changes were observed with febuxostat 80 mg/day compared to allopurinol (300 or 100 mg/day) in the proportion of patients requiring treatment for gout flares. In contrast, the proportion of patients requiring treatment for gout flares was statistically significantly higher ($p \leq 0.05$) with febuxostat 120 mg/day than with allopurinol (300 or 100 mg/day), both during (weeks 1–8) and after (weeks 9–52) prophylaxis. The difference was more marked during the initial weeks of treatment. No statistically significant differences were found between groups in the percentage reduction in tophus area except at week 28. At week 28, significantly greater reductions were observed in primary tophus size from baseline with febuxostat 120 mg/day than with allopurinol.

As noted by the Committee (Section 4.5), this initial response to active treatment – the induction of mobilization flares at treatment initiation – has been observed and documented with all uric acid-lowering therapies. Although the mechanism is not completely understood, it is believed to relate to the rate of change in serum uric acid concentration, with treatments that reduce serum uric acid concentration more effectively and rapidly giving a more pronounced induction effect (Borstad et al., 2004).

Therefore, the SPC for febuxostat recommends flare prophylaxis for at least 6 months with an NSAID or colchicine at treatment initiation (Ipsen, 2008), which is

in line with the latest EULAR recommendations for initiating uric acid-lowering therapies (EULAR).

It is noteworthy in the APEX and FACT clinical trials that a similar incidence of initiation gout flares was reported in patients treated with febuxostat 80 mg and allopurinol (300 or 100 mg/day) and a higher incidence was reported in patients treated with febuxostat 120 mg, especially at the very start of treatment. As recommend in the SPC, patients will start treatment with febuxostat 80 mg, therefore the effect of initiation gout flares will be similar to allopurinol for the majority of patients. Only patients switching from febuxostat 80mg to 120mg might have increased initiation gout flares compared to allopurinol (this was also the modelling basis of the economic analysis).

The incidence of gout flares is influenced by at least 4 important parameters:

- Maintenance of sUA above the saturation level (approx 6.8 mg/dL but depending on pH and temperature, therefore the saturation level is lower in the extremities of the body)
- Rapid changes, and especially decreases in sUA levels.
- The constant presence of crystals in the body which potentially mean that a gout flare is possible.
- The adequate use of anti-inflammatory drugs such as colchicines or NSAIDs that can inhibit the inflammatory process linked to crystal deposition and mask the flaring symptoms.

A recognition of the requirement to decrease sUA levels below the saturation level (≤0.36 mmol/l (6.0mg/dL)) is the basis of the EULAR recommendations. The BSR recommends a further decrease of sUA to ≤5.0 mg/dL, thus ensuring a more rapid dissolution of crystals. Decreasing sUA to levels below 0.36 mmol/l (6.0mg/dL) or 0.30 mmol/l (5.0mg/dL) has been recognized as a means of achieving crystal dissolution and preventing crystal formation and is the therapeutic goal of long-term therapy in gout (Zhang et al, 2006; Jordan et al, 2007).

These factors explain why a long-standing history of gout should be treated with:

- Drugs that efficiently decrease sUA to levels below the saturation point for a sufficient duration to eradicate the presence of crystals.

- Concomitant use of colchicine or NSAIDs for a duration that is dependent on the severity of gout and on the potency of the urate lowering therapy. The initial rise in clinical flares (the induction effect) can be diminished or prevented with the use of an NSAID or colchicine as a prophylaxis during the first months of treatment.

During the first months of any urate lowering therapy a comparable or higher incidence of gout flares can be observed in treated compared with non-treated patients. It is only after several months of therapy, during which sUA levels are maintained below the saturation point that the incidence of gout flares decreases to almost zero in the treated group (see Figures 5-13; 5-14, 5-15 in the STA submission; summarising the open-label trial data on flares).

The pivotal studies were not designed to demonstrate a difference between treatments on the incidence of gout flares; indeed there is no consensus definition of gout flare as a clinical endpoint that could be used. In addition, there are several reasons why it was not possible to demonstrate a difference in clinical symptoms between treatment groups:

- The duration of the studies was limited to 12 months. This could be considered as a short period of time for eradicating the crystals particularly for a population of patients with severe gout. Patients had a long history of active gout, with the majority experiencing at least one gout flare in the year prior to study entry. Patients therefore required a long duration of treatment before being symptom-free. Thus a difference in the incidence of gout flares between the ≤0.36 mmol/l (6.0mg/dL) and the >0.36 mmol/l (6.0mg/dL) groups was observed only at the end of the 1-year study period, and this confirms again the relevance of the primary endpoint.
- Due to the higher potency of the febuxostat 120 mg dose, a greater decrease in sUA was observed in this group and mean sUA reached was 4.4 to 4.8 mg/dl vs 5.03 to 5.34 mg/dl with febuxostat 80 mg and 6.3 to 6.5mg/dl with allopurinol. Hence, more gout flares were observed during initiation of therapy due to the rapid decrease in sUA level observed in the febuxostat 120 mg group, and the fact that the prophylaxis regimen (8 weeks) was too short to prevent flares. During the final months of the study, however, an opposite trend was observed with a lower incidence of flares in the febuxostat 120 mg group compared to the other groups (see

Figure 5-15 in the STA submission; data from APEX, FACT and open-label extension studies).

- The period of prophylaxis was short resulting in an increase in flares when prophylaxis ceased, therefore the total number of flares could have been higher in the overall period of assessment due to the initial mobilization flares increase that lasted longer than the decrease due to the progressive dissolution of monosodium crystals. There is a strong interference between the removal of prophylaxis treatment, which disturbs a possible relation between treatment effect and impact of patient-reported need for treatment of flares.

Data from the pivotal studies resulted in a recommendation in the SPC that patients should start febuxostat therapy using the 80 mg dose. Treatment with this dose was associated with a comparable incidence of gout flares as reported for allopurinol. A longer period of gout flare prophylaxis was also recommended. Thereafter patients should remain on long-term urate lowering treatment to prevent the formation of urate crystals, continue and complete the dissolution of existing crystals and reduce symptoms such as the incidence of flares and the size and the number of tophi.

To produce a decrease in tophi size, sUA levels should be maintained well below the saturation level for a sufficient period of time. This was demonstrated by Perez-Ruiz (Arthritis and Rheumatism 2002) who reported a relationship between the time to decrease tophi volume and sUA levels reached. The lower the sUA level the quicker the tophi volume reduction. It is noteworthy that Perez-Ruiz observed a mean time from onset of ULT to disappearance of the target tophus for the entire series of 20.8± 10.2 months (range 6-64 months). It is therefore not unexpected that no statistically significant effect has been demonstrated between the groups at 6 and 12 months in the studies. Importantly only 20% of patients had tophi at baseline which meant that the study was underpowered for this secondary endpoint. It should be noted that tophi size is measured by methods with significant variability, and the location of tophi should be also taken into consideration ; as compared to other rheumatology diseases (like polyarthritis) no “score” for this assessment is available.

Some evidence for the need of a long-term maintenance of sUA levels below 0.36 mmol/l (6.0mg/dL) for improving the clinical outcomes was provided by the results of the long-term extension studies. Indeed, when patients were treated for

at least 24 months, the incidence of gout flares decreased to 3% and 54% of primary tophi disappeared (100% reduction of tophi size).

ACD Paragraph 3.5

Post-hoc subgroup analysis of the pooled data showed that febuxostat was more effective ($p \leq 0.05$) than allopurinol in lowering serum uric acid concentration to below 6.0 mg/100 ml in three subgroups of patients defined according to baseline serum acid concentrations of below 9 mg/100 ml, between 9 and 10 mg/100 ml and above 10 mg/100 ml. The proportion of patients receiving febuxostat who achieved a target serum uric acid concentration of below 5 mg/100 ml was higher ($p \leq 0.05$) than among those receiving fixed-dose allopurinol. No subgroup analyses were conducted for patients with renal impairment and non-responders to allopurinol.

The following provides comment specific to the two patient groups raised; renal impairment and non-responders

Patients with renal impairment

Patients with renal impairment have very limited options in the treatment of gout, and existing treatment options may present certain safety hazards to these patients, when prescribed at what would normally be considered as optimal treatment effect doses. It should also be noted that a significant proportion of gout patients have renal impairment to a variable extent.

- Uricosuric agents are unsuitable for patients with impaired renal function or a high renal excretion of urate because of the increase in risk of renal stones (Underwood, 2006).
- Patients with renal impairment are more likely to have adverse reactions to allopurinol and should be prescribed lower doses of allopurinol (Underwood, 2006; Anderson and Adams, 2002). 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.
- The UK SPC for allopurinol clear states that in patients with renal impairment a low-level daily dose of less than 100mg should be considered, or less frequent dosing at 100mg per dose. An alternative for dialysis patients is a dosage of 300-400mg taken immediately after each dialysis session (where dialysis is given 2 to 3 times per week).

- Whilst taking allopurinol close monitoring of plasma oxipurinol concentrations is also recommended to maintain plasma oxipurinol levels below 100 µmol/litre (15.2 mg/litre).
- This low dose of allopurinol may not be efficacious enough to lower the sUA to a therapeutic level and, in fact, the most common reason for inadequate effectiveness of allopurinol cited in the literature is dose-limiting renal failure (Perez-Ruiz et al., 1999; Bardin, 2004).
- Sulfinpyrazone, the only second line approved treatment in the UK, is contraindicated in patients with urolithiasis or reduced renal function and appears less effective than allopurinol (Zhang et al., 2006a)
- Probenecid is not approved in the UK.

Because of the significant unmet medical need in renal impaired patients, with allopurinol prescribed at sub-optimal dose levels, and other treatments either contraindicated or unlicensed, febuxostat provides an effective and medically relevant alternative treatment option in gout patients with renal impairment.

Upward dose adjustments of allopurinol are not indicated in patients with renal failure due the potential for adverse health outcomes in this population. The SPC approved for febuxostat indicates that no dosage adjustment is necessary in patients with mild or moderate renal impairment.

Efficacy and safety of febuxostat have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).

Randomised trial data in renal impaired patients

A proportion of patients (approximately 3% in total) in the phase III randomized clinical trials of febuxostat (the APEX and FACT studies) were classed as having renal impairment (3% based on baseline serum creatinine levels of >1.5mg/dL; 6% based on creatinine clearance <50mL/min).

A post-hoc analysis conducted pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups using a Cochran-Mantel-Haenszel (CMH) general association test adjusting for study and subgroup of the pooled clinical trial data (Integrated summary of efficacy [ISE] 1.5.2.5.2).

The subgroup analysis confirmed superior efficacy in terms of the percentage of patients with sUA below 0.36 mmol/l (6.0mg/dL) was maintained in the febuxostat treated groups compared to the allopurinol group in patients with renal impairment either defined by baseline serum creatinine or baseline calculated creatinine clearance (Table 1 and Table 2).

Table 1. Percentage with sUA below 0.36 mmol/l (6.0mg/dL) of patients with renal impairment defined by baseline serum creatinine

Table 3.3d Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Baseline Serum Creatinine - ITT Subjects (Phase 3 Pivotal Studies)

Baseline Serum Creatinine	Placebo		Febuxostat 80 mg QD[a,m]		Febuxostat 120 mg QD[a]		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
≤1.5 mg/dL	0/131	(0%)	257/506	(51%)	322/504	(64%)	88/127	(69%)	112/508	(22%)
>1.5 mg/dL	0/3	(0%)	5/11	(45%)	7/15	(47%)	4/7	(57%)	1/11	(9%)

Phase 3 pivotal studies included: C02-009 and C02-010.

a Statistically significant difference versus allopurinol 300/100 mg QD ($p \leq 0.05$) using a CMH test adjusting for subgroup and study.

m Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

Table 2. Percentage with sUA below 0.36 mmol/l (6.0mg/dL) of patients with renal impairment defined by baseline calculated creatinine clearance

Table 3.3e Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Baseline Calculated Creatinine Clearance - ITT Subjects (Phase 3 Pivotal Studies)

Baseline Calculated Creatinine Clearance	Placebo		Febuxostat 80 mg QD[a,#,m]		Febuxostat 120 mg QD[a]		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD[a]	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<50 mL/min	0/9	(0%)	19/28	(68%)	20/26	(77%)	8/14	(57%)	16/35	(46%)
50-<80 mL/min	0/36	(0%)	92/153	(60%)	102/157	(65%)	27/37	(73%)	43/145	(30%)
80-<120 mL/min	0/65	(0%)	122/261	(47%)	175/280	(63%)	48/68	(71%)	48/269	(18%)
≥120 mL/min	0/24	(0%)	29/75	(39%)	32/55	(58%)	9/15	(60%)	6/66	(9%)
Missing	0/0	--	0/0	--	0/1	(0%)	0/0	--	0/4	(0%)

Phase 3 pivotal studies included: C02-009 and C02-010.
Note: Baseline calculated Cl_{cr} was based on ideal body weight.
Statistical significant difference among subgroups within this treatment group (p≤0.05) using a CMH test adjusting for study.
a Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05) using a CMH test adjusting for subgroup and study.
m Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using a CMH test adjusting for subgroup and study.
Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

Source: Integrated efficacy report. Volume 164. September 2005 (IPSEN).

Long-term data in renal impaired patients

In the long-term phase 2 trial with febuxostat, 59% of patients enrolled had impaired renal function (serum creatinine >1.5 mg/dL or calculated creatinine clearance <80 mL/min).

- When outcome data were stratified based on baseline renal function, the proportion of patients achieving an sUA level of ≤0.36 mmol/l (6.0mg/dL) (360 µmol/L) was comparable between patients with normal renal function and those with impaired renal function.
- Across the visits (weeks 28, 52, 80, and 104), 75% to 81% of patients with impaired renal function had reductions in sUA levels to ≤0.36 mmol/l (6.0mg/dL), compared to 72% to 84% of patients with normal renal function (Ipsen TMX-01-005, 2004).
- Febuxostat was effective in patients with renal impairment and the results were sustained long-term.

Adverse events in renal impaired patients

There were no specific safety events observed in the subgroup of patients with renal impairment.

Conclusion on renal impairment

In conclusion, febuxostat can be safely used in gout patients with mild and moderate renal impairment (as suggested by the phase I trial data and confirmed by the clinical trial data). The superiority of febuxostat over allopurinol (300/100 mg) in decreasing sUA levels to ≤0.36 mmol/l (6.0mg/dL) has been sufficiently demonstrated in this patient subpopulation, particularly considering the lack of effective treatment alternatives.

Patients not adequately controlled on allopurinol

The only data that exist in the subgroup of patients not adequately controlled on allopurinol were for a subset of patients in the extension studies that began treatment with allopurinol and switched to febuxostat.

During the first 6 months of the long-term extension EXCEL study, it was possible to switch and/or titrate patients to the alternative treatment based on serum urate level, safety, and/or investigator discretion (after medical director approval) efficacy and tolerance.

- It was observed that 18% (54/299) of patients treated with febuxostat 80 mg, 8% (22/291) of patients treated with febuxostat 120 mg, and 57% (82/145) of patients treated with allopurinol 300 mg, were switched to another treatment due to lack of efficacy (sUA level of >0.36 mmol/l (6.0mg/dL)).
- Of the patients who switched from allopurinol to febuxostat, 67% (55/82) achieved a sUA level ≤0.36 mmol/l (6.0mg/dL). The corresponding data for all febuxostat 80 mg patients enrolled in the Phase III studies was 73%.
- By comparison, only 9% (2/22) of patients who were switched from febuxostat to allopurinol in the EXCEL study achieved a sUA level ≤0.36 mmol/l (6.0mg/dL).

The limited data available for the efficacy of febuxostat in allopurinol non-responders suggests that the efficacy of febuxostat in achieving an sUA level of ≤0.36 mmol/l (6.0mg/dL) is similar to that seen in the first-line treatment setting. This is unlike allopurinol which had a greatly reduced level of sUA control in the small proportion of patients who failed to gain adequate control on febuxostat.

Conclusion

In addition to the clinical value of febuxostat treatment in the overall population of patients suffering from gout, as evidenced through the improved control of sUA levels seen in the pivotal trials against allopurinol, febuxostat also has further advantages in certain patient subgroups.

The sUA control treatment effect of febuxostat can be clearly seen in patients with renal impairment, and has also been observed in patients who failed to achieve adequate control of their sUA levels on standard treatment with allopurinol.

It is clear that there are key categories of patients that cannot be sufficiently treated by allopurinol, or who will likely received sub-optimal dosing in clinical practice, and there is an acknowledged paucity of available treatment options for these patients.

IPSEN believe that febuxostat is a clear treatment option both for the overall gout population including specific patient groups who are unlikely to be suitable to continued treatment with allopurinol. Not recommending use of febuxostat would preclude all these patient subgroups with a very high unmet need from accessing febuxostat as an effective treatment in the absence of any real alternative.

ACD Paragraph 3.6

Results from the EXCEL extension study showed that more patients receiving febuxostat (80 mg/day or 120 mg/day) remained on initial treatment than among those receiving fixed-dose allopurinol (300 or 100 mg/day) after more than 24 months of follow-up. For each year of febuxostat treatment in the EXCEL trial, the number of gout flares decreased over time. However, the ERG considered that this evidence should be treated with caution, since statistical comparisons between treatment groups were not reported; nor were data provided on withdrawals due to gout flares, adverse events or non-response to treatment.

In the EXCEL study, the most common reason for switching medication was lack of efficacy. A greater percentage changed from allopurinol to febuxostat (57%) than from febuxostat to allopurinol (18% [80 mg], 8% [120 mg]) due to lack of efficacy i.e., sUA levels ≥ 0.36 mmol/l (6.0mg/dL) at 6 months (Becker et al., 2007a) (Figure 1).

In addition, a greater percentage of those who switched to febuxostat from allopurinol reached the sUA levels ≤ 0.36 mmol/l (6.0 mg/dL) at 6 months, than those switching to allopurinol from febuxostat (Figure 2). This demonstrates clearly that febuxostat has efficacy in both a first and second line use, unlike allopurinol which appears to have a poor efficacy in patients who have already failed on a prior ULT treatment, i.e. febuxostat.

