NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Febuxostat for the management of hyperuricaemia in patients with gout

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide additional information and clarification relating to systematic reviews carried out, clinical effectiveness and cost effectiveness data presented and used in the economic model, and methodology used to assess uncertainty in the economic results.

Indicative licensed indication

Febuxostat (Adenuric, Ipsen) does not currently have a UK marketing authorisation. However, the EMEA Committee for Medicinal Products for Human Use adopted a positive opinion in February 2008, recommending febuxostat for the treatment of chronic hyperuricaemia in conditions where urate/uric acid deposition has already occurred (including a history, or the presence, of tophus and/or gouty arthritis).

Key issues for consideration

Clinical effectiveness

- Is there robust evidence on the clinical effectiveness of febuxostat within its proposed licensed indications compared with the principal alternative treatment, allopurinol, taking into account the following:

  - The pooled efficacy analysis presented by the manufacturer and the results of the ERG's meta-analysis.
  - The comparison with a fixed dose of allopurinol of 300 mg/day (which may be the treatment option usually used in routine clinical practice), rather than with dose titration of allopurinol according to serum uric acid (sUA) levels (which is the recommended approach in BSR and EULAR guidelines - see appendix B)?
- Is the post hoc analysis of patient subgroups on the basis of sUA levels appropriate and valid?
- Is the reliance on therapeutic targets for sUA levels as a surrogate endpoint for clinical outcomes appropriate?
- What are the Committee's views on the clinical effectiveness of febuxostat in cases where allopurinol cannot be used given the absence of evidence in this population?

Cost effectiveness

- What is the impact of the uncertainties in the manufacturer's model and the results of the economic analysis, taking into account the following:
  - The absence of modelling of a sequence of treatment strategies that allows patients to receive alternative treatments once they show non-response or are intolerant to initial treatments (over a lifetime horizon)?
  - The relationship between sUA levels and:
    - ◊ gout flares
    - ◊ tophi reduction
    - ◊ long-term development of gouty arthritis?
  - The assumption of full compliance and usage over the modelled time horizon, considering the discontinuation rate observed in the EXCEL trial?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with hyperuricaemia in whom urate deposition has already occurred (including a history, or the presence, of tophus and/or gouty arthritis).
Intervention	Febuxostat (80 or 120 mg once daily).
Comparators	Fixed-dose allopurinol (300 mg/day).
Outcomes	Serum uric acid levels; gout flares; reduction in tophi size; tolerance; health-related quality of life.
Economic evaluation	Cost effectiveness expressed in incremental cost per quality-adjusted life year (QALY) over 2 years (based on 1-year trial data and a further 1-year extrapolation).

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered that the manufacturer's description of the eligible patient population was appropriate; that is, adults with hyperuricaemia in whom urate deposition has already occurred (including a history, or the presence, of tophus and/or gouty arthritis). Although the MS states that no subgroup analyses were presented (since the data from subgroups lacked statistical power), primary outcomes were analysed according to baseline sUA levels and the proportion of patients achieving a defined therapeutic target.

1.2.2 Intervention

The ERG noted that febuxostat is a novel, orally administered, nonpurine selective inhibitor of xanthine oxidase, and that the proposed course of treatment is continuous at a recommended dose of 80mg daily, which can be increased to 120 mg daily if an additional sUA lowering effect is required.

1.2.3 Comparators

The comparators specified in the decision problem in the MS do not match completely with the comparators listed in the NICE final scope document for the appraisal. The MS excludes alternative treatments such as: (1) sulphinpyrazone, benzbromarone (not licensed in the UK but used off-license), probenecid, or a combination of these treatments for adults unresponsive or intolerant to allopurinol and (2) allopurinol (dose adjusted according to glomerular filtration rate), benzbromarone, or a combination of these treatments for adults with renal impairment. The MS argues that alternative treatments were not considered as appropriate comparators because they are rarely used in clinical practice in the UK (fewer than 3% of patients receive them) because of limitations in efficacy, safety profile and contraindications. The ERG, however, considered these alternative treatments to be relevant comparators in patients unresponsive or intolerant to allopurinol and/or in patients with renal impairment.

1.2.4 Outcomes

The health outcomes listed in the manufacturer's decision problem reflect the NICE final scope. Although the ERG acknowledges that sUA levels are an appropriate surrogate outcome measure, there is no clear rationale given in the MS, or discussion of the evidence used in support of the therapeutic targets chosen or advocated by the British Society of Rheumatology and British Health Professionals in Rheumatology (BSR) and European League Against Rheumatism (EULAR) guidelines (see appendix B); nor is any evidence supplied supporting the relationship between sUA levels and clinical outcomes (for instance, gout recurrence and reduction in tophi). In addition, the MS does not present details of the criteria and features used to define gout flares (including severity). The ERG notes that currently there are no standardised or validated tools available to measure tophus size as an outcome, and that tophus size can be measured in several ways. It is not clear whether the techniques employed for measuring tophus size in the APEX and FACT trials were reliable and accurate.

1.2.5 Economic evaluation

The time frame of the economic model presented in the MS does not extend to patients over a lifetime horizon. The MS argues that a time horizon of longer than 2 years will require extrapolation beyond the available trial data.

1.3 Statements from professional/patient groups and nominated experts

Gout is the commonest type of inflammatory arthritis in men and it is treated mainly in primary care. The objectives of treatment are: (1) to manage the pain associated with acute attacks of gout; (2) to give advice on how the patient can modify their lifestyle and diet, and how they can reduce other modifiable risk factors, in order to lower their sUA levels; and (3) to reduce tissue uric acid levels and maintain them below the saturation point at which urate crystals can form; this will prevent further urate crystal formation and result in existing crystals dissolving ('cure').

The clinical specialists stated that allopurinol is the main (and often the only) urate-lowering treatment used by GPs in the UK. It can be used in patients who are under-excretors of uric acid (the usual situation) or over-producers of uric acid (less common). However, recent audits of quality of care in the UK show that only around one-third of patients with gout receive urate-lowering therapy. Of those who receive treatment, almost all receive fixed-dose allopurinol (300 mg/day), which is insufficient for many patients. Allopurinol can be titrated up to 900 mg/day to achieve target sUA levels, but should be used with caution in patients with renal impairment, since prolonged excretion of its metabolite oxipurinol leads to increased toxic effects, including allopurinol hypersensitivity syndrome. The lower the sUA level is below this target value, the faster will be the both the reduction in tophi size and the elimination of urate crystals, and the sooner the patient is 'cured'.

According to one clinical specialist, febuxostat is effective in patients with renal impairment (such patients are at a greater risk of allopurinol toxicity and

cannot be treated with uricosurics); in addition, because of febuxostat's selective inhibition of xanthine oxidase, it is potentially less toxic. Thus for some patients who are unable to tolerate allopurinol, and for some patients with renal impairment, or who have had a treatment-related adverse event, the availability of an alternative treatment such as febuxostat will be beneficial. Febuxostat may also be particularly appropriate for patients with tophaceous gout. Uricosuric drugs (for example, sulphinpyrazone and probenecid) are less effective urate-lowering agents than allopurinol, are not widely available and are contraindicated in patients with renal impairment. Benzbromarone is a more active uricosuric agent that can be used in patients with mild to moderate renal impairment, but it has limited availability and it is reported to cause hepatotoxicity.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The evidence on the clinical effectiveness of febuxostat presented in the MS is based on the results of three randomised controlled trials (RCTs). These are the FACT (n = 762 patients) and APEX (n = 1072 patients) trials, which are direct head-to-head, phase III, randomised comparisons of febuxostat with allopurinol; and the TM-00-004 study (n = 153 patients), which is a phase II trial comparing febuxostat with placebo. The FACT trial evaluated 80 and 120 mg/day doses of febuxostat versus 300 or 100 mg/day allopurinol over 52 weeks. The APEX trial evaluated doses of febuxostat 80 mg/day (n = 262), 120 mg/day (n = 269), 240 mg/day (n = 134) versus 300 or 100 mg/day allopurinol over 28 weeks. Supplementary data from two open-label extension studies were presented in support of the clinical efficacy and safety profile of febuxostat: the EXCEL extension study that enrolled a subset of patients (n = 735) from the FACT/APEX trials, and the FOCUS extension study that enrolled patients (n = 116) who completed the TM-00-004 trial. See the MS (pages 59–90) and the ERG report (pages 29–49) for further details.

Table 1 summarises the evidence from the MS on the clinical effectiveness of febuxostat (80 mg/day) versus fixed-dose allopurinol (300 or 100 mg/day) based on pooled analysis (not meta-analysis) of data from the APEX and FACT trials.