Figure 1. Percentage of Patients Who Switched Treatment Due to Lack of Efficacy

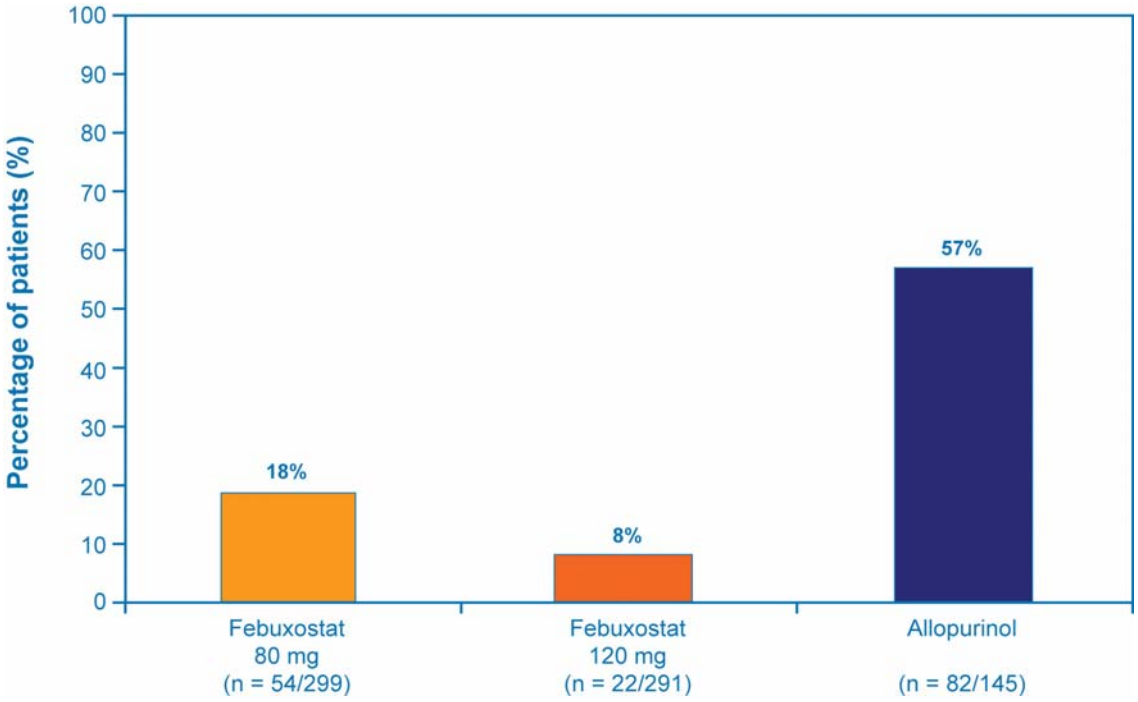
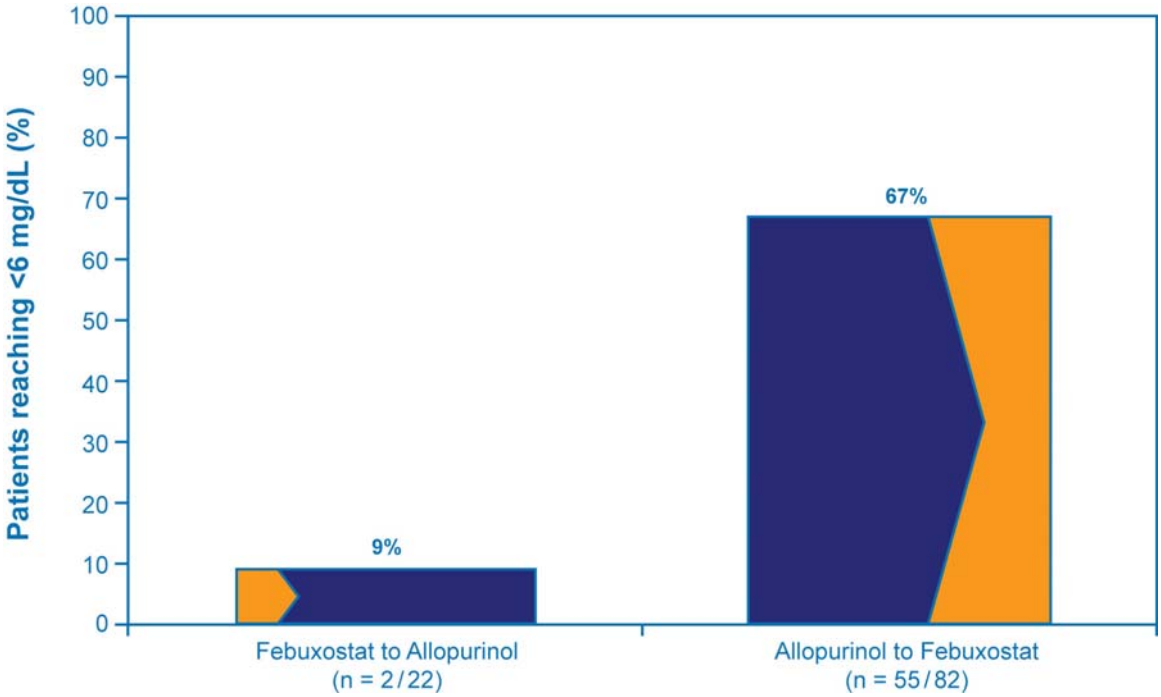


Figure 2. Percentage of Patients Who Switched Therapy Who Reached sUA Levels ≤0.36 mmol/l (6.0mg/dL)



More patients in the allopurinol group (62%) than in the febuxostat 80mg (32%) and febuxostat 120 mg (44%) groups were prematurely withdrawn from the EXCEL study. Data on withdrawals due to gout flares, adverse events and non-response to treatment are provided in Table 3 (Reproduced from Study C02-021, Final CSR, Table 10.1.a).

More patients in the febuxostat treatment groups than in the allopurinol treatment group were withdrawn from the study due to an adverse event (9%, 6% and 2% of patients for febuxostat 80 mg, 120 mg and allopurinol respectively).

More patients in the allopurinol group than in the febuxostat treatment groups were withdrawn from the study due to therapeutic failure (2%, 10% and 24% of patients for febuxostat 80 mg, 120 mg and allopurinol respectively).

Few patients were withdrawn due to gout flares in all study arms (0.3%, 0.8% and 0% of patients for febuxostat 80 mg, 120 mg and allopurinol respectively).

The majority of withdrawals in the EXCEL study occurred during the first year of the study.

Formal statistical comparisons between treatment groups were not possible in the EXCEL study, as patients whose sUA levels were ≥ 0.36 mmol/l (6.0mg/dL) after Month 6 of the study had to be withdrawn. The aim of EXCEL study was to evaluate safety in patients on long-term treatment. Per protocol, patients that did not reduce sUA below 0.36 mmol/l (6.0mg/dL) were removed from the study after 6 months and no further data are available for these patients.

Table 3. Timing and Reasons for Premature Discontinuation

Evaluation	Final Stable Treatment			All Subjects n (%)
	Febuxostat 80 mg n (%)	Febuxostat 120 mg n (%)	Allopurinol 300 mg n (%)	
Enrolled	606	388	92	1086
Prematurely Discontinued	194 (32.0)	171 (44.1)	57 (62.0)	422 (38.9)
Timing of Premature Discontinuation[a]				
Year 1	78 (12.9)	86 (22.2)	32 (34.8)	196 (18.0)
≤1 Month	11 (1.8)	9 (2.3)	3 (3.3)	23 (2.1)
1-2 Months	11 (1.8)	3 (0.8)	3 (3.3)	17 (1.6)
2-3 Months	5 (0.8)	7 (1.8)	3 (3.3)	15 (1.4)
3-6 Months	18 (3.0)	15 (3.9)	4 (4.3)	37 (3.4)
6-12 Months	33 (5.4)	52 (13.4)	19 (20.7)	104 (9.6)
Year 2	75 (12.4)	55 (14.2)	15 (16.3)	145 (13.4)
Year 3	41 (6.8)	30 (7.7)	10 (10.9)	81 (7.5)
Primary Reason for Premature Discontinuation				
Did Not Continue Under Amendment 4	1 (0.2)	1 (0.3)	2 (2.2)	4 (0.4)
Adverse Event	54 (8.9)	22 (5.7)	2 (2.2)	78 (7.2)
Protocol Violation	6 (1.0)	3 (0.8)	3 (3.3)	12 (1.1)
Personal Reason(s)	39 (6.4)	31 (8.0)	8 (8.7)	78 (7.2)
Lost to Follow-up[b]	42 (6.9)	39 (10.1)	9 (9.8)	90 (8.3)
Therapeutic Failure	10 (1.7)	38 (9.8)	22 (23.9)	70 (6.4)
Gout Flare	2 (0.3)	3 (0.8)	0	5 (0.5)
Other[c]	40 (6.6)	34 (8.8)	11 (12.0)	85 (7.8)

a The denominator is the number of subjects enrolled. A year is 365.25 days. A month is 30.44 days.

b Procedures for trying to contact subjects who were lost to follow-up included calling twice (documented in source documents) and sending a certified letter (proof of delivery kept on file). Attempts at contacting subjects were recorded as study notes when possible.

c Other reasons included: Site closure or other administrative issues (30 subjects), withdrawn consent (18 subjects), noncompliance (21 subjects), principal investigator or sponsor request (3 subjects), subject moving or traveling (3 subjects), subject chose not to continue with implementation of Amendment 3 or 4 (4 subjects), uncontrolled sUA (3 subjects), abnormal labs in C02-009, started another trial, started taking Celebrex, and chronic dietary indiscretions (1 subject each). One additional subject cited both moving and withdrawn consent as reasons for discontinuation, and one subject was discontinued both due to noncompliance and principal investigator request.

Cross-references: Statistical Table 14.1.2 and Appendices 16.2.1.1 and 16.2.8.5

(Reproduced from Study C02-021, Final CSR, Table 10.1.a)

ACD Paragraph 3.7

The ERG considered that the evidence presented in support of the clinical effectiveness of febuxostat in comparison with allopurinol may not be adequate. This is because guidelines for gout management by the British Society of Rheumatology and British Health Professionals in Rheumatology (BSR) and the European League Against Rheumatism (EULAR), and the SPC for allopurinol, recommend dose titration for allopurinol according to therapeutic targets. It is possible that dose-titrated allopurinol may be more effective than fixed-dose allopurinol, and that the additional clinical benefits of febuxostat may not be as great in **routine practice** as is suggested by the results from RCT comparisons with fixed-dose allopurinol. However, the ERG noted that dose titration of allopurinol is rarely carried out in routine clinical practice.

A systematic review recently conducted for IPSEN has not identified any evidence from randomised controlled trials that provides a clear demonstration that dose-titrated allopurinol is more effective than fixed-dose allopurinol in the control of sUA levels and the symptoms of gout.

Furthermore, allopurinol 300 mg is the most typical daily dose and treatment for gout in the UK, and represents current routine practice. Data from epidemiological studies, including very recent studies suggest that the 300 mg dose (or lower) is the most commonly used allopurinol dose both in the United States (Sarawate et al, 2006) and in Europe (Annemans et al, 2007).

- Allopurinol was prescribed at a daily dose of 300 mg or less in 98% of gout allopurinol-treated patients in the UK, and in 96% of patients in Germany (Annemans et al, 2007).
- In the US, only 2.9 % of adult gout patients evaluated in a managed care situation and who were taking allopurinol received doses >300 mg/day (Sarawate et al, 2006).
- Hoskison and Wortmann, (2007) also recognized that the most prescribed dose of allopurinol is 300 mg/day.
- In a retrospective study Li-Yu, reported that only 4 out of 57 patients had their allopurinol dose increased to over 300 mg QD and to a limit of 600 mg QD at one point, but not throughout the duration of the course of their disease (Li-Yu et al, 2001).
- In the IMS observational study (UK, Germany, France), only 6.2% of the patients were prescribed allopurinol >300mg.

Within the STA submission it is clear from the NICE guidelines that the obligation of the manufacturer is to make a direct or indirect comparison of the clinical and economic effectiveness of the new treatment against current routine clinical practice (even if this is an off-label use of the treatment).

> *"An STA typically compares the licensed use of a health technology with current standard treatment in the NHS in England and Wales. The Institute will develop a scope for the STA in consultation with consultees and commentators. The Institute's approach to scoping is outlined in 'Guide to the technology appraisal process' (section 3). Unless the Department of Health indicates otherwise, recommendations will not be made on unlicensed indications for the product being appraised."* Guide to the NICE single technology appraisal process; September 2006

The NICE Guide to Methods of Technology Appraisal section 2.2.3 states *"All relevant comparators are identified, with consideration given to current practice and the natural history of the condition without suitable treatment. Although best alternative care is the essential comparator, treatments representing routine UK care are also important where they differ from best alternative care."*

Following NICE guidance indicating that treatment has to be compared with routine practice, IPSEN has provided comparative data between febuxostat and allopurinol 300mg.

It is correct that the clinical guidelines make reference to both the titration and fixed-dose formulations of allopurinol for the treatment of gout. However, the situation in terms of comparability of treatment effect is absolutely unclear due to a complete lack of comparative clinical data. Although the clinical guidelines have identified that allopurinol may need to be titrated to higher doses to achieve a clinical effect, there are many safety and treatment compliance reasons that mean this approach is very seldom a possibility for patients. There is also no evidenced based data to support either efficacy or safety on higher doses of allopurinol.

The EULAR guidelines confirm this in the statement that "the titration-dose regimen may provide advantages over a fixed-dose regimen; however, formal comparison between the two regimens has not been undertaken".

The EULAR recommendation states the following, regarding to titration of allopurinol: “Allopurinol is an appropriate long-term urate lowering therapy. It should be started at a low dose (e.g., 100mg daily) and increased by 100 mg every 2-4 weeks if required. The dose must be adjusted in those with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent or allopurinol desensitisation (the latter only in cases of mild rash).”

Although the BSR guidelines recommend the titration of allopurinol and higher doses, with a maximum dose of 900 mg, in order to counteract the limited efficacy observed for allopurinol, they do not identify or provide any evidence for superior efficacy of higher doses. The BSR guidelines state that “the usual dose of allopurinol is 200-300 mg daily when creatinine clearance level is >80 ml/min, and lower doses should be used below this creatinine clearance level”. A significant proportion of gout patients have some degree of renal impairment (35% in the pivotal studies).

Therefore, it is expected that allopurinol doses will be capped at 300 mg or below in a significant proportion of gout patients. Consequently, little experience has been gained on the clinical use of doses of allopurinol higher than 300 mg, and it is therefore very unlikely that physicians will use higher allopurinol doses than the conventional dose. In addition, the possible side effects of allopurinol listed in the BSR guidelines include “transient rashes which usually respond to reduction in dose, especially in those with impaired renal function such as the elderly”.

Interestingly, the BSR guidelines reference data from the FACT clinical study (Becker NEJM 2005) for the efficacy of allopurinol, presumably because there is so little comparative trial data evaluating the efficacy of allopurinol in either its fixed or titrated dose regimen.

Therefore, from an evidence based medicine perspective, dose-titrated allopurinol has not been proven to be more effective than fixed-dose allopurinol. Furthermore, a systematic review revealed that comparative safety of dose-titrated and fixed-dose allopurinol has not been formally investigated in a randomised trial setting or sufficiently evaluated using other study designs.

Dose titration of allopurinol may be unattractive from the perspective of avoiding adverse effects, which is likely why doses of >300 mg are rarely used. The side-effects of allopurinol are likely to be dose-related (Mac Innes et al., 1981).

Conclusion

In summary, from an evidence based medicine perspective, dose-titrated allopurinol has not been proven to be more effective than fixed-dose allopurinol, its safety has not been formally investigated in a randomised trial setting, and doses higher than 300mg are rarely used in clinical practice due to safety considerations (e.g., heightened potential for allopurinol hypersensitivity reactions at higher doses; problems in using higher doses in renally impaired patients) and the prevalence of renal impairment.

We therefore assert that there is substantive evidence that fixed dose allopurinol (i.e., 300 mg) is the appropriate comparator for febuxostat reflecting routine practice for urate lowering therapy. Therefore the conclusions drawn from the pivotal studies can be extended to UK clinical practice, indicating that the proportion of patients reaching a therapeutic target of ≤ 0.36 mmol/l (6.0mg/dL) is 2 to 3 fold higher with febuxostat than with allopurinol.

ACD Paragraph 3.8

The ERG expressed concerns about the analysis of clinical efficacy based on pooling data across trials because this approach fails to preserve randomisation in the RCT evidence, which may introduce bias. The ERG carried out a corrected meta-analysis (based on both fixed- and random-effects modelling) using the RCT data and evidence presented by the manufacturer.

The rationale for presenting a pooled analysis rather than a meta-analysis has been outlined in the response to question B3 of the manufacturer response to clarification letter (Feb 2008).The following provides additional rationale to address specific concerns raised:

- The approach taken does not introduce bias as the analysis uses a CMH test stratified by study. Therefore any bias and confounding in the analysis by pooling data from the two-studies is accounted for by stratifying the analysis by study.

- The randomisation is still preserved in the pooled analysis, since both studies included are randomised clinical trails. By pooling the data from the two trials the fact that they were still randomised remains unaffected and any differences between studies were accounted for in the analysis by stratifying by study.

- Also, for all the primary and secondary endpoints, the pooled results were similar to those obtained in the separate analyses of each study. The meta-analysis also produced similar conclusions to the pooled analysis, therefore the choice of statistical approach in this case does not affect the conclusions which are drawn from the data.

ACD Paragraph 3.12

The ERG noted a number of areas of uncertainty around the cost-effectiveness analyses undertaken in the manufacturer's submission. The ERG noted that the natural history of hyperuricaemic patients with gout who did not receive treatment was not modeled, and hence no inference could be made as to the cost-effectiveness of febuxostat in comparison with no treatment. The ERG requested that a sequence of strategies where patients progress to an alternative intervention (allopurinol, febuxostat or no treatment) following lack of response should be evaluated. The manufacturer declined the request, arguing that estimation of a sequential strategy was not feasible because of a lack of clinical data. In addition the manufacturer argued that it was unethical to consider febuxostat as second-line therapy when it is cost-effective as first-line therapy, and that the only appropriate comparison was that investigated in the pivotal RCTs; that is, at first-line therapy. The ERG asserted that appropriate modelling assumptions could have been made to allow some exploratory analysis.

Available data on natural history and response

From a natural history perspective the best data that we have available on sUA based treatment response comes from the randomised placebo arm of the APEX clinical trial, which compared against febuxostat and allopurinol. In this case the data is very clear indeed, that patients with gout and treated with placebo can be expected to have a zero level of treatment response, when response is defined as the proportion of patients who can achieve an sUA level of ≤0.36 mmol/l (6.0mg/dL).

- Patients in APEX had a mean baseline sUA level of 9.80 mg/dL.
- No placebo patients in APEX had a decrease of sUA below 0.36 mmol/l (6.0mg/dL) at the last 3 consecutive visits.
- The APEX trial data demonstrated that a mean change in sUA level was -3.58 % (actual value of 9.45 mg/dL at final visit). However, 63% of patients remained in the 8 mg/dL < sUA ≤ 10 mg/dL range, and the remaining 37% of patients actually progressed to a higher level of sUA, and became at a great risk of gout flares and other chronic gout-related symptoms.

- The mean change in sUA level was -3.58 % (actual value of 9.45 mg/dL at final visit).

It is therefore expected that the natural history of patients with gout is that they would continue to experience gout flares and would not experience a decrease in tophi size when their sUA levels had not fallen below the target sUA level. The long-term follow-up of untreated patients with gout and persistent, long-term hyperuricaemia demonstrates that severe tophaceous gout will develop, and almost double in its prevalence from 30- 60% after 5-10 years of follow-up post the onset of gout symptoms (Gutman, 1973).

A set of Number Needed to Treat (NNT) analysis has also been conducted against placebo for the APEX clinical study. In this case the primary clinical endpoint was the likelihood of achieving an sUA level ≤ 0.36 mmol/l (6.0mg/dL) for three consecutive visits. The NNT was 2.1 for febuxostat 80mg vs placebo and 1.5 for febuxostat 120mg vs placebo.

Placebo data in the economic model

In the submitted economic model the primary comparison for febuxostat was set to current active clinical treatment based on fixed-dose allopurinol at 300mg. A placebo arm / natural history was not included in the model as it was felt not a viable treatment option to leave patients untreated in the first-line indication.

The natural history of disease was indeed not modeled:

- The analysis focused on the treatment most likely to be replaced based on the indications of febuxostat in the marketing authorization. In view of the above provided information, allopurinol is the most likely to be replaced.

- Treatment with allopurinol is considered as current “golden standard”, and therefore the key comparator in the health economic evaluation. Patients with clinical gout who present at a physician will most often be prescribed to allopurinol; no treatment will be rarely indicated. Patients who succeed to reduce their sUA level without medical treatment (e.g. by changing their lifestyle habits: diet, reducing alcohol consumption etc) will not be prescribed allopurinol either; therefore a comparison of febuxostat versus no treatment seems inappropriate.

- Modeling was based on the clinical trial data, comparing allopurinol with febuxostat.

- Lack of data on patients without treatment: one could assume that the sUA level of patients without treatment would remain constant over a time horizon of 1 year. However, NICE also requests a life time horizon; the evolution of the sUA level in untreated patients over a life time perspective is unknown.

An exploratory analysis has been conducted to now include the outcomes for a placebo arm within the current model, in order to make direct comparisons against febuxostat, and to understand the baseline costs and outcomes for untreated patients. Parameters for the placebo arm from the APEX study used to estimate the cost and utility of no treatment are provided in Table 4. The base case parameters were used for febuxostat (Section 5 in the STA).

This analysis does not account for the longer term progression of disease with no treatment mentioned above (Gutman, 1973).

Table 4. Parameters used to estimate costs and QALY of no treatment

Parameter	Value
Unit cost placebo	£0.00
Proportions sUA levels Placebo	
sUA ≤ 0.36 mmol/l (6.0mg/dL)	0
6.0 mg/dL > sUA ≤ 8.0 mg/dL	0
8.0 mg/dL > sUA ≤ 10.0 mg/dL	0.634328
sUA >10.0 mg/dL	0.365672

Note: The proportion of sUA levels are calculated from placebo baseline sUA assuming all patients followed inclusion criteria sUA ≥8.0mg/dL in the APEX study (C02-009) (Table 3.1 e Integrated Summary of Efficacy).

Since flare prophylaxis will not be applied in the placebo setting, (6 month prophylaxis resulting in 78% flare reduction), flare reduction of 78% during the first 3 months was only applied to the febuxostat treated group of patients and not to the untreated patients. On the other hand, in the treated group of patients, an additional cost of flare prophylaxis (£87.66) was added to the treatment costs (1mg colchicine/day at £0,48/mg). The results of the analyses found that febuxostat was cost-effective with an ICER of £3,727 (Table 5).

Table 5. Cost-effectiveness of febuxostat (80 mg and 120 mg) against no treatment.

	Total Cost (£)	Incremental cost (£)	QALY	QALYG	ICER (£/QALYG)
24 months after treatment initiation					
Febuxostat (80mg + 120mg pooled)	3,233	549	1.430	0.147	3,727
Placebo	2,684		1.282		

Sequential Treatment Modelling

The ACD raises the issue of an economic model based on sequential treatment sequences for managing gout, in which patients who fail to gain a response move onto a next level of therapy (i.e. a model incorporating a 1st line, 2nd line and subsequent treatment or no treatment option).

The original model was developed as a first-line treatment comparison versus allopurinol as this was felt to the primary comparator, based on standard UK clinical practice. The placebo analysis reported above helps to look at the costs and benefits of febuxostat when no other treatment option is available (i.e. if they are contraindicated for allopurinol or if allopurinol had failed to control sUA below the saturation point). Data are available from the APEX and FACT studies that show a similar clinical effect for febuxostat in allopurinol failure patients than seen in first-line treatment.

Conclusion

The issue with developing a sequential treatment model was the lack of good quality data for treatment effect based on prior treatment, and the fact that the clinical trial data is predominantly a first-line treatment comparison. Although this has been raised as an issue in the initial ERG comments and the ACD it is not possible to utilise the current economic model to generate this type of comparison within the available timeframe of the NICE STA review.

ACD Paragraph 3.13

The ERG noted that no data were provided on the likely serum uric acid concentration of patients who receive no treatment, and that the model assumes full treatment adherence and usage over the time horizon modelled. However, evidence from the FACT and APEX trials showed that treatment continuation rates were lower for febuxostat than for allopurinol. Contradictory evidence from the open-label EXCEL trial reports gave treatment continuation rates of 35% for 80 mg daily febuxostat, 10% for 120 mg daily febuxostat but only 5% for allopurinol. Additional evidence presented by the manufacturer suggested that in a randomised subset of the EXCEL trial, 76% of patients receiving 80 mg/day febuxostat, 71% of patients receiving 120 mg/day febuxostat and 40% of patients receiving allopurinol remained on initial treatment after more than 24 months. The ERG stated that the lack of data on the likely serum uric acid concentrations of patients who receive no treatment made it difficult to accurately account for treatment discontinuation rates in the manufacturer's economic model. An assumption of full treatment adherence and usage over the time horizon could potentially bias the economic results in favour of febuxostat.

The ACD highlights a possible contradiction in terms of drop-out rates between the shorter-term pivotal clinical trials (APEX and FACT) and the long-term extension study (EXCEL) in which treatment switching was allowed to the alternative treatment arm once a lack of efficacy was present.

This effect is explained by the initial flare effect that is seen with all treatments, and which is higher for treatments of greater efficacy – rapid changes in sUA levels (increases or decreases) will induce flare events early in the treatment. For this reason, febuxostat had a higher incidence of discontinuation over the first 6-12 month of treatment, in particular for the 120mg dose (this is the rationale for the recommendation of an 80mg start dose, which will be sufficient for the majority of patients). In the long-term extension, the sUA levels were stabilised and maintained over the longer term, the induction flare effect was no longer present and patients were also allowed to switch treatment after 6-months. More patients were seen to withdraw on allopurinol then with febuxostat, supporting further the high efficacy of febuxostat.

The ACD and ERG reports raise the issue of an alternative modeling approach for gout based on a treatment sequence framework (1st, 2nd line etc) and also the inclusion of treatment drop-out rates to drive these switches of treatment. Also, as part of this approach, they recommend that phases of 'no treatment' be

included into the model to allow for patients who move through all the limited treatment options.

The current model does not allow for discontinuation of therapy over the short term, and is not easily adapted to do so. This was why the time horizon of the model was limited to 1-year and 2-year in the primary analyses. The approach taken was that the recommendation for chronic-treatment would imply a high level of adherence.

Full treatment adherence was applied in the model, since there were no data available (in the databases we received from the FACT and APEX trial) on how patients evolve after treatment discontinuation.

It should however be noted that full adherence also implies a constant treatment cost over the entire time horizon, which is much higher for febuxostat than for allopurinol. Treatment discontinuation will therefore not solely decrease effectiveness on an ITT basis, but will also substantially decrease the costs.

IPSEN agree that a treatment sequence and life-time modeling approach is a valid alternative that could be adopted to further consider the economic profile of both 1st line and 2nd line treatments for gout. Further, IPSEN would be prepared to develop such a model if it was felt to provide additional value to NICE in the consideration of febuxostat, and NICE could confirm that such a model would add to the decision making process, despite the paucity of data on alternative comparators. There are a number of practical issues that this raises with respect to a new model approach and the current ACD and STA process;

- Firstly, this type of model would almost certainly require a Markov health state structure, as opposed to the decision tree calculations in the existing model. This would require enough development time to re-design to the existing model.

- Secondly, the model would also require a wider review of the natural history data for gout, in order to allow the time horizon of the model to be extended out to a life-time horizon. Also, such a model would provide an opportunity to include non-flare symptoms, such as tophi, which would be applicable over the longer term and may be linked statistically to sUA levels.

- Due to the lack of hard data on 2nd line treatments, such a model would require a number of assumptions to be developed covering issues such as timing of switch from allopurinol to febuxostat, head-to-head or indirect comparisons with other second-line treatment options (e.g. no treatment, remaining on allopurinol, switching to other treatments). The assumptions on the effectiveness of febuxostat in allopurinol “non-responders”, effectiveness of allopurinol in febuxostat “non-responders” could be based on the long term extension study results.

- Finally, there is also no data to our knowledge on the likely level of compliance for allopurinol or febuxostat in actual clinical practice (outside of clinical trials), in particular that included the effects of the latest recommendation for 6-months of prophylaxis treatment for the flare induction effect.

The development time necessary to design, construct and populate such a model, to the necessary level of complexity and flexibility, and to fully document this is well outside of the time available to IPSEN following the initial ERG comments and the current ACD document and review period. Our current estimate is that this work would require 4- to 6-months to complete, dependent of the availability of cost and effectiveness data.

IPSEN would therefore welcome comment from NICE on the potential value to them of such a model once developed.

ACD Paragraph 3.14

The ERG noted that in the manufacturer's economic model, data on the number of gout flares within the initial 3 months of treatment were taken from the pooled analysis of the results from the APEX trials. The flare rates were reduced by 78% by assuming that patients received 3 months of colchicine prophylaxis. However, this reduction may be an overestimate, since in the APEX and FACT trials colchicine prophylaxis was given for only 8 weeks. After the first 3 months of treatment, the proportion of gout flares was assumed to be related to serum uric acid concentration on the basis of a multivariate analysis of data provided in confidence by the manufacturer. The significance of the correlation between serum uric acid concentration and the number of gout flares disappears in the manufacturer's 'multivariate analysis' when other significant covariates are included. However, the manufacturer's 'multivariate analysis' appears to be the same as a bivariate analysis of the relationship between serum uric acid concentration and the odds of gout flares occurring (the p values for both analyses were identical). The ERG argued that a proper multivariate analysis, in which a backward stepwise analysis is carried out, should be presented. The ERG further expressed concerns about discarded data points from the datasets used in the analysis showing a relationship between serum uric acid concentration and gout flares. The ERG stated that a relationship, not necessarily linear, between serum uric acid concentration and number of gout flares may still be found with more appropriate analysis and larger or different datasets.

Extended flare prophylaxis

In clinical studies, where an increase of gout flares was reported at initiation of treatment, the prophylaxis was only 8 weeks for all treatment groups. The SmPC for febuxostat recommends a 6-months prophylaxis in line with EULAR recommendation and the Borstadt et al 2004 study.

IPSEN has performed two types of economic modeling.

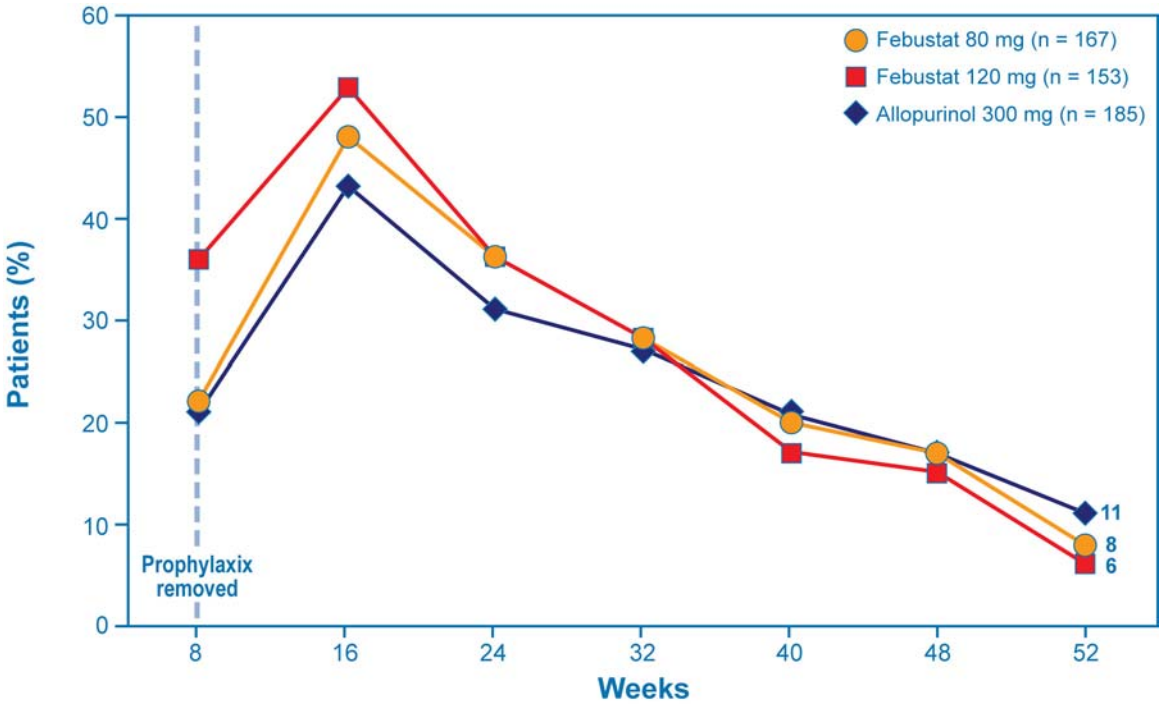
- The first model includes 2 months (8 weeks) prophylaxis, and
- The second model includes a longer extended prophylaxis.

The model was divided into 1-3 months and 4-12 months time periods and was populated with data from APEX and FACT which used 8-week of prophylactic treatment. As the majority of flares occur when the flare prophylactic treatment is discontinued (Figure 3) after 2 months, and as the latest recommendation is for

extended prophylaxis treatment, an algorithm was added to the model to estimate the reduction of flare rates with a longer time period of prophylaxis. The 78% reduction in initial flaring is based on the Borstadt study (Borstadt et al 2004), the key reference in the literature evidencing and quantifying the reduction of gout flares at initiation with 6-months prophylaxis. Importantly, both models (2-months and extended prophylaxis) show cost-effectiveness.

A sensitivity analysis varying the percentage of additional flare reduction due to extended flare prophylaxis (ranging from 0% to 100% produced an ICER ranging between £14,725 and £18,826). This showed the model is moderately sensitive to the flare prophylaxis algorithm, but Ipsen would like to highlight that even without this assumption the ICER was below £20,000.

Figure 3. FACT study: percentage of patients requiring treatment for a gout flare over 52 weeks



Sources: Becker et al., 2005a[1]; Ipsen, C02-010, 2004[3]
STA p. 67

Linear / Non-linear relationship between flare rates and urate levels

Clinical studies have demonstrated that, in patients with gout, an increasing sUA level correlates to increasing incidence of adverse health outcomes, including number of gout flares and development of painful and debilitating tophi (Zhang et al., 2006b; Thompson et al., 1962). The relationship between reduction of sUA

concentration and the reduction in risk of recurrent gout attacks has been demonstrated as clinically significant in a retrospective study of 267 patients who had experienced at least one gout attack and were receiving ULT (Shoji et al., 2004). Figure 7 shows that at sUA levels ranging from 7.5-9.5 mg/dL, the incidence of experiencing gout flare(s) ranges from 40% to over 80%, whereas the incidence of gout flares is under 20% for those patients maintained at or below recommended sUA levels.

NICE incorrectly refers to a linear correlation between sUA level and number of flares. For examining the impact of sUA level on flare frequency, a 2-step approach was applied:

The model applies a monthly number of flares in each of the 4 predefined sUA levels:

- ≤ 6.0 mg/dl
- > 6.0 mg/dl and ≤ 8.0 mg/dl
- > 8.0 mg/dl and ≤ 10.0 mg/dl
- > 10.0 mg/dl

These estimates of monthly number of flares were based on an observational study in gout patients in the UK, Germany and France (IMS report). A two-phase approach was applied:

(1) First, we determined the impact of sUA level on the odds of experiencing flares (cfr. Sarawate et al. 2006; Shoji et al.2004). We applied logistic regression, which is per definition a non-linear relationship, and is similar to the technique described in the papers. We observed a relationship with sUA.

(2) Second, within the group of patients that experienced a flare, we examined whether increasing sUA level was associated with the log10 transformed yearly number of flares (also a non-linear relationship). We could not detect a significant relationship. Log transformation was performed because yearly number of flares was not normally distributed.

The monthly number of flares figures applied in the model for each of the 4 sUA levels is the multiplication of the proportion of patients with flares (1) with the monthly number of flares (2).

Neither of the 2 applied statistical techniques for estimating these parameters (1) and (2) for calculating the monthly number of flares were based on a linear relationship. This is further explained in detail below (sub-section 1 and sub-section 2).

Moreover, 2 papers were identified in which the relationship between sUA level and probability of experiencing flares were assessed, using the same statistical technique of logistic regression. Both papers report a significant risk of experiencing flares with increased sUA, confirming the findings of the IMS observational study. Although the classification in sUA levels was not identical, the impact of applying the estimates from the peer reviewed papers in the health economic model was assessed. It appeared that the outcomes are similar, and even a lower ICER was obtained with one of the published data. This is further explained in sub-section 3.