Table 1 Comparison of the clinical effectiveness of febuxostat (80 mg/day) versus fixed-dose allopurinol (300 or 100 mg/day)

Outcomes[1]	Febuxostat (80 mg/day)	Allopurinol (300 or 100 mg/day)	Absolute difference	97.5% CI[2]	p value
sUA[3] levels < 6.0 mg/100 ml at last 3 visits	51%	22%	29%	22.5, 35.3	< 0.001
sUA levels < 6.0 mg/100 ml at final visit[4]	73%	38%	NR[5]	NR	≤ 0.05
Reduction in number of tophi	NR	NR	-	-	-
Recurrent gout flares needing treatment:					
day 1 to week 8 (prophylaxis)	25%	22%	NR	NR	NS[6]
week 9 to week 52	59%	55%	NR	NR	NS
day 1 to week 52	60%	58%	NR	NR	NS
Percentage change from baseline in sUA levels at final visit (mean ± SD[7])	−45.0±18.6	−33.6±15.0	NR		≤ 0.05
Percentage change from baseline in tophus size (median):					
week 28	−34.7	−28.6	NR	-	NS
week 52	−83.4	−49.7	NR	-	NS
final visit	−43.9	−25.0	NR	-	NS
Subgroup analysis: sUA levels < 6 mg/100 ml at final visit for patients with baseline sUA levels of:					
< 9 mg/100 ml					

[1] Results given as percentages reflect the number of patients achieving the desired endpoint as a proportion of the number of patients evaluated for the outcome measure in each treatment arm.
[2] CI = confidence interval.
[3] sUA = serum uric acid.
[4] This is measured on the last visit of a specific patient. Analysis of this outcome measure was not based on the intention-to-treat population.
[5] NR = not reported.
[6] NS = not significant at the 5% level.
[7] SD = standard deviation.

9 to < 10 mg/100 ml	86%	56%	NR	NR	≤ 0.05
≥ 10 mg/100 ml	75%	40%	NR	NR	≤ 0.05
	64%	21%	NR	NR	≤ 0.05
sUA levels at final visit:					
< 5.0 mg/100 ml					
< 4.0 mg/100 ml	47%	13%	NR	NR	≤ 0.05
	19%	2%	NR	NR	≤ 0.05

Table 2 summarises the evidence on the clinical effectiveness of febuxostat (120 mg/day) versus fixed-dose allopurinol (300 mg/day) based on pooled analysis (not meta-analysis) of data from the APEX and FACT trials. See the MS (pages 59–90) and the ERG report (pages 29–49) for further details.

Table 2 Comparison of the clinical effectiveness of febuxostat (120 mg/day) versus fixed-dose allopurinol (300 or 100 mg/day)

Outcomes	Febuxostat (120 mg/ day)	Allopurinol (300 or 100 mg/day)	Absolute difference	97.5% CI	p-value
sUA levels < 6.0 mg/100 ml at last 3 visits	63%	22%	42%	35.4, 47.9	< 0.001
sUA levels < 6.0 mg/100 ml at final visit	79%	38%	NR	NR	≤ 0.05
Reduction in number of tophi	NR	NR	–	–	–
Recurrent gout flares needing treatment:					
day 1 to week 8 (prophylaxis)	36%	22%	NR	NR	≤ 0.05
week 9 to week 52	61%	55%	NR	NR	≤ 0.05
day 1 to week 52	67%	58%	NR	NR	≤ 0.05
Percentage change from baseline in sUA levels at final visit (mean ± SD)	−51.7±18.9	−33.4±15.0	NR	–	≤ 0.05
Percentage change from baseline in tophus size (median):					
week 28	−52.7	−28.6	NR	–	≤ 0.05
week 52	−65.5	−49.7	NR	–	NS
final visit	−43.8	−25.0	NR	–	NS
Subgroup analysis:					
sUA levels <6 mg/100 ml at final visit for patients with baseline sUA levels of:					
< 9 mg/100 ml	88%	56%	NR	NR	≤ 0.05

9 to < 10 mg/100 ml	89%	40%	NR	NR	≤ 0.05
≥ 10 mg/100 ml	67%	21%	NR	NR	≤ 0.05
sUA levels at final visit:					
< 5.0 mg/100 ml	47%	13%	NR	NR	≤ 0.05
< 4.0 mg/100 ml	39%	2%	NR	NR	≤ 0.05

2.2 Evidence Review Group comments

The ERG noted that the key issue limiting the robustness and generalisability of the evidence on clinical effectiveness presented in the MS is that febuxostat is compared with fixed-dose allopurinol (300 mg/day) in the FACT and APEX trials. BSR and EULAR guidelines and the summary of product characteristics for allopurinol generally recommend dose titration of allopurinol according to therapeutic outcomes. It is possible that dose-titrated allopurinol is more effective than fixed-dose allopurinol at lowering sUA levels. However, it is understood that dose titration (escalation) of allopurinol is rarely used in routine clinical practice in the UK.