Sub-section 1. Logistic regression for estimating the proportion of patients that experienced ≥ 1 flare

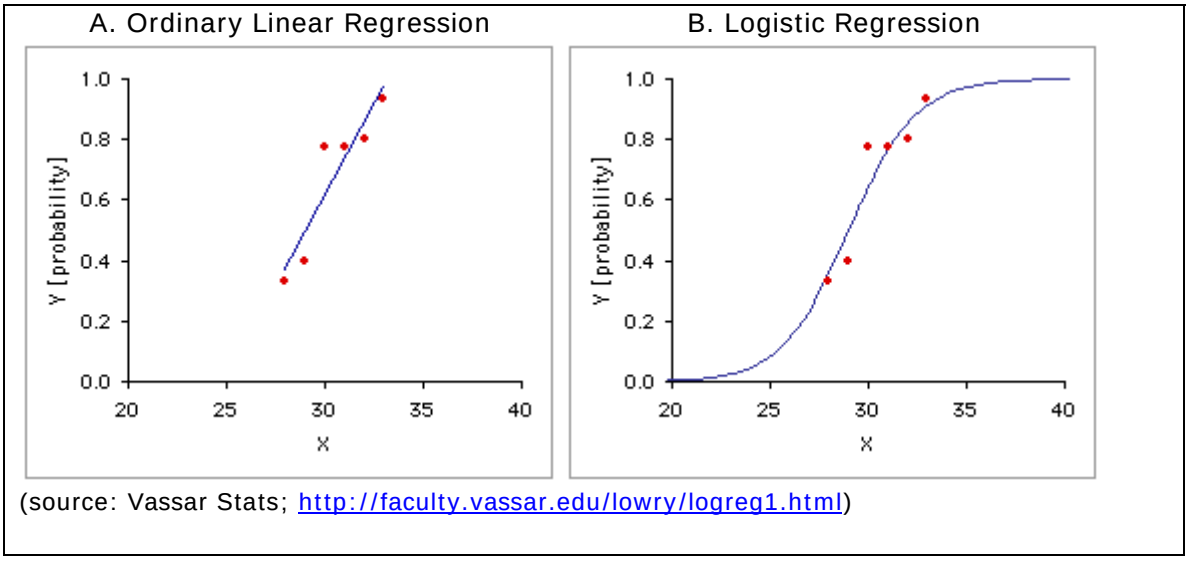
For this step, patients (N=230) were classified in 2 groups:

- Patients who experienced ≥ 1 flare during the observation period (N=155).
- Patients who did not experience flares during the observation period (N=75).

Logistic regression was applied in order to estimate the effect of sUA level on the odds of experiencing flares. These odds were recalculated to probabilities.

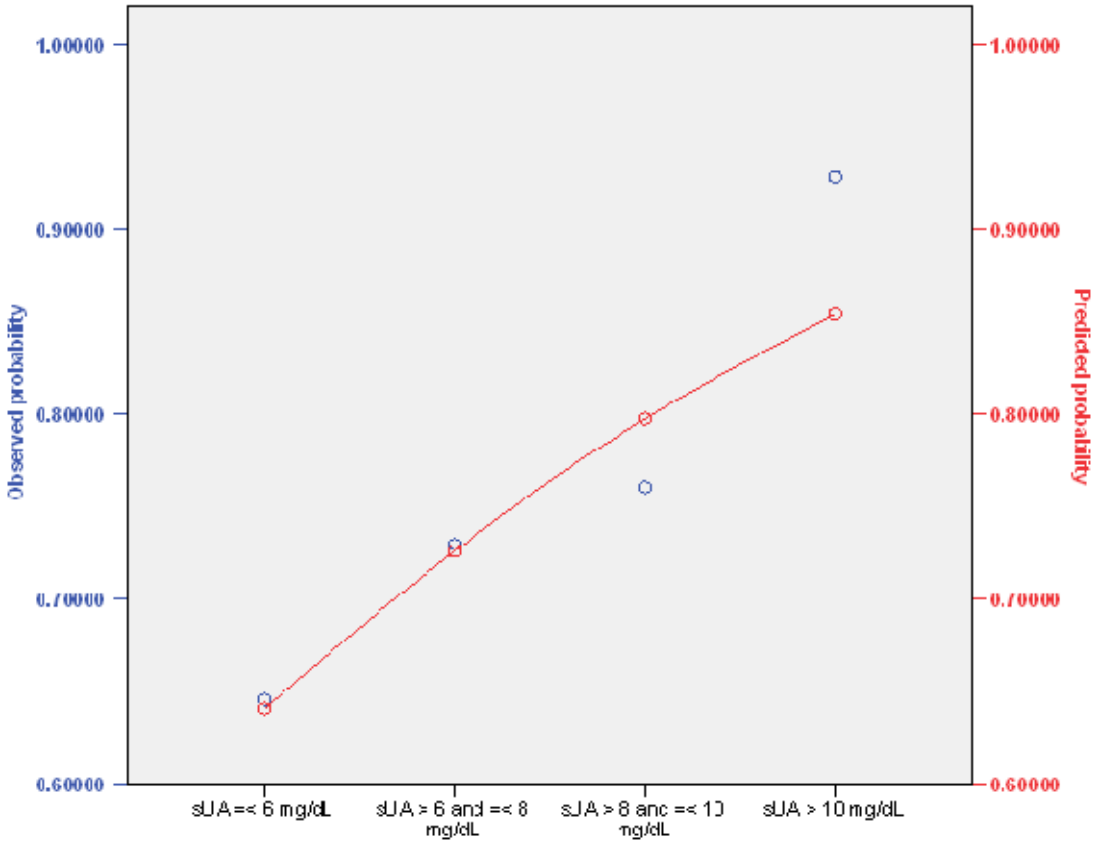
Logistic regression applies a logit function of the probability. Per definition, this logit function is non-linear, but has a typical S-shape, since probabilities should remain between 0 and 1. The difference between a linear relationship and the logistic regression relationship is shown in Figure 4 and Figure 5, the non-linear relationship between sUA level and probability of experiencing flares, as estimated by the IMS observational study, is graphically displayed.

Figure 4: Example of difference between linear relationship and logistic regression



(source: Vassar Stats; http://faculty.vassar.edu/lowry/logreg1.html)

Figure 5: Logistic curve estimate of the probability of experiencing flares for the 4 sUA levels – IMS observational study (blue bullets: observed probabilities; red line: predicted probabilities applied in the health economic model)



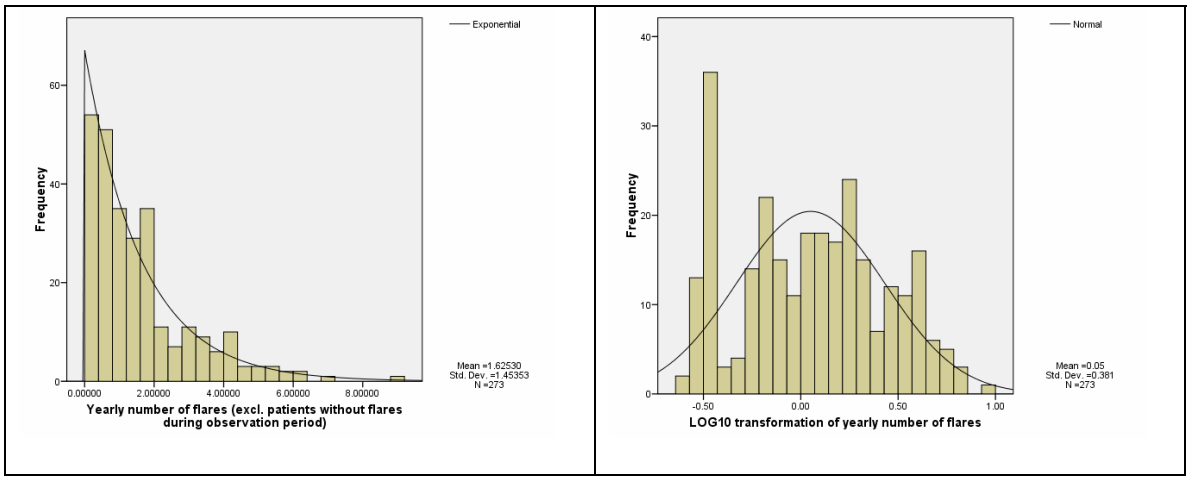
Sub-section 2. Regression for estimating the number of flares in patients who experienced flare(s).

It was observed that the distribution of the yearly number of flares (in patients who experienced flares; N=155) was skewed and tended to be exponential. For that reason the number of flares was $\log_{10}$ transformed (Figure 6). It is therefore not correct to state that a linear relationship is applied.

It appeared from the analyses on the log-transformed variable that the yearly number of flares in the subgroup of patients who experienced at least 1 flare was not significantly influenced by sUA level. Therefore, the general estimate, irrespective of sUA level, was applied.

The yearly number of flares in the population that experienced flares (N=155) was recalculated to a monthly number of flares (dividing by 12). This value was used for calculating the monthly number of flares in the overall population including patients who did not experience flares (N= 230). As mentioned above, this was performed by multiplying the probability for experiencing ≥1 flare (for each of the 4 sUA levels) with the monthly number of flares estimated in the population that experienced flares.

Figure 6: Distribution of the yearly number of flares in patients who experienced flares – IMS observational study (left: untransformed; right: $\log_{10}$ transformed)



Sub-section 3. Sensitivity analysis: estimated ICER based on 2 published papers

Two published papers report in the relationship between sUA level and the probability of experiencing flares. As an additional sensitivity analyses, these probabilities were applied for calculating the monthly number of flares in the model. The ICERs obtained in these sensitivity analyses are comparable to the ones of the original model.

Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum. 2004 Jun 15;51(3):321-5.

The association between sUA level and the probability of experiencing flares is graphically displayed in Figure 7. From this figure, probabilities for the 4 sUA levels in the febuxostat economic model were estimated:

- ≤ 6.0 mg/dL – logistic predicted curve estimate at sUA 5.5 mg/dl: 13%

  Monthly number of flares applied in the model: 0.0176

- > 6.0 and ≤ 8.0 mg/dL – logistic predicted curve estimate at sUA 7.0 mg/dl: 35%

  Monthly number of flares applied in the model: 0.0474

- > 8.0 and ≤ 10.0 mg/dL – logistic predicted curve estimate at sUA 9.0 mg/dl: 74%

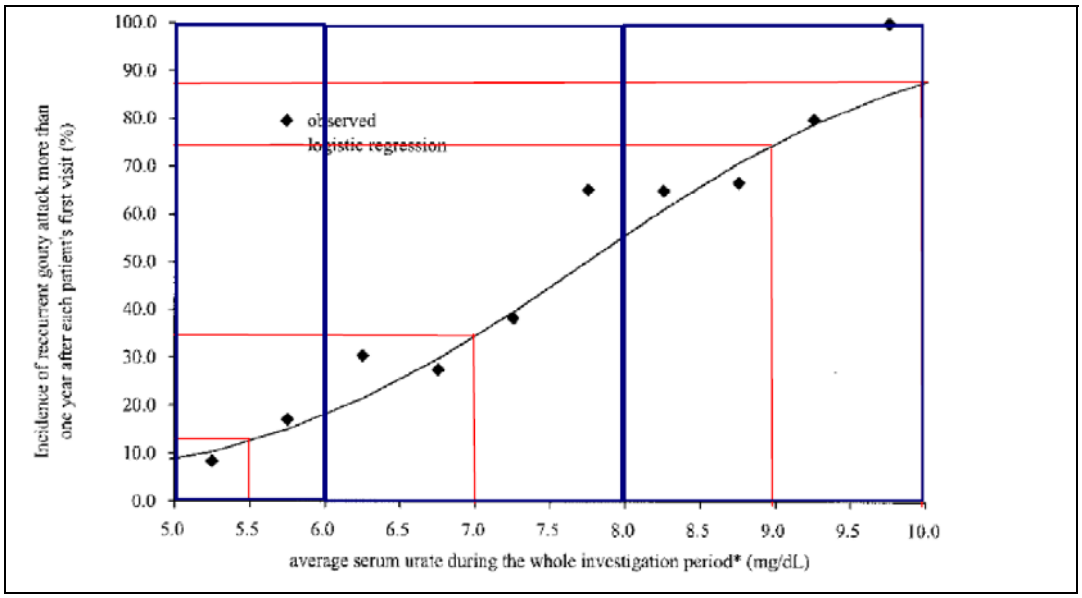
  Monthly number of flares applied in the model: 0.1002

- > 10.0 mg/dL – logistic predicted curve estimate at sUA of 10.0 mg/dl: 88%

  Monthly number of flares applied in the model: 0.1192

Based on these data, the ICER at 12 months is €15,050/QALY (compared to €16,574/QALY in the original model), and the ICER at 24 months is €13,336/QALY (compared to €15,565/QALY in the original model)

Figure 7: Relationship between sUA level and probability of experiencing flares – Shoji et al. study



Sarawate CA, Patel PA, Schumacher HR, Yang W, Brewer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheumatol. 2006 Apr;12(2):61-5.

In this paper, the reported proportions of patients in 3 sUA levels are:

- ≤ 6.0 mg/dL : 23%

  Monthly number of flares applied in the model: 0.0312

- > 6.0 and ≤ 8.0 mg/dL : 33%

  Monthly number of flares applied in the model: 0.0447

- > 8.0 mg/dL : 45%

  Monthly number of flares applied in the model for > 8.0 and ≤ 10.0 mg/dL: 0.0609

  Monthly number of flares applied in the model for > 10.0 mg/dL: 0.0609

Based on these data, the ICER at 12 months is €17,412/QALY (compared to €16,574/QALY in the original model), and the ICER at 24 months is €15,775/QALY (compared to €15,565/QALY in the original model).

Multivariate vs Bivariate

In the multivariate analysis, sUA was fixed as a constant (since reducing sUA was the only observed effect in the clinical trial, which could not demonstrate a significant reduction in flares). Therefore, the results of the bivariate analysis are the same as the results of the multivariate analysis.

ACD Paragraph 3.15

The ERG noted that the relationship between serum uric acid concentration and the expected number of gout flares (with a 'chronic utility gain' associated with lower serum uric acid concentrations and decreased utility associated with gout flares) is a key driver of the economic results presented by the manufacturer. Therefore uncertainty about this relationship translates into uncertainty about the ICER estimates presented by the manufacturer. The ERG considered that this uncertainty has not been adequately investigated. In an exploratory analysis provided by the ERG, removing the 'chronic utility gain' associated with lower serum uric acid concentrations, the base case ICER increased to £81,000 per QALY over a 2-year time horizon. A similar analysis over a 1-year time horizon gave an ICER of £696,000 per QALY and over a 5-year time horizon, the analysis gave an ICER of £150,000 per QALY.

Incorrect assessment of the relationship between flares and sUA chronic utility

As indicated previously, it is incorrect to state that the chronic utility gain incorporates the relationship between sUA level and the number of flares. It is therefore not correct to remove the 'chronic utility gain' for estimating the impact of the uncertainty around relationship between sUA concentration and the expected number of gout flares.

The two parameters are considered independently in the model:

- impact of sUA level on number of flares (and associated disutility)
- impact of sUA level on utility in absence of flares. (called chronic utility gain)

Removing the chronic utility gain from the model does not provide any insight on whatsoever on the impact of the uncertainty around the number of flares. The exploratory analysis does not therefore address the issues raised by ERG.

We performed an analysis in which the number of flares was assumed to be independent of sUA level (so number of flares identical in all 4 sUA levels):

- Over 1-year time horizon: £18,156
- Over 2-year time horizon: £17,166

The non-linear relationship between serum uric acid concentration and the expected number of gout flares is discussed in Section 3.14.

Section 4.3 also addresses the related issue of the use of sUA as a surrogate marker for clinical outcome, and the validity of this approach.

The link between sUA and utility

The following addresses the specific issue raised in 3.15 regarding the link between sUA levels and utility, to reflect variation in HRQoL.

In the open label extension study FOCUS statistically significant ($p<0.05$) improvements (associated with sUA) from baseline were observed in several of the SF-36 domains, the Physical Component Summary (PCS) and Health Transition. Statistically significant improvements were observed most typically in the domains associated with physical function, but not those associated with emotional function. These statistically significant improvements were most notable in the following domains: Role-Physical, Bodily Pain, and Vitality. Statistically significant changes were also observed in Health Transition, which is a general measure of change in the past year, and the PCS scale.

In the Gout Assessment Questionnaire (GAQ) there were statistically significant improvements from baseline at week 52 and final visit in the Gout Concern, Well-Being, Productivity, and Gout Pain and Severity Domains.

Results from the two assessments, i.e. SF-36 and GAQ, are similar as they both consistently show improvements in patient reported outcomes; these improvements were observed in the more physical aspects of functioning as opposed to the more emotional aspects of functioning.

Similar data have been obtained on QoL in the EXCEL study: subjects on all treatment groups experienced improvements in all SF-36 scales from baseline to the final visit. These improvements were statistically significant in the Scales of

Role-Physical, Bodily Pain, Vitality, Reported Health Transition, Physical Component Summary, and MOS Health Distress. The greatest improvements in the treatment groups were noted in Role-Physical and Bodily Pain. Because only subjects whose sUA levels were controlled remained in study, the QoL results are representative of only subjects who responded to treatment.

It can be concluded from the QoL evaluation conducted in the long-term extension studies that maintaining sUA level below 6.0 mg/dl for a long period of time decreases progressively the symptomatic burden of gout, and this has been associated with an improvement of the SF-36 domains associated with physical function, particularly on Role-Physical, Bodily Pain and Vitality domains.

The model uses sUA level as the key driver of treatment decisions in the model, as is seen in clinical practice and recommended by the treatment clinical guidelines. Higher sUA is associated with (a) an increased flare frequency (acute effect), and (b) reduced HRQoL irrespective of gout flare frequency (chronic effect). Both are considered independently in the model.

The principle for the chronic effect being that well controlled sUA levels will lead to an avoidance of crystallization which in turn is known to cause gout-related symptoms (including but not limited to tophi, joint erosions, renal complications). For the acute effect, the figures in the response for 3.14 show that the relationship between sUA levels and gout flares is well established.

For the chronic effect, the model links sUA levels to utility through an assessment of HRQoL using an EQ-5D approach. This is done independent of the acute impact of temporary gout flares.

We agree that the magnitude of chronic long-term utility associated with each serum-urate level is difficult to estimate. No studies have been conducted on the utility associated with chronic gout complications developed over years of untreated urate levels. Gout is certainly a condition with a lower QoL than the population in general (Sundy et al., 2006; Roddy et al., 2007; Osterhaus et al., 2005). Several studies have shown a correlation between the clinical outcomes and high sUA level (Perez-Ruiz et al., 2002; Shoji et al., 2004).

It’s a well accepted fact that long-term treatment with urate lowering therapy prevents gout flares (acute effect) and may also resolve gout complications of tophi and renal impairment causing disability with an impaired QoL. The FOCUS

and EXCEL studies have shown that good control of sUA levels below the target level of 6.0 mg/dL with febuxostat was associated with a reduction of gout flares (97% of patients did not require a treatment for flares at Month 16-24) and reduction of tophi (54% of patients with tophi at a complete resolution of tophi in the same timeframe – ref. Adenuric (febuxostat) SmPC).

The IMS study has measured the QoL directly with EQ-5D (a generic HRQoL self-assessment instrument) in a gout population of 417 patients in the UK, France, and Germany. The study found that elevated sUA levels (regardless of flare rates) are significantly associated with reductions in health-related quality of life. This study was performed in accordance with NICE recommendations of methods to collect data to provide utility estimates with EQ-5D direct from the patient population (NICE, 2004 section 5.53).

These data were used in the cost-effectiveness model to provide estimates of utility by sUA levels which directly links the surrogate endpoint sUA and the gout patients' perception of quality of life.

The 'chronic utility gain' associated with lower serum uric acid concentrations integrate the benefit of preventing long-term complications of gout e.g. tophi and renal impairment, which is the ultimate aim with this form of therapy (together with prevention of gout flares). Febuxostat is a urate lowering drug used to prevent gout and its complications in the long-term.

By removing the chronic utility gain of maintaining a lower serum level, the ERG makes an extreme assumption that the QoL in a gout patient is totally driven by flare events, and by implication is not impacted by chronic conditions such as tophi, joint damage, chronic inflammation and renal impairment. The ERG disregards the benefit of preventing disabling long-term complications of gout that are causing most suffering for the individual and costs for the NHS.

We agree that the magnitude of the incremental utility is subject to a degree of uncertainty : a sensitivity analysis varying the utility increments from 0.02 to 0.05 varies the ICER between ICER (cost per QALY) £26,018 and ICER (cost per QALY) £10,786.

4 Consideration of the evidence

ACD Paragraph 4.2

The Committee discussed the decision problem presented in the manufacturer's submission. It noted that the manufacturer had presented evidence for the clinical and cost-effectiveness of febuxostat only as a first-line therapy, whereas the marketing authorisation does not make this restriction. It heard from the clinical specialists that in current clinical practice allopurinol is used as standard first-line therapy, and that febuxostat was a plausible improvement on current second-line options. These options are considered where allopurinol is not appropriate (for example due to intolerance or lack of response), and include benzbromarone, sulphinpyrazone and probenecid, all which have limitations such as limited availability, adverse effects and poor effectiveness. The Committee concluded that other second-line therapies should be considered as comparators for febuxostat.

The benefit-risk for the use of febuxostat in patients with chronic gout has been demonstrated in comparison to allopurinol as supported by the registration granted from the European authorities.

As allopurinol is the current gold standard for the treatment of gout and is the treatment received by 97.9% of all prescription medicine treated gout patients, all modelling has been performed against allopurinol representing current standard treatment. Other active drug treatments are very rarely used in the UK, Europe and the US and as such there is no rationale to compare febuxostat to products that are used in less than 2% of patients, when febuxostat has clearly been proven to be more efficacious (in terms of sUA control – the primary target of treatment of gout) than the most commonly used product, which is clearly allopurinol.

We absolutely consider allopurinol as the most appropriate comparator, as reflected by use in routine practice in the UK.

From a 2nd line perspective (following allopurinol) it is reasonable to expect that febuxostat would be seen as cost-effective, as the majority of patients in this situation would not be actively treated, or treated with an experimental treatment with no clear evidence base. The additional analyses based on a placebo (no treatment) comparator arm (as presented in response to 3.7) is useful in demonstrating clear cost-effectiveness for febuxostat in a situation where the only alternative is no treatment. The fact that the efficacy of febuxostat was

maintained in the renal impairment group and also in those patients switching from allopurinol in the EXCEL study, further supports the expectation of a cost-effective profile for febuxostat in a 2nd line indication (alongside it's cost-effective 1st line use).

Data from the pooled APEX and FACT clinical trials show that febuxostat 80mg has a 1.95 relative risk (RR) of patients achieving an sUA ≤ 6.0 mg/dL at last visit when compared to allopurinol, equivalent to a NNT of 2.8. The corresponding data for febuxostat 120mg vs allopurinol were a RR of 2.11 and a NNT of 2.4.

Summary of existing second-line treatment options

Other products are very rarely used in the UK, Europe and the US (Roddy et al., 2007; Annemans et al., 2007) and as such there is no clinical experience comparing febuxostat to other urate lowering therapies. Benzbromarone has been compared to allopurinol in a RCT (Perez-Ruiz et al, 1998) and seems to have a higher efficacy than allopurinol 300 mg. However, benzbromarone has been withdrawn in most EU countries and is restricted in others as a second- or third-choice drug, due to occasional cases of severe liver toxicity. As benzbromarone and probenecid are not approved on the UK market, they can by definition not be considered as used in standard clinical care in the UK.

The BSR guidelines recommend: "Uricosuric agents should be used only as second-line drugs in the chronic treatment of gout, in those producing and under-excreting a normal or reduced amount of urate, and in those resistant to or intolerant of allopurinol. The preferred drugs are suphinpyrazone 200–800 mg/day in patients with normal renal function, benzbromarone 50–200 mg/day in patients with mild or moderate renal insufficiency (creatinine clearance 30–60 ml/min) on a low purine diet, 24 h excretion of less than 3 mmol urate, or a Urate/creatinine ratio of <0.35 mmol/mmol in an untimed random urine."

Taking these guidelines into account ***Sulfinpyrazone*** (Anturan , Novartis) is the only uricosuric drug that can be freely prescribed in the UK at the present time:

- Sulfinpyrazone has been shown to be effective in reducing the frequency of gout attacks, and in reducing tophi as well as in reducing plasma urate levels in observational studies when administered in doses of 200–800 mg/day (Yu et al., 1958; Persellin et al., 1961; Kuzell et al., 1964).

- The side-effects include gastrointestinal side-effects and occur in 10–15% of 125 patients. Inhibition of platelet function can lead to bleeding and gastrointestinal haemorrhage.
- Marrow failure is an uncommon but serious side effect.
- Sulfinpyrazone has a specific contraindication in patients with renal impairment which constitute a significant subpopulation in gout.

Probenecid (Benuryl, Benemid, Probecid) is no longer available for general prescription in the UK but can be obtained on a named patient basis through IDIS. In doses of 0.5–2.0 g/day it has been shown to be effective in increasing urate excretion and lowering plasma urate concentration in observational studies [159–161], providing renal function is relatively normal (plasma creatinine <200 µmol/l). It was however, less effective than sulphinpyrazone in reducing the plasma urate in one small crossover study [162]. The side-effects include dyspepsia and reflux oesophagitis and can be troublesome in about 10% of patients and it can interact with all renally excreted anionic drugs.

(sourced from BSR guidelines and reference numbers are retained as per the BSR guidelines)

Benzbromarone (Desuric) has never been licensed for use in the UK but can be obtained for use on a named patient basis through IDIS. It is the most potent of the uricosuric agents and was until recently very widely used, even as a first line urate-lowering drug, in many countries in Europe, South Africa and Japan. It has been shown to be effective in lowering plasma urate levels in doses of 50–200 mg daily in a number of observational studies [163–166]. It was more recently shown in a comparative study to be as effective as allopurinol in reducing plasma urate concentrations in patients with renal impairment, with a plasma creatinine up to 500µmol/l [152]. Side-effects include diarrhoea that can be troublesome in about 10% of 25 patients. Rarely it has been associated with hepatotoxicity, and even fatal hepatic necrosis. As a result its availability for general prescribing has been recently restricted in France, Germany and Spain. However, benzbromarone can be a very useful drug for patients who cannot tolerate allopurinol, for patients with mild or moderate renal insufficiency and for managing patients with renal transplants when allopurinol is contraindicated [152, 167].

(sourced from BSR guidelines and reference numbers are retained as per the BSR guidelines)

We agree wholeheartedly with the committees comment that benzbromarone, sulphinpyrazone and probenecid all have limitations such as restricted availability, adverse effects and poor effectiveness. As febuxostat has been shown to have a favourable benefit-risk when compared to allopurinol, it was not considered necessary to further demonstrate the benefit risk against products with a lower benefit risk than allopurinol, especially considering direct access to these medicines is very limited in the UK..

ACD Paragraph 4.3

The Committee discussed first-line use of febuxostat and identified the following issues. Firstly, it has been established (as set out in BSR and EULAR guidelines) that allopurinol could be most effective when given in a titrated regimen depending on serum uric acid concentrations. The Committee concluded that up-titrated allopurinol (to a maximum of 900 mg) should be considered as a comparator for febuxostat.

As discussed previously (section 3.7), we assert that a high dose of allopurinol (maximum of 900 mg) is not a relevant comparator.

The following adds to and reiterates some key elements of the discussion on the view of routine clinical practice with allopurinol provided in 3.7

The BSR guidelines recommend the titration of allopurinol, with a maximum dose of 900 mg. The guidelines state that “in recent years it has become apparent that <50% of patients receiving allopurinol 300 mg/day in comparative trials were achieving optimum reductions in plasma urate concentrations. This suggests that many patients may need higher doses for optimal control of the sUA. Occasional patients have been shown to need doses of up to 900 mg/day for optimum effect”.

Consequently, little experience has been gained on the clinical use of doses of allopurinol higher than 300 mg. In addition, the possible side effects of allopurinol listed in the BSR guidelines include “transient rashes which usually respond to reduction in dose, especially in those with impaired renal function such as the elderly”. In Table 3 of the BSR publication it is indicated that “the usual dose of allopurinol is 200-300 mg daily when sUA level is >80 ml/min, and lower doses

should be used below this creatinine clearance level". As a significant proportion of gout patients have some degree of renal impairment (35% in the pivotal studies) it is expected that allopurinol doses will be capped to lower doses than 300 mg in a significant proportion of patients. In addition, as there is little clinical experience with doses higher than 300 mg reported in the literature, it is very unlikely that physicians will use higher allopurinol doses than the conventional dose.

Data from epidemiological studies, including very recent studies suggest that the 300 mg dose is the most commonly used allopurinol dose both in the United States [Sarawate et al, 2006] and in Europe [Annemans et al, 2007]. Allopurinol was prescribed at a daily dose of 300 mg or less in 98% of gout allopurinol-treated patients in the UK, and in 96% of patients in Germany [Annemans et al, 2007]. In the US, only 2.9 % of adult gout patients evaluated in a managed care situation and who were taking allopurinol received doses >300 mg/day [Sarawate et al, 2006].

Although doses of allopurinol ranging from 50 mg ->800 mg have been recommended in some textbooks, in current medical practice, doses >300 mg are rarely used for safety reasons. This was confirmed by Hoskison and Wortman, 2007, who described such a dose range in their recent review article, and recognised that the most prescribed dose is 300 mg/day. In a retrospective study Li-Yu, reported that only 4 out of 57 patients had their allopurinol dose increased to over 300 mg QD and to a limit of 600 mg QD at one point, but not throughout the duration of the course of their disease [Li-Yu et al, 2001].

The EULAR guidelines state that "although allopurinol has been used as an effective treatment for gout for decades, its clinical efficacy has not been examined in placebo controlled RCTs." The guidelines also explain that the titration-dose regimen may provide advantages over a fixed-dose regimen; however, formal comparison between the two regimens has not been undertaken. Conversely, the superiority of febuxostat over allopurinol (300 mg fixed dose) has been demonstrated in two double-blind RCTs. It is noteworthy that the data from the FACT clinical study [Becker NEJM 2005] have been referenced in the BSR guidelines as there were very few comparative data with allopurinol with which to evaluate allopurinol efficacy.

In the allopurinol SPC, titration of allopurinol is recommended for safety reasons. This view is also reported in the EULAR guidelines as one of the justifications for using a titration scheme for allopurinol. A recent published study from Roddy et al, 2007 showed that in the UK treatment of chronic gout is often suboptimal and poorly concordant with EULAR recommendations. Allopurinol is the only urate lowering therapy used and is taken by 30% of gout patients, with 70% of patients taking 300 mg and 4% taking doses of >300 mg.

In conclusion it is expected that the febuxostat pivotal studies reflect the current management of gout in the UK, with allopurinol 300 mg being the standard urate lowering therapy. Therefore the conclusions drawn from the pivotal studies can be extended to UK clinical practice, indicating that the proportion of patients reaching a therapeutic target of 6.0 mg/dL is 2 to 3 fold higher with febuxostat than with allopurinol.

ACD Paragraph 4.3 cont

Secondly, the Committee considered the outcomes in the decision problem, and in doing so explored the relationship between hyperuricaemia and the clinical manifestations of gout. In particular, it discussed the surrogate outcome of serum uric acid concentration. It heard from the clinical specialists that a significant proportion of the population have high serum uric acid concentrations but that comparatively few people present with clinical symptoms related to gout. The relationship between serum uric acid concentration and symptoms is complex and not completely understood. The Committee understood from patient experts that quality of life is affected by the symptoms experienced and not by serum uric acid concentration itself. The Committee was persuaded that reduction of the serum uric acid concentration below the 'saturation point' (approximately 6.0 mg/100 ml) was necessary to avoid precipitation of uric acid crystals in tissues in the long-term. However, it concluded that there was uncertainty regarding the relationship between serum uric acid concentration above this level and clinical benefits, such as gout flare control and reduction in tophi size and number.

Asymptomatic versus symptomatic hyperuricaemia

One of the clinical advisors to NICE raises the fact that amongst a population with hyperuricaemia, not all individuals will develop gout. This is certainly true in the sense that a high sUA level is not a guarantee of developing gout symptoms. However, a critical point for us to clarify for NICE, and reiterate from the original STA submission, is that the clinical studies on the use of febuxostat were conducted within a cohort defined as having diagnosed gout, and were not simply hyperuricaemic in terms of observed sUA levels.

Ipsen has conducted all the febuxostat clinical studies and cost-effectiveness modelling in a cohort based on patients with gout (i.e. specifically excluding patients with asymptomatic hyperuricaemia). Therefore, the key question which should really be discussed is the true value of sUA levels as an outcome measure in assessing treatment efficacy (in patients with diagnosed gout); rather than the value of sUA levels as a prognostic measure of the risk of developing gout (for which there is today limited information, as highlighted by the NICE clinical advisor).

Quality of Life

The key outcome for NICE decision making is the QALY; all cost-utility analyses use some method of linking clinical outcomes to QALYs, via utility weights. In this case, a direct association was made between the primary trial end-point (sUA) and the final outcome (utility) using methodology favoured by NICE (EQ-5D data collected within a study for patients of various sUA levels). This measure may therefore be considered to represent the total impact of high sUA on quality of life, resulting from gout flares on one hand (acute effect), and tophi, and any others symptoms on the other hand (chronic effect). It was not necessary to define the relationship between hyperuricaemia and the clinical manifestations of gout, since a direct relationship between sUA and utility was applied.

We agree that quality of life is affected by the symptoms experienced and not by serum uric acid concentration itself. However, it is clear that the treatment of asymptomatic hyperuricemia is outside the scope of this submission (see initial comments above) as the label of febuxostat is limited to “the treatment of chronic hyperuricaemia for conditions in which urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis)” which excludes patients with asymptomatic hyperuricaemia. The surrogate outcome measure of sUA was measured in clinical studies that included only clinical gout patients (not asymptomatic hyperuricaemia individuals), as per febuxostat’s marketing authorization.

The pathology hallmark for the development of gout is the deposition of monosodium urate (MSU) crystals in the articular and periarticular tissues (Yu &Yu, 1974). Hyperuricaemia can lead to MSU crystal formation and is an

important risk factor for gout. Other risk factors such as age, BMI and hypertension appear to act through their ability to raise sUA (Campion et al, 1987). The aim of chronic gout therapy is to reduce serum urate to sub-saturating levels thus reducing the incidence of flares, initiating the dissolution of tophi and preventing the development of chronic arthropathy.

A number of factors should be considered with regard to the control of serum urate levels. These include the identification of a suitable cut-off point for the effective control of uricaemia and consideration of clinical outcomes during short and long-term treatment.

Cut-off point for uricaemia during chronic gout therapy

Recommendations for the cut-off point for gout therapy proposed by the EULAR Task Force were evidence-based (Zhang et al, 2006). The cut-off point for the saturation of urate is considered to be 6.8 mg/dL and most experts support the view that achieving serum urate levels below this saturation cut-off during urate therapy is a clear and accepted objective (Wortmann, 2006). The evidence for such recommendations, however, is, unfortunately, not based on long-term RCTs, as no long-term, placebo-controlled clinical trial has ever been conducted in patients with chronic gout. This is primarily because the long-term follow-up of untreated patients with gout and persistent, long-term hyperuricaemia, demonstrate that severe tophaceous gout will develop, nearly doubling in its prevalence from 30- 60% after 5-10 years of follow-up post the onset of gout symptoms (Guttman 1973). Thus, continuation of a placebo arm in a long-term follow-up study is not a viable or ethical option.

The cut-off point for effective control of urate levels has been empirically set at 6.0 mg/dL. Most experts consider 6.0 mg/dL to be acceptable for clinical practice (Zhang et al, 2006; Wortmann, 2006), and as such the majority of authors evaluating outcomes during urate-lowering therapy have used this expert-based recommendation as the minimum level to achieve during long-term urate-lowering therapy (Perez-Ruiz et al, 2006). Nevertheless, an inverse correlation has been observed between average serum urate levels and the velocity of reduction of subcutaneous tophi (Perez-Ruiz et al, 2002; Perez-Ruiz et al, 2007; Perez-Ruiz & Martin, 2006) and also with the reduction of periarticular tophi measured with ultrasonography during urate-lowering therapy (Perez-Ruiz et al, 2007; Schumacher et al, 2007; Perez-Ruiz & Naredo, 2007). It has therefore

been suggested that in some patients with extensive tophi and a presumed high crystal load that the therapeutic target of sUA levels should be much lower than this minimum level (Zhang et al, 2006).