The evidence on clinical effectiveness presented in the MS is based on pooled analysis of data from the APEX and FACT trials; effectively, the studies were treated as one large study (data from the TMX-00-004 study were not included in the pooled analysis since this study only included data for 4 weeks of treatment). A pooled analysis relying on treatment groups rather than on studies fails to preserve randomisation in the RCT evidence and introduces bias and confounding. A better methodological approach would be meta-analysis of the data sets. The ERG therefore carried out a meta-analysis (based on both fixed- and random-effects modelling) using the RCT data and evidence presented by the manufacturer. The results of the meta-analysis showed that the probability of reaching sUA therapeutic targets was significantly higher for patients receiving febuxostat (80 or 120 mg/day) relative to those receiving fixed-dose allopurinol (300 mg/day) ($p < 0.00001$ for all comparisons) (see tables 3 and 4). For the post hoc subgroup analysis of patients with baseline sUA levels below 9 mg/100 ml and who achieved sUA

levels below 6 mg/100 ml at the last three visits, the probability was higher ($p < 0.0002$). The difference in the number of gout flares needing treatment during (weeks 1–8) or after prophylaxis (weeks 9–52) for patients receiving 80 mg/day febuxostat compared with those receiving fixed-dose allopurinol was not statistically significant ($p > 0.18$). The number of gout flares needing treatment during or after prophylaxis was significantly lower with fixed-dose allopurinol than with 120 mg/day febuxostat ($p < 0.05$).

A test for statistical heterogeneity between the trial results was not significant for any of the outcome measures ($p > 0.05$). However, it should be noted that prophylactic treatment of gout flares following initiation of treatment in the APEX and FACT trials was for only 8 weeks. This is a shorter period than is recommended in the BSR guidelines for prophylaxis with colchicine (up to 6 months following initiation of a urate-lowering therapy). A longer period of prophylaxis may decrease the incidence of gout flares in the first few months of therapy. Prophylactic treatment included the use of colchicine or naproxen (a non-steroidal anti-inflammatory drug [NSAID]).

Table 3 summarises results of the ERG's meta-analysis comparing febuxostat (80 mg/day) with allopurinol (300 or 100 mg/day) (intention-to-treat analysis).

Table 3 Meta-analysis comparing febuxostat (80 mg/day) with allopurinol (300 or 100 mg/day). Values in parentheses represent 95% confidence interval (CI).

Outcomes	Febuxostat (80 mg/day)	Allopurinol (300 or 100 mg/day)	Relative risk (fixed effects)	Relative risk (random effects)	Risk difference (fixed effects)	Risk difference (random effects)
sUA levels < 6.0 mg/100 ml at last 3 visits	51%	22%	2.33 (1.94, 2.80)	2.32 (1.93, 2.79)	29% (+23%, +34%)	29% (+23%, +34%)
sUA levels < 6.0 mg/100 ml at final visit[8]	73%	38%	1.95 (1.72, 2.21)	1.95 (1.72, 2.20)	36% (+30%, +41%)	36% (+30%, +41%)
Recurrent gout						

[8] Results are not based on intention-to-treat analysis but on available cases. A sensitivity analysis conducted by the ERG using all randomised patients yielded similar results. The sensitivity analysis was, however, not reported in the ERG report.

flares needing treatment:						
day 1 to week 8 (prophylaxis)	25%	22%	1.14 (0.91, 1.42)	1.14 (0.91, 1.42)	3% (−2%, +8%)	3% (−2%, +8%)
week 9 to week 52	60%	55%	1.08 (0.97, 1.20)	1.08 (0.97, 1.26)	4% (−2%, +11%)	4% (−2%, +12%)
day 1 to week 52	60%	58%	1.05 (0.95, 1.16)	1.04 (0.92, 1.18)	3% (−3%, +9%)	3% (−3%, +10%)
Subgroup analysis: sUA levels < 6 mg/100 ml at last 3 visits for patients with baseline sUA levels of:						
< 9 mg/100 ml	61%	38%	1.61 (1.26, 2.06)	1.62 (1.26, 2.07)	23% (+12%, +35%)	23% (+12%, +35%)
9 to 10 mg/100 ml	55%	23%	2.35 (1.74, 3.18)	2.36 (1.74, 3.19)	31% (+22%, +41%)	31% (+22%, +41%)
≥ 10 mg/100 ml	41%	9%	4.59 (2.88, 7.32)	4.56 (2.85, 7.28)	32% (+25%, +40%)	32% (+20%,+44%)
Subgroup analysis: sUA levels < 6 mg/100 ml at final visit[8] for patients with baseline sUA levels of:						
<9 mg/100 ml	86%	56%	1.54 (1.31, 1.80)	1.55 (1.32, 1.81)	30% (+20%, +40%)	31% (+19%, +43%)
9 to <10 mg/100 ml	75%	40%	1.85 (1.51, 2.29)	1.85 (1.51, 2.26)	34% (+24%, +44%)	34% (+25%, +44%)
≥ 10 mg/100 ml	64%	21%	2.99 (2.24, 4.00)	2.99 (2.24, 4.00)	+43% (+34%, +51%)	43% (+34%, +51%)
Subgroup analysis: sUA levels at final visit[8]:						
< 5.0 mg/100	47%	13%	3.62	3.62	34%	34%

ml			(2.83, 4.63)	(2.83, 4.63)	(+28%, +39%)	(+28%, +39%)
< 4.0 mg/100 ml	19%	2%	9.68 (5.10, 18.36)	9.47 (4.99, 17.97)	17% (+13%, +21%)	17% (+13%, +21%)

Table 4 summarises the results of the ERG's meta-analysis comparing febuxostat (120 mg/day) versus allopurinol (300 or 100 mg/day) (intention-to-treat analysis).

Table 4 Meta-analysis comparing febuxostat (120 mg/day) versus allopurinol (300 or 100 mg/day). Values in parentheses represent 95% confidence interval (CI).

Outcomes	Febuxostat (80 mg/day)	Allopurinol (300 or 100 mg/day)	Relative risk (fixed effects)	Relative risk (random effects)	Risk difference (fixed effects)	Risk difference (random effects)
sUA levels < 6.0 mg/100 ml at last 3 visits	63%	22%	2.91 (2.44, 3.47)	2.91 (2.44, 3.47)	42% (+36%, +47%)	42% (+36%, +47%)
sUA levels < 6.0 mg/100 ml at final visit[8]	79%	38%	2.11 (1.87, 2.38)	2.11 (1.87, 2.38)	42% (+36%, +47%)	42% (+36%, +47%)
Recurrent gout flares needing treatment:						
day 1 to week 8 (prophylaxis)	36%	22%	1.65 (1.36, 2.02)	1.65 (1.36, 2.02)	14% (+9%, +20%)	14% (+9%, +20%)
week 9 to week 52	61%	55%	1.12 (1.00, 1.25)	1.11 (1.00, 1.24)	7% (0%, +13%)	6% (0%, +13%)
day 1 to week 52	67%	58%	1.16 (1.06, 1.28)	1.15 (1.04, 1.29)	9% (+3%, +15%)	9% (+3%, +15%)
Subgroup analysis: sUA levels < 6 mg/100 ml at last 3 visits for patients with baseline sUA levels of:						
< 9 mg/100 ml	74%	38%	1.95 (1.55, 2.46)	1.95 (1.55, 2.46)	36% (+26%, +47%)	36% (+26%, +47%)
9 to <10 mg/100 ml	74%	23%	3.19 (2.40, 4.23)	3.19 (2.40, 4.23)	51% (+41%, +60%)	51% (+41%, +60%)
≥ 10 mg/100 ml	48%	9%	5.29 (3.33, 8.40)	5.29 (3.33, 8.39)	39% (+31%, +47%)	39% (+31%, +47%)
Subgroup analysis: sUA levels < 6 mg/100 ml at final visit[8] for patients with baseline sUA levels of:						

< 9 mg/100 ml	88%	56%	1.56 (1.33, 1.82)	1.56 (1.33, 1.83)	32% (+22%, +41%)	32% (+22%, +41%)
9 to <10 mg/100 ml	89%	40%	2.19 (1.81, 2.64)	2.18 (1.80, 2.64)	48% (+39%, +57%)	48% (+39%, +57%)
≥ 10 mg/100 ml	67%	21%	3.11 (2.33, 4.15)	3.10 (2.32, 4.14)	45% (+36%, +54%)	45% (+36%, +54%)
Subgroup analysis: sUA levels at final visit[8]:						
<5.0 mg/100 ml	47%	13%	5.07 (4.01, 6.42)	5.07 (4.01, 6.42)	52% (+47%, +57%)	52% (+47%, +57%)
<4.0 mg/100 ml	39%	2%	19.92 (10.68, 37.14)	19.53 (10.47, 36.42)	37% (+33%, +42%)	37% (+33%, +42%)

According to the ERG report, short- to medium-term clinical trial data (up to 1 year) suggest that the adverse event profile for febuxostat is similar to that for allopurinol, although published long-term safety data are lacking. The rates of discontinuation in the FACT and APEX RCTs suggest that febuxostat is not as well tolerated as allopurinol. However, no statistical comparisons between rates of discontinuation were reported in the submitted evidence or in the requested supplementary data.

The most common adverse event leading