Outcomes during long-term control of uricaemia

The long-term control of hyperuricaemia in patients with gout is associated with a decrease and ultimate disappearance of acute flares and tophi.

Darmawan reported that the long-term control of serum urate levels was associated with the presence of gout flares in just 10% (18/226) of patients with 83% (24/29) of patients free from subcutaneous tophi (Darmawan et al, 2003). In a prospective study, a progressive reduction in the number of flares to 4% was observed in the 2nd year of follow-up with 90% of patients clear of tophi. This outcome was independent of the urate-lowering drug dispensed if proper control of urate levels was achieved (Perez-Ruiz et al, 1999). In both studies, long-term prophylaxis of between 6 to 24 months was prescribed. The observation that patients with high serum urate levels tend to have worse outcomes than patients with lower serum urate was also seen in a retrospective study of 267 patients where the higher the average of the serum urate level during the 3-year study period, the higher the probability of recurrent gouty attacks (Shoji et al, 2004). The same effect of sUA level on gouty attacks was observed by Sarawate et al 2006.

In patients with effective long-term control of serum urate levels the reduction in subcutaneous tophi (Perez-Ruiz et al, 2002) and periarticular deep tophi measured with ultrasonography (Perez-Ruiz et al, 2007) was inversely related to serum urate levels during follow-up. Conversely, inadequate control of serum urate was associated with either no change or an increase in the size of tophi (McCarthy et al; 1991; Perez-Ruiz & Martin, 2006), and radiologic progression (McCarthy et al; 1991).

Withdrawal of long-term treatment with anti-hyperuricaemic agents is associated with an increase in serum urate levels and a subsequent recurrence of tophi and acute gout attacks (Perez-Ruiz et al, 2006; Ghast, 1987; Van Lieshout-Zuidema, 1993). Non-compliance has also been shown to contribute to worsening of disease. In a study of 60 patients with gout, non-compliant patients had higher sUA levels (>9 mg/dL), clinically and radiographically evident tophaceous gout with crystals seen in the knee synovial fluid of 14 out of 16 patients with current

serum urate levels above 6.0 mg/dL, compared with 7 out of 16 patients with serum urate levels at or below 6.0 mg/dL, and patients experienced more frequent polyarticular gout attacks (Li-Yu et al, 2001).

In order to evaluate the magnitude of the reduction of gout flares, the baseline gout flare rate was estimated using the gout flare rate from the placebo group of the Phase III study (APEX). Already in the Phase III studies a trend for a difference in gout flares and decrease in tophi size was apparent between patients with a sUA below or above 6mg/dL at the last time interval (week 48-52).

The average percentage of patients in Phase III studies requiring treatment for a gout flare during a 2-month period after prophylaxis was 20% (20/101) in the placebo group. Using this as reference for baseline gout flare rate, the results from the long-term studies show that the reduction of serum urate is associated with a marked reduction in the number of gout flares. The 20% incidence of gout flares recorded in the placebo group (APEX) in the previous 2-month period post prophylaxis fell to < 2% after 14 months in Study EXCEL. After month 22, no patients experienced gout flares. In the LTE Study FOCUS, <10% of patients experienced a gout flare after the first year of therapy, and the overall incidence of gout flares gradually declined over 4 years of febuxostat treatment. These findings are consistent with that reported in the literature.

Conclusion

In the long-term treatment of gout the primary aim is to reduce and maintain serum urate levels below the saturation limit. The target sUA level of ≤6.0 mg/dL has been clearly specified by the EULAR taskforce on gout management, and the BSR has recommended to decrease sUA levels even further to ≤0.30 mmol/l (5.0mg/dL). Long-term maintenance of sUA at or below 6.0 mg/dL in patients with gout has been associated with both a decrease in the incidence of gout flares and a reduction in the size and number of tophaceous deposits. These data strongly support the use of serum urate levels as a valid surrogate endpoint for clinical outcome (Perez-Ruiz, 2007).

ACD Paragraph 4.4

The Committee discussed the evidence for the clinical effectiveness of febuxostat, and specifically the randomised controlled trials (RCTs and extension

studies in which febuxostat was compared with fixed-dose allopurinol. It noted the ERG critique of the efficacy results from the pooled analysis of data from the APEX and FACT trials and agreed that the approach was methodologically inappropriate, in that it failed to preserve randomisation in the RCT evidence. The Committee noted that the manufacturer was asked to conduct a meta-analysis of the RCT data but this was not provided. The Committee noted, however, that an appropriately conducted meta-analysis from the ERG showed very similar results, demonstrating that febuxostat is more effective than allopurinol in lowering serum uric acid concentration.

The rationale for presenting a pooled analysis rather than a meta-analysis has been outlined in the response to question B3 of the manufacturer response to clarification letter (Feb 2008). The following provides additional rationale to address specific concerns raised:

- The approach taken does not introduce bias as the analysis uses a CMH test stratified by study. Therefore any bias and confounding in the analysis by pooling data from the two-studies is accounted for by stratifying the analysis by study.

- The randomisation is still preserved in the pooled analysis, since both studies included are randomised clinical trails. Pooling the data from the two trials does not affect the fact that they were still randomised and any differences between studies were accounted for in the analysis by stratifying by study.

- Also, for all the primary and secondary endpoints, the pooled results were similar to those obtained in the separate analyses of each study. The meta analysis also produced similar conclusions to the pooled analysis, therefore the choice of statistical approach in this case does not affect the conclusions which are drawn from the data.

IPSEN notes with interest that ERG has conducted a meta-analysis, and that this did not impact significantly on the assessment of the technology, as compared to results from pooled studies.

ACD Paragraph 4.6

The Committee accepted that febuxostat is more effective at reducing the serum uric acid concentration than fixed-dose allopurinol. However, it concluded that the benefits of febuxostat compared with allopurinol in improving clinical outcomes, such as flare control, reduction in tophi size and number and avoidance of joint and organ damage due to urate deposition, in the longer term had not been clearly demonstrated. In addition, it queried the generalisability of the RCT results to UK clinical practice. The Committee heard from the clinical specialists that the patient population in the APEX and FACT trials had more 'severe' manifestations of the disease (for example, the presence of tophi) than might be seen in UK general practice. Moreover, there was a lack of evidence about the clinical effectiveness of febuxostat compared with up-titrated allopurinol or second-line therapies.

The discussions in 3.4, 3.5, 3.7, 4.2, 4.3 and 4.4 addresses the issues raised above.

Clinical Efficacy

Febuxostat has demonstrated a consistent and clear clinical superiority and advantage over allopurinol based on the use of the recommended surrogate marker (sUA) as referred to in the latest clinical guidelines on the clinical management of gout.

In addition we have well designed and large clinical trials that have demonstrated the longer-term stability of this response, with an improved long-term treatment adherence over allopurinol (EXCEL study). The long term extension studies have demonstrated that control of sUA level below 6.0 mg/dL with febuxostat considerably reducing the frequency of gout flares over time and is associated with a complete resolution of tophi in more than half patients with tophi at treatment initiation (EXCEL study).

Generalisability of the data for the UK

Regarding the generalisability of efficacy data to patients with a milder disease, the clinical trials reflect a population with mild to severe gout with an sUA >8 mg/dL, a mean sUA at initiation of treatment of 9.8 mg/dL, 20-26% of the gout patients have tophi and 35% have mild-to-moderate renal impairment.

Even if on average the gout population in the UK might be seen to have a milder manifestation of gout, subgroup analyses have shown febuxostat has superior effect against allopurinol regardless of baseline sUA level, renal impairment or presence of tophi (see discussion comment 3.4). We believe this evidences the generalisability of the treatment effect advantage of febuxostat over allopurinol across the potential patient group variations in the UK.

ACD Paragraph 4.7 The Committee considered the adverse effects associated with febuxostat in comparison with fixed-dose allopurinol. In particular, it noted that there was a higher incidence of cardiovascular events and deaths across the febuxostat arms of the APEX, FACT and EXCEL studies. It noted that the manufacturer had reported such differences as not being statistically significant, but that the ERG had found a lack of clarity in reporting, despite requests for clarification. It concluded that consideration of these adverse effects, however uncertain, was an essential part of comparing relative clinical outcomes of the intervention and comparator and this should have been included in the economic modelling.

The most commonly reported adverse reactions with febuxostat were; headache, diarrhoea, nausea, rash, LFT abnormalities, and hypertension. These reactions were reported at similar incidences in patients taking allopurinol and patients taking febuxostat in the pivotal phase III and long-term extension studies.

The differences in cardiovascular adverse effects between the febuxostat and allopurinol groups were minor and not statistically significant and are therefore not included in the economic model.

Below follows more detail of a comparison of safety profiles between febuxostat and allopurinol.

Cardiovascular adverse events

In the pivotal Phase III studies (APEX and FACT), a total of 30 serious cardiovascular adverse events, were reported by 25 febuxostat-treated subjects. The most commonly reported events were cardiac failure congestive (6 events in 4 subjects) and myocardial infarction (5 events in 5 subjects).

In the LTE studies, a total of 72 serious cardiovascular events were reported in 54 febuxostat-treated subjects. The most commonly reported events were myocardial infarction (17 events in 15 subjects), coronary artery disease (9

events in 8 subjects), atrial fibrillation (9 events in 8 subjects) and cardiac failure congestive (8 events in 5 subjects).

Single events of lacunar infarction and cerebrovascular accident (CVA) were considered possibly related to febuxostat. All other events were considered to be unlikely or not related to febuxostat.

The outcomes of all the cardiovascular serious adverse events reported in the pivotal Phase III and LTE studies are outlined below (Table 6).

Table 6. Cardiovascular serious adverse events

Outcome	Number of SAEs
Death	9
Resolved	81
Ongoing	10
Unknown	2
Total	102

Cardiovascular adverse events in phase III and long term studies

Cardiovascular events were classified by Antiplatelet Trialist Collaboration (APTC) criteria and are presented in 2 different ways:

1. As reported by the investigators
2. After blinded adjudication by an independent cardiologist, Dr White.

Different study designs require that the incidence of the cardiovascular events are considered separately when evaluating the safety profile of febuxostat.

The Phase III studies were randomized and double blind, while the long term extension studies allowed patients to switch from one treatment group to another group at treatment failure (defined as failure to achieve sUA ≤6.0 mg/dl). More patients were exposed to febuxostat than to allopurinol as the febuxostat had a lower rate of treatment failures. The cardiovascular event analyses were done post-hoc, which increase the risk that some results can be obtained by chance when repeating the analysis.

Adjudication into APTC events

The APTC Endpoints were originally developed to assess safety and efficacy of

antiplatelet drugs and contain standard endpoints used to evaluate any drug for CV adverse events. These endpoints have subsequently been modified by Dr. White and colleagues to include only those events that have a common underlying thromboembolic pathology.

The primary APTC endpoints include cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and non-fatal cardiac arrest. The secondary APTC endpoints include angina, coronary revascularisation, transient ischemic attack, venous or arterial thrombotic event, and coronary heart failure.

Analyses of the investigator-reported primary APTC events in the pivotal Phase III studies revealed no statistically significant difference between treatment groups. The overall incidence of investigator-reported, treatment-emergent primary APTC events for the febuxostat total group was 0.8% (9 in 1177) compared to 0.2% (1 in 521) for allopurinol, with a substantial overlap of Confidence Intervals (CIs). For primary and secondary APTC events combined, the overall incidence for the febuxostat total group was 2.1% compared to 1.3% for allopurinol, also with an overlap of CIs. Despite the numerical differences between the febuxostat and allopurinol groups, there was no increasing incidence of primary, or primary plus secondary APTC events with increasing febuxostat dose.

The data from the long term extensions studies (EXCEL and FOCUS) are essentially observational and non-randomised, therefore cannot be expected to provide reliable evidence of a safety concern. Multiple factors make these data difficult to interpret. Initially, all patients were treated with febuxostat. Later, the protocol for the larger study (C02-021) was amended to include random allocation to treatment with either allopurinol or febuxostat, but patients were allowed to change treatment, if the lowering of serum uric acid was considered insufficient. Therefore, there is a complex mixture of patients in the LTE studies, who may have been non-randomly allocated to febuxostat, allocated randomly to allopurinol and then changed to treatment with febuxostat or vice versa. There were also some patients who were randomly allocated to febuxostat or allopurinol and remained on their allocated treatment throughout. However, more patients were changed from allopurinol to febuxostat than the other way round. Therefore, the total number of patients who received allopurinol (n=178) and the allopurinol patient-years (PYs) exposure (PYs=145.4) were far smaller than the corresponding figures for the febuxostat group (n=1143 and PYs=2120.7).

A number of established cardiovascular risk factors were found to have a significant association with APTC events such as congestive heart failure and coronary artherosclerotic disorder. A high percentage of subjects in each treatment group in the febuxostat pivotal Phase III studies and long-term extension studies, had prior cardiovascular medical histories and corresponding risk factors including hypertension (>38%), hyperlipidemia (>32%), diabetes (>6%), obesity (>55% with a BMI of ≥30 kg/m2), and atherosclerotic disease (>8%). Many subjects (25%) were on low-dose aspirin during the long-term extension studies, probably for cardiovascular disease. In addition, in the long-term extension studies, there were more subjects in the febuxostat total group than in the allopurinol group with pre-existing congestive heart failure (2% versus 0%).

The observed incidence of APTC events and cardiovascular events overall is consistent with what would be expected in a gout disease population. Generally, there is a known association of cardiovascular events with gout and all individuals with APTC events had preexisting conditions/risk factors.

In addition to the lack of statistically significant difference between treatment groups, there is further evidence which refutes a cardiovascular safety risk associated with febuxostat:

While there is a numerical difference between the febuxostat and allopurinol groups in the clinical studies, the incidence of primary APTC events is well within the range expected for patient populations with gout and a similar cardiovascular risk profile, which have been reported in the literature.

If febuxostat was truly associated with a cardiovascular safety risk the incidence of cardiovascular adverse events might be expected to increase with dose. There was no increasing incidence of primary, or primary plus secondary APTC events with increasing febuxostat dose in either the pivotal Phase III or LTE studies. Neither was there any significant difference between treatment groups in the time to first APTC event. The absence of a relationship between APTC events and

increasing dose or time to event supports the lack of a causal relationship between the use of febuxostat and cardiovascular morbidity and mortality.

The numbers of primary and secondary APTC events per 100 PYs for the febuxostat 80 and 120 mg groups were lower in the LTE studies (2.9 and 3.3, respectively) than in the Phase III studies (4.2 and 3.6, respectively). Therefore, the incidence of APTC events does not increase with long-term febuxostat treatment.

Based on these data, Ipsen concludes that the numerically, but not statistically significant, increased incidence of primary APTC events seen in the febuxostat groups compared to allopurinol in the Phase III studies is most likely due to chance.

The CHMP adopted a cautious approach by recommending the following warning in the febuxostat SPC (2008) for patients already identified with cardiovascular disease.

> **"4.4 Special warnings and precautions for use**
> *Cardio-vascular disorders*
> Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended (see section 4.8). "…
> **"4.8 Undesirable effects**
> …A numerically greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the pivotal Phase III (1.3 vs 0.3 events per 100 PYs) and long-term extension studies (1.4 vs 0.7 events per 100 PYs), 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..."

A post-marketing prospective, randomised, open, blinded endpoint study in patients exposed to febuxostat or allopurinol in the clinical setting will be initiated to further assess any potential risk of cardiovascular events being related to febuxostat treatment.

ACD Paragraph 4.8

The Committee discussed the economic model presented by the manufacturer and the ERG's subsequent critique. It had a number of concerns with the model structure and parameter assumptions in the model. It thought that the evidence base was incomplete because the comparison presented by the manufacturer was limited to a suboptimal (that is, fixed-dose) regimen of allopurinol. The Committee noted that no estimate had been made of the cost-effectiveness of febuxostat in cases of non-response or intolerance or contraindicated to allopurinol. It heard from clinical specialists that new and relatively unfamiliar drugs are often used, initially at least, when current drugs are inappropriate or have failed to achieve a response. The Committee was mindful that the ERG had made a request for modelling of sequential use when patients progress to alternative treatments or no-treatment options, and that the manufacturer had declined the request on the basis of lack of evidence. The Committee concluded that without evidence that febuxostat is cost-effective either when compared with up-titrated allopurinol or in sequential comparisons, it could not recommend its use either as an alternative to up-titrated allopurinol or as a second-line therapy.

Selection of allopurinol as 300 mg current standard treatment

A systematic literature review recently conducted for IPSEN has not identified any randomised controlled trial evidence that provides a clear demonstration that dose-titrated allopurinol is more effective than fixed-dose allopurinol in the control of sUA levels and the symptoms of gout.

Furthermore, allopurinol 300 mg is the most typical daily dose and treatment for gout in the UK, and represents current routine practice. Data from epidemiological studies, including very recent studies suggest that the 300 mg dose is the most commonly used allopurinol dose both in the United States (Sarawate et al, 2006) and in Europe (Annemans et al, 2007).

- Allopurinol was prescribed at a daily dose of 300 mg or less in 98% of gout patients treated with allopurinol in the UK, and in 96% of patients in Germany (Annemans et al, 2007).
- In the US, only 2.9 % of adult gout patients evaluated in a managed care situation and who were taking allopurinol received doses >300 mg/day (Sarawate et al, 2006).

- Hoskison and Wortmann, (2007) also recognized that the most prescribed dose of allopurinol is 300 mg/day.
- In a retrospective study Li-Yu, reported that only 4 out of 57 patients had their allopurinol dose increased to over 300 mg QD and to a limit of 600 mg QD at one point, but not throughout the duration of the course of their disease (Li-Yu et al, 2001).
- In the IMS observational study (UK, Germany, France), only 6.2% of the patients were prescribed to allupurinol >300mg.

In summary, allopurinol is unlikely ever to be considered as a titrated treatment approach in routine clinical practice, and the likelihood of available clinical data to support its use is extremely questionable.

Within the STA submission it is clear from the NICE guidelines that the obligation of the manufacturer is to make a direct or indirect comparison of the clinical and economic effectiveness of the new treatment against current routine clinical practice (even if this is an off-label use of the treatment).

> *"An STA typically compares the licensed use of a health technology with current standard treatment in the NHS in England and Wales. The Institute will develop a scope for the STA in consultation with consultees and commentators. The Institute's approach to scoping is outlined in 'Guide to the technology appraisal process' (section 3). Unless the Department of Health indicates otherwise, recommendations will not be made on unlicensed indications for the product being appraised." Guide to the NICE single technology appraisal process; September 2006*

Following NICE guidance indicating that treatment has to be compared with routine practice, IPSEN has provided comparative data between febuxostat and allopurinol 300mg.

It is correct that the clinical guidelines make reference to both the titration and fixed-dose formulations of allopurinol for the treatment of gout. However, the situation in terms of comparability of treatment effect is unclear due to a complete lack of comparative clinical data. Although the clinical guidelines have identified that allopurinol may need to be titrated to higher doses to achieve a clinical effect, there are many reasons on convenience, safety and treatment compliance that means this approach is very seldom a possibility for patients. There is also

no evidenced based data to support either efficacy or safety on higher doses of allopurinol.

The EULAR guidelines confirm this in the statement that “the titration-dose regimen may provide advantages over a fixed-dose regimen; however, formal comparison between the two regimens has not been undertaken”.

The EULAR recommendation states the following, regarding to titration of allopurinol: “Allopurinol is an appropriate long-term urate lowering therapy. It should be started at a low dose (e.g., 100mg daily) and increased by 100 mg every 2-4 weeks if required. The dose must be adjusted in those with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent or allopurinol desensitisation (the latter only in cases of mild rash).”

Although the BSR guidelines recommend the titration of allopurinol and higher doses, with a maximum dose of 900 mg, in order to counteract the limited efficacy observed for allopurinol, they do not identify or provide any evidence for superior efficacy of higher doses. The BSR guidelines state that “the usual dose of allopurinol is 200-300 mg daily when CrCl >80 ml/min, and lower doses should be used below this creatinine clearance level”. A significant proportion of gout patients have some degree of renal impairment (35% in the pivotal studies). Therefore, it is expected that allopurinol doses will be capped at 300 mg or below in a significant proportion of gout patients. Consequently, little experience has been gained on the clinical use of doses of allopurinol higher than 300 mg, and it is therefore very unlikely that physicians will use higher allopurinol doses than the conventional dose. In addition, the possible side effects of allopurinol listed in the BSR guidelines include “transient rashes which usually respond to reduction in dose, especially in those with impaired renal function such as the elderly”.

Interestingly, the BSR guidelines reference data from the FACT clinical study (Becker NEJM 2005) for the efficacy of allopurinol, presumably because there is so little comparative trial data evaluating the efficacy of allopurinol in either its fixed or titrated dose formulation.

Therefore, from an evidence based medicine perspective, dose-titrated allopurinol has not been proven to be more effective than fixed-dose allopurinol. Furthermore, a systematic review revealed that comparative safety of dose-

titrated and fixed-dose allopurinol has not been formally investigated in a randomised trial setting or sufficiently evaluated using other study designs.

The SPC for allopurinol recommends dose titration for safety reasons, which are linked to the renal issues related to higher dose levels of allopurinol. The UK SPC for allopurinol also clearly states that in patients with renal impairment a low-level daily dose of less than 100mg should be considered, or less frequent dosing at 100mg per dose. An alternative for dialysis patients is a dosage of 300-400mg taken immediately after each dialysis session (where dialysis is given 2 to 3 times per week). However, dose titration is rarely carried out in routine clinical practice. Furthermore, doses >300 mg are rarely used. The side-effects of allopurinol are likely to be dose-related (Mac Innes et al., 1981).

In summary, from an evidence based medicine perspective, dose-titrated allopurinol has not been proven to be more effective than fixed-dose allopurinol, its safety has not been formally investigated in a randomised trial setting, and doses higher than 300mg are rarely used in clinical practice due to safety considerations (e.g., heightened potential for allopurinol hypersensitivity reactions at higher doses; contraindication of higher doses in renally impaired patients) and the prevalence of renal impairment.

We therefore assert that there is substantive evidence that fixed dose allopurinol (i.e., 300 mg/dL) is the appropriate comparator for febuxostat reflecting routine practice for urate lowering therapy. Therefore the conclusions drawn from the pivotal studies can be extended to UK clinical practice, indicating that the proportion of patients reaching a therapeutic target of 0.36 mmol/l (6.0mg/dL) is 2 to 3 fold higher with febuxostat than with allopurinol.

Second-line consideration of febuxostat / sequential comparisons

The ACD raises the issue of an economic model based on sequential treatment sequences for managing gout, in which patients who fail to gain a response move onto a next level of therapy (i.e. a model incorporating a 1st line, 2nd line and subsequent treatment or no treatment option).

The original model was developed as a first-line treatment comparison versus allopurinol as this was felt to the primary comparator. The placebo analysis (provided in section 3.12) helps to look at the costs and benefits of febuxostat when no other treatment option is available (i.e. if they are contraindicated for

allopurinol or if allopurinol has failed). We have data from APEX and FACT that shows a similar clinical effect for febuxostat in allopurinol failure patients as observed in patients on 1st line febuxostat.

The issue with developing a sequential treatment model was the lack of good quality data for all treatments based on prior treatment, and the fact that the clinical trial data is predominantly a first-line treatment comparison.

Although this has been raised as an issue in the initial ERG comments and the ACD, it is not possible to utilise the current economic model to generate this type of comparison within the available timeframe of the NICE STA review.

There are a number of practical issues that this raises with respect to a new model approach and the current ACD and STA process;

- Firstly, this type of model would almost certainly require a Markov health state structure, as opposed to the decision tree calculations in the existing model.

- Secondly, the model would also require a wider review of the natural history data for gout, in order to allow the time horizon of the model to be extended out to a life-time horizon. Also, such a model would provide an opportunity to include non-flare symptoms, such as tophi, which would be applicable over the longer term and may be linked statistically to sUA levels provided such data exists.

- Due to the lack of hard data on 2nd line treatments, such a model wouldl require a number of assumptions to be developed covering issues such as the effectiveness of febuxostat in allopurinol “non-responders”, effectiveness of allopurinol in febuxostat “non-responders”, timing of switch from allopurinol to febuxostat, head-to-head or indirect comparison with other second-line treatment options (e.g. no treatment, remaining on allopurinol, switching to other treatments).

- Finally, there is also no data to our knowledge on the likely level of compliance for allopurinol or febuxostat in actual clinical practice (outside of clinical trials), in particular that included the effects of the latest recommendation for 6-months of prophylaxis treatment for the flare induction effect.

The development time necessary to design, construct and populate such a model, to the necessary level of complexity and flexibility, and to fully document this is well outside of the time available to IPSEN following the initial ERG comments and the current ACD document and review period. Our current estimate is that this work would require 4- to 6-months to complete.

ACD Paragraph 4.9

The Committee discussed the linear relationship assumed in the cost-effectiveness model between serum uric acid concentration and frequency of gout flares, and how this may translate into improvements in health-related quality of life. Firstly, the Committee considered the ERG's concerns about the validity of the 'multivariate analysis' conducted to inform the assumption of a linear relationship between serum uric acid concentration and frequency of gout flares. It noted the ERG's critique that this was based on a dataset from which some data points had been selectively excluded. It agreed with the ERG that there had not been adequate explanation of this data selection. The Committee further considered the statements from the clinical specialists that although a relationship between serum uric acid concentration above the saturation point and frequency of gout flares is plausible, it is unlikely to be linear. The Committee concluded that the relationship between serum uric acid concentration and frequency of flares was implausible and was likely to lead to overestimation of the incremental QALYs gained.

The full discussion in comment 3.14 provides data about the relationship between sUA levels and flare rates that was used in the model, and an exploratory analysis regarding the impact on ICER of the uncertainty around flare rates in the model.

In summary the relationship modeled was not of a linear form and was similar to other published approaches to model the relationship between sUA levels and flare rates.

Relationship between sUA and flares

Clinical studies have demonstrated that an increasing sUA level correlates to increasing incidence of adverse health outcomes in gout patients, including number of gout flares and development of painful and debilitating tophi (Zhang et al., 2006b; Thompson et al., 1962). The relationship between reduction of sUA

concentration and the reduction in risk of recurrent gout attacks has been demonstrated as clinically significant in a retrospective study of 267 patients who had experienced at least one gout attack and were receiving ULT (Shoji et al., 2004). At sUA levels ranging from 7.5-9.5 mg/dL, the incidence of experiencing a gout flare ranges from 40% to over 80%, whereas the incidence of gout flares is under 20% for those patients maintained at or below recommended sUA levels.

It is incorrect for the ERG to state that the health economic model applied a linear relationship between sUA level and number/frequency of flares.

The model applies a monthly number of flares in each of the 4 predefined sUA levels:

- ≤ 0.36 mmol/l (6.0mg/dL)
- > 0.36 mmol/l (6.0mg/dL) and ≤ 0.48 mmol/l (8.0 mg/dL)
- > 0.48 mmol/l (8.0 mg/dL) and ≤ 0.60 mmol/l1(0.0 mg/dL)
- > 0.60 mmol/l (10.0 mg/dL)

These estimates of monthly number of flares were based on an observational study in gout patients in the UK, Germany and France (IMS report). A two-phase approach was applied:

(1) The proportion of patients experiencing ≥ 1 flare was estimated (yes/no variable, applied to the total population) – statistical technique: logistic regression

(2) In patients who experienced flares (i.e. a subgroup of the total population), the monthly number of flares was estimated.- statistical technique: linear regression with the $\log_{10}$-transformed number of flares as dependent variable.

The monthly number of flares figures applied in the model for each of the 4 sUA levels is the multiplication of the proportion of patients with flares (1) with the monthly number of flares (2).

Neither of the 2 applied statistical techniques for estimating these parameters (1) and (2) for calculating the monthly number of flares were based on a linear relationship. This is explained in detail in 3.14 sub-section 1 and sub-section 2.

Moreover, 2 papers were identified in which the relationship between sUA level and probability of experiencing flares were assessed, using the same statistical technique of logistic regression. Both papers report a significant risk of experiencing flares with increased sUA, confirming the findings of the IMS observational study. Although the classification in sUA levels was not identical, the impact of applying the estimates from the peer reviewed papers in the health economic model was assessed. It appeared that the outcomes are similar, and even a lower ICER was obtained with one of the published data. This is further explained in 3.14 sub-section 3.

ACD Paragraph 4.10

The Committee then considered how improvements in health-related quality of life obtained with febuxostat had been estimated. The Committee noted that estimates reported in the manufacturer's submission had been based on utility decrements associated with gout flares and on a 'chronic utility gain' associated with lower serum uric acid concentrations. It noted that this had been reported in the manufacturer's submission on the basis of a separate analysis in which a linear relationship between utility and serum uric acid concentration had been assumed. The Committee considered that the evidence supporting this linear relationship was uncertain and speculative. In particular, it considered the exploratory ERG analysis that showed the incremental QALY gain associated with the effect of lowering serum uric acid concentration (0.032), which includes the incremental QALY gain from avoidance of gout flares, as compared with the incremental QALY gain from avoidance of gout flares alone (0.006), was very high and the impact of this factor on the final ICER proportionately substantial. The Committee noted that removing the component of incremental QALY gain associated with only serum uric acid concentrations, increased the ICER from the base case of £15,000 per QALY gained to £81,000 per QALY gained over a 2-year time horizon.

See discussion in section 3.15.

Corrections

Firstly, it is important that we highlight and error in the ERGs interpretation of the utioity data. In the exploratory ERG analysis they considered that *'the effect of lowering serum uric acid concentration (0.032), which includes the incremental QALY gain from avoidance of gout flares, as compared with the incremental QALY gain from avoidance of gout flares alone (0.006)'.* This is incorrect, as the utility of the sUA level, and the decrement between levels, was fully independent of any disutility from a gout flare.

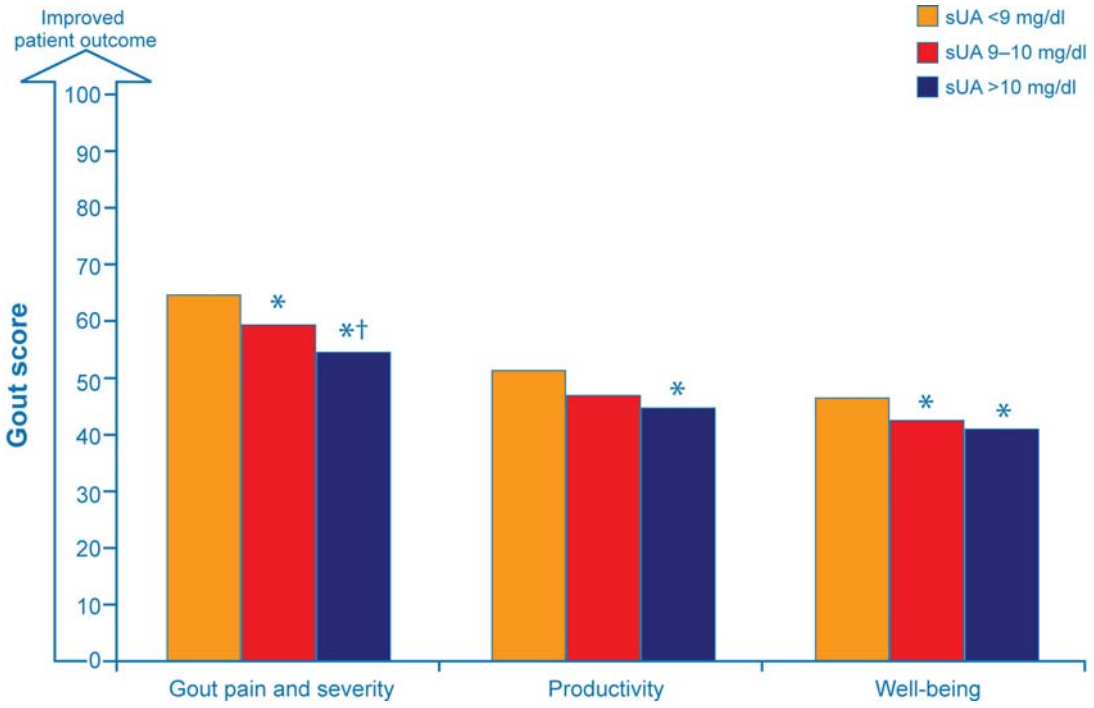
Relationship between maintained sUA level and HRQoL in gout

Increase in sUA levels is associated with progressive deterioration in quality of life for gout patients (independent of acute flares). Patients with uncontrolled gout and high sUA levels experience tophus build-up causing greater pain and complications that translate into progressive physical impairment and negative impact on patient quality of life. Increasing symptoms and complications of gout in patients with elevated sUA levels can also impair physical functioning, ability to work, productivity, and overall well-being.

All measures of physical health and function, as measured by the SF-36, were significantly lower in patients with tophi, and those with sUA levels >9 mg/dL, as reported in a quality-of-life study in 52 patients with severe gout (both $P<0.05$) (Sundy et al., 2006).

- An increased sUA had a greater negative impact on the ability to perform everyday tasks because of the significant pain and physical symptoms associated with gout.
- Patients with higher sUA levels, tophi, and/or arthropathy reported significantly more pain and pain-associated effects on quality of life.
- Gout-related pain was significantly greater in patients with higher sUA levels in a study of patient-reported outcomes in 1,823 patients with chronic gout. (Osterhaus et al., 2005) (Figure 8)
- Patients with tophi also experienced significantly more pain compared to those without tophi (Osterhaus et al., 2005)

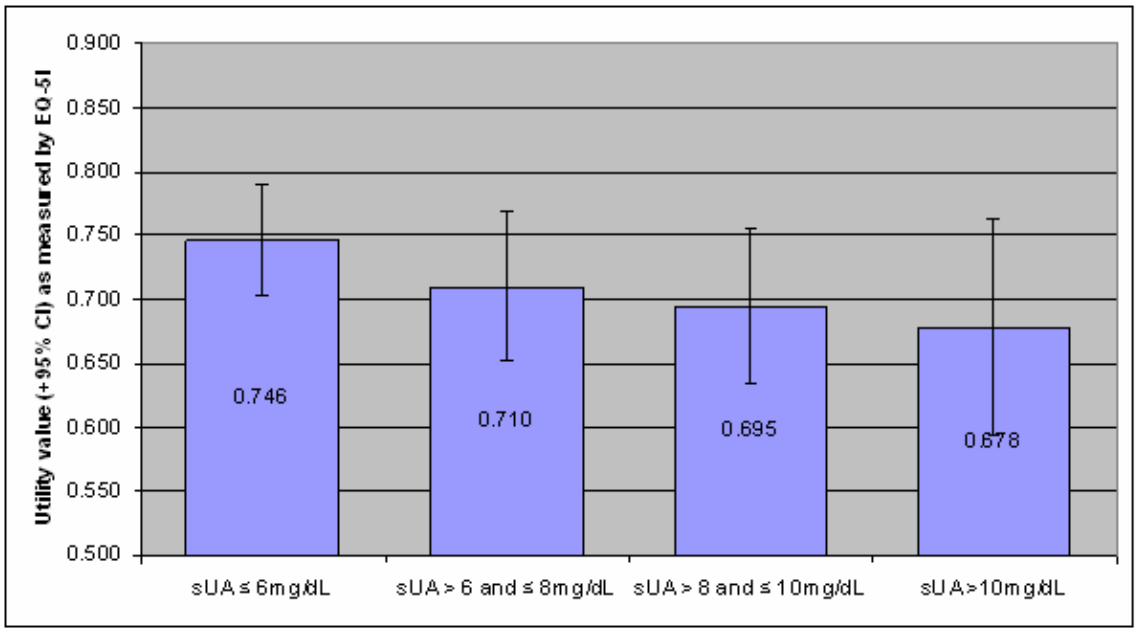
Figure 8. Impact of sUA Levels on Pain, Productivity, and Well-being in Patients With Gout



*P<0.05 vs. sUA <9 mg/dL; †P<0.05 vs. sUA 9-10 mg/dL.

Source: Osterhaus et al., 2005.

Figure 9. Relationship between sUA level and utility



In the open label extension study FOCUS statistically significant ($p<0.05$) improvements for febuxostat were observed from baseline scores in several of the SF-36 domains, the Physical Component Summary (PCS) and Health Transition. Statistically significant improvements were observed most typically in the domains associated with physical function, but not those associated with emotional function. These statistically significant improvements were most notable in the following domains: Role-Physical, Bodily Pain, and Vitality. Statistically significant changes were also observed in Health Transition, which is a general measure of change in the past year, and the PCS scale.

In the Gout Assessment Questionnaire (GAQ) there were statistically significant improvements from baseline at week 52 and final visit in the Gout Concern, Well-Being, Productivity, and Gout Pain and Severity Domains.

Results from the two assessments, i.e. SF-36 and GAQ, are similar as they both consistently show improvements in patient reported outcomes; these improvements were observed in the more physical aspects of functioning as opposed to the more emotional aspects of functioning.

Similar data have been obtained on QOL in the EXCEL study: subjects on all treatment groups experienced improvements in all SF-36 scales from baseline to the final visit. These improvements were statistically significant in the Scales of Role-Physical, Bodily Pain, Vitality, Reported Health Transition, Physical Component Summary, and MOS Health Distress. The greatest improvements in the treatment groups were noted in Role-Physical and Bodily Pain. Because only subjects whose sUA levels were controlled remained in study, the QOL results are representative of only subjects who responded to treatment.

It can be concluded from the QOL evaluation conducted in the long-term extension studies that maintaining sUA level below 0.36 mmol/l (6.0mg/dL) for a long period of time decreases progressively the symptomatic burden of gout, and this has been associated with an improvement of the SF-36 domains associated with physical function, particularly on Role-Physical, Bodily Pain and Vitality domains.

Utility linked to sUA level

The magnitude of utility associated with each serum-urate level is difficult to estimate. Few studies have been conducted on the utility associated with gout

complications developed over years of untreated urate levels and the utility increments may as well be underestimated. The IMS study has done the best effort to assess the level of utility associated with each serum level. A sensitivity analysis varying the utility increments from 0.02 to 0.05 varies the ICER between ICER (cost per QALY) £26,018 and ICER (cost per QALY) £10,786.

Gout is a condition with a lower QoL than the population in general (see Section 3.15). Several studies have shown a correlation with development of gout and high serum level. It is well accepted that long-term treatment with urate lowering therapy level prevents gout flares and may resolve gout complications of tophi and renal impairment causing disability with an impaired QoL. Febuxostat is a urate lowering drug used to prevent gout in the long-term. By removing the chronic utility gain of a lower serum levels, ERG makes an extreme assumption that the QoL in a gout patient is only associated with the rate of gout flares; In addition, ERG disregards the disabling long-term complications of gout that are causing most suffering for the individual and costs for the NHS.

Impact of chronic gout on patient quality of life has been considered comparable to the chronic condition rheumatoid arthritis.

Excluding the impacts of flare, chronic gout also has a negative impact on patient well-being and quality of life, which is comparable to that of rheumatoid arthritis (RA). RA is a chronic, progressive and destructive condition that, if untreated, is well-recognized as having a significant impact on patient outcomes and quality of life (Ware et al., 1993; Ware et al., 2002; Haroon et al., 2007). Chronic gout and RA are similar in terms of patient quality-of-life effects on the following:

- Physical functioning and the physical roles and activities that patients can assume in daily life,
- Bodily pain, and
- General health and vitality.

A patient-reported outcomes study of 245 patients with RA and 12 with chronic gout, who were not experiencing flares, revealed similar effects on key health and other patient outcomes (Brown et al., 1987) (Table 7).

Table 7. Patient Effects of Rheumatoid Arthritis Versus Gout

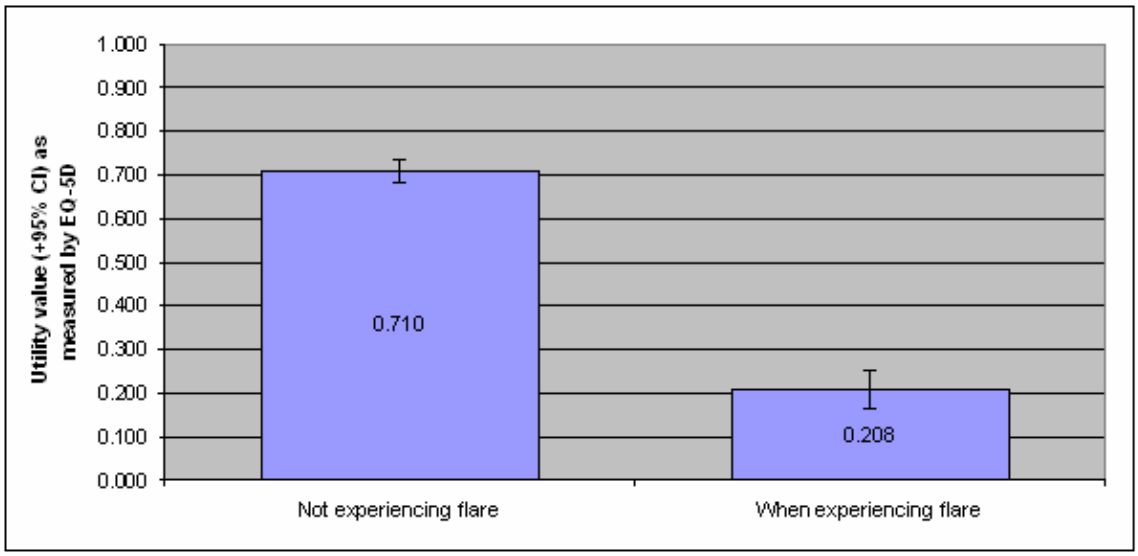
Effect on Patient	Rheumatoid arthritis	Gout
Pain	63%	50%
Stiffness	61%	42%
Inability to perform daily tasks	43%	25%
Immobility	15%	18%
Inability to work	24%	17%
Loneliness	13%	8%
Financial problems	21%	17%

Source: Brown et al., 1987.

ACD Paragraph 4.11

The Committee also considered that the difference in quality of life between experiencing a flare or not might have been overestimated because of bias in the research used to inform this parameter, since individuals had been asked to recall or imagine states they were not currently in. While it understood that the pain of flares can be extreme, it thought that the reported difference in EQ-5D scores for experiencing a gout flare of 1 week duration was an overestimate. On the other hand, it heard from a patient expert that the assumption that gout flares lasted for 1 week might be a significant underestimate. Overall, the Committee thought that there was considerable uncertainty over the estimation of disutility associated with gout flares. The Committee noted that there were a number of anomalous responses, such as better overall health when experiencing a flare than when not, and perfect health during a flare.

Figure 10: Impact of a flare on utility (IMS)



Potential bias in data linking flare to QoL

A set of bivariate analyses were performed with an independent variable set to: "whether or not the patient was experiencing a gout flare at the moment of assessment". The bivariate analyses was performed in order to evaluate the impact of the recall technique, by assessing if there was a significant difference in HRQoL scores reported by the group of patients when stratified by patients expereicning and no experiencing flare at the moment of inclusion.

No significant difference was observed patients that experienced at flare at the moment of study inclusion versus patient that were not experiencing a flare.

We therefore considered the effect of recall bias as negligable.

Sensitivity in flare disutility

A univariate analysis (20% variation) was also performed on the utility decrease associated with a gout flare. The impact of this scale of variance in disutility was minor; a £224 change in ICER after 12 months and a £218 change after 24 months. Corresponding data for a 50% variation were changes of £561 and £545 respectively. Moreover, setting the disutility of a flare at zero (i.e. ignoring the QoL impact of flares) resulted in an ICER of £17,154 and £16,130 for 1-year and 2-year, respectively.

Anomalous response

Regarding the anomalous responses, patients were ananonomyzed. We could therefore not re-contact them for re-considering their responses. We could have opted to exclude these patients from the analyses, but then the difference between flare and no flare would even be more extreme.

ACD Paragraph 4.12

The Committee discussed the time horizons used in the manufacturer's model. It thought that for this chronic illness requiring life-long therapy, a lifetime time horizon would have been appropriate. The Committee took into account evidence from the open-label EXCEL extension study showing that a higher percentage of patients receiving febuxostat discontinued treatment compared with those receiving allopurinol. The Committee believed that the assumption over the 2-year time horizon that patients would remain on treatment, even if only a partial treatment effect was achieved, potentially biased the economic results in favour of febuxostat. It also noted that there could potentially be long-term benefits associated with febuxostat, such as avoidance of adverse renal events in comparison with other therapies. The Committee considered the univariate sensitivity analysis, which showed that an extension of the manufacturer's economic model to 5 years had marginal impacts on the base-case ICER. However, it noted that this simply reflects the assumption that patients continue to accrue treatment benefits beyond the 2-year time horizon.

Life-time horizon

IPSEN note the comments from NICE and the ERG on the potential merits of a life-time horizon model. However, at present long-term effect data are limited and the current model did not allow for lifetime perspective without making several assumptions, which added further to the uncertainty in the model. We felt the most robust approach was to base the model duration over the same time horizon as seen in the key clinical trial evidence base. In this way we accepted that many of the long-term advantages of stable controlled sUA and gout were not included in the model results. However, we felt that this was a more conservative approach to have taken given the limited data on the key comparator, allopurinol.

Therefore, a 2-year model was selected as a base case to give an estimate of cost-effectiveness with a reasonable certainty.

Discontinuation in the EXCEL study

The model was based on a first-line treatment comparison, and did not include treatment sequencing, and as such discontinuation data were not included in the model.

We do have a point of correction to make to the ACD statement. In 4.12 the committee state that *'the open-label EXCEL extension study showing that a higher percentage of patients receiving febuxostat discontinued treatment compared with those receiving allopurinol.'.* This is an incorrect statement and in fact the opposite was true. In the EXCEL study by far the greatest level of treatment withdrawal was seen in the allopurinol patients, with the level of withdrawal for febuxostat much lower.

In the EXCEL study, the most common reason for switching medication was lack of efficacy. A greater percentage changed from allopurinol to febuxostat (57%) than from febuxostat to allopurinol (18% [80 mg], 8% [120 mg]) due to lack of efficacy i.e., sUA levels ≥0.36 mmol/l (6.0mg/dL) at 6 months (Becker et al., 2007a) (Figure 11). In addition, a greater percentage of those who switch to febuxostat from allopurinol reached the sUA levels ≥0.36 mmol/l (6.0mg/dL) at 6 months, than those switching to allopurinol (Figure 12).

Figure 11. Percentage of Patients Who Switched Treatment Due to Lack of Efficacy

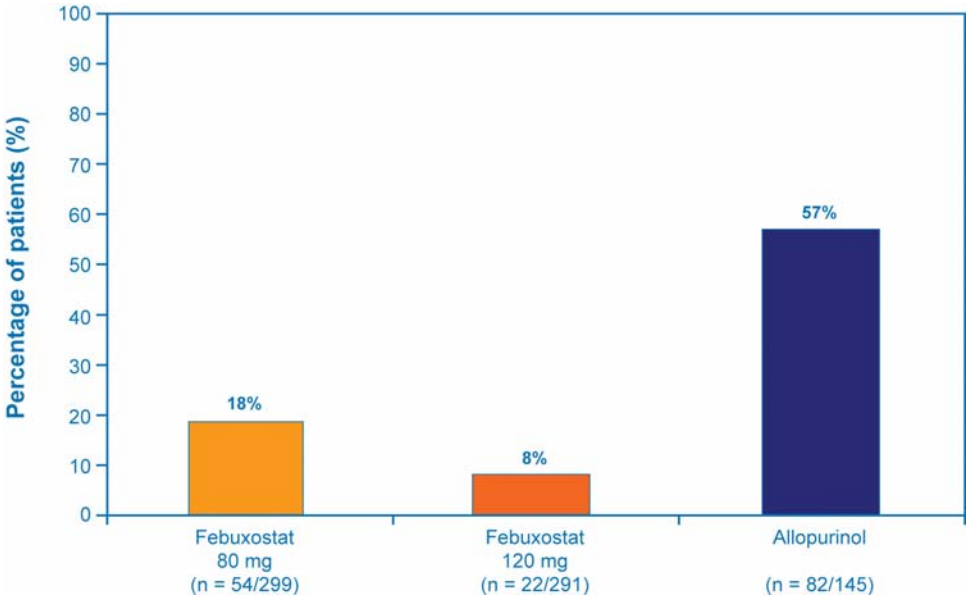
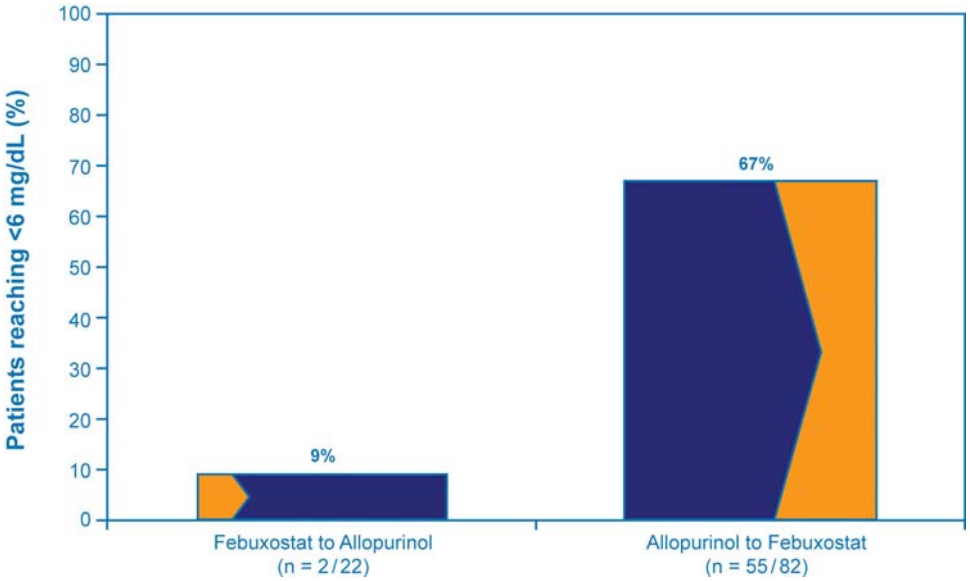


Figure 12. Percentage of Patients Who Switched Therapy Who Reached sUA Levels ≤0.36 mmol/l (6.0mg/dL)



More patients in the allopurinol group (62%) than in the febuxostat 80mg (32%) and febuxostat 120 mg (44%) groups were prematurely withdrawn from the EXCEL study.

Therefore, if treatment discontinuation and switch to a 'no treatment' option had been included in the model then the allopurinol arm would have experience a much greater reduction in clinical benefit than that seen with febuxostat.

Finally, as previously stated in 3.13, full treatment adherence was applied in the model, since there were no data available (in the databases we received from the FACT and APEX trial) on how patients evolve after treatment discontinuation.

It should however be noted that full adherence also implies a constant treatment cost over the entire time horizon, which is much higher for febuxostat than for allopurinol. Treatment discontinuation will therefore not solely decrease effectiveness on an ITT basis, but will also substantially decrease the costs.

ACD Paragraph 4.13

The Committee discussed cost assumptions in the model. It considered it plausible that the main drivers of incremental cost would be the drug cost (noting the 13-fold difference between febuxostat and allopurinol), and the costs saved by avoiding treatment costs associated with any flares. It concluded that the total cost avoided by reduction in flares may have been overstated because the difference in expected number of flares may have been overestimated, as discussed above.

The discussion in comment 3.14 provides data about the relationship between sUA levels and flare rates and an exploratory analysis regarding the impact on ICER of the uncertainty around flare rates in the model.

ACD Paragraph 4.14

Overall, the Committee concluded that, on the basis of the evidence presented, febuxostat had not been shown to be clinically effective or cost-effective compared with the appropriate comparators, which are up-titrated allopurinol and second-line therapies. It agreed that febuxostat had been shown to be more effective than fixed-dose allopurinol in lowering serum uric acid concentrations. It concluded that recommending febuxostat for the management of chronic hyperuricaemia in patients with gout would not be a cost-effective use of NHS resources.

The NICE Guide to Methods of Technology Appraisal section 2.2.3 states “All relevant comparators are identified, with consideration given to current practice and the natural history of the condition without suitable treatment. Although best alternative care is the essential comparator, treatments representing routine UK care are also important where they differ from best alternative care.”

The appraisal committee’s recommendations have not taken into consideration the current clinical practice of gout where 97% of the patients treated with allopurinol at a fixed dose of ≤ 300mg.

Furthermore, there is not good quality randomized clinical evidence to suggest that dose-titrated allopurinol may be more effective than fixed-dose allopurinol; and it is clearly seldom used in clinical practice (for very clear reasons of safety and tolerability, given the renal issues associated with these patients). A recent

systematic review has failed to identify any randomised controlled trial evidence that can provide efficacy and safety data that can confirm the efficacy and safety of higher doses of allopurinol.

For this reason we feel that the decision of NICE to identify titrated high-dose allopurinol as the preferred comparison in this analysis goes against the general guidelines for developing economic analyses for submission to NICE.

Regarding other suggested comparators (which fall more in the 2nd line level of treatment); benzbromarone and probenecid are not licensed in the UK and can therefore not be considered as best clinical practice or standard clinical practice in the UK. The fact that they are mentioned in the BSR guidelines reflects the unmet need of effective and safe gout therapy in patients who cannot tolerate or fail treatment with allopurinol. However, these drugs are simply not available under normal prescribing conditions in the UK. Therefore in a 2nd line setting the only possible comparator that could be considered after allopurinol would be sulphinpyrazone or 'no treatment'.

- Febuxostat is clearly more effective than 'no treatment' when comparing against placebo. It is also proven that the clinical efficacy of febuxostat is comparable if treatment is given before allopurinol or after failure on allopurinol (see the EXCEL open label extension trial).

- Sulphinpyrazone, like allopurinol, is only suitable in patients with at most limited renal impairment.

We agree wholeheartedly with the BSR guideline comment that benzbromarone, sulphinpyrazone and probenecid all have limitations such as restricted availability, adverse effects and poor effectiveness. As febuxostat has been shown to have a favourable benefit-risk when compared to allopurinol, it was not considered necessary to further demonstrate the benefit risk against products with a lower benefit risk than allopurinol, especially considering direct access to these medicines is very limited in the UK..

As discussed throughout the document it is clear that febuxostat can provide a significant clinical benefit to all patients suffering from gout. These clinical benefits are achieved through an improved control of patients' sUA levels to fall below current target levels of 0.30 mmol/l (5.0mg/dL) and 0.36 mmol/l (6.0mg/dL), as set out in the BSR and EULAR guidelines. In addition, there are

key categories of patients who cannot be sufficiently treated by allopurinol and for whom there is a paucity of available treatment options. This is a clear un-met need. Not recommending use of febuxostat would preclude these patients from accessing febuxostat as an effective treatment alternative in a reversible disabling disease.

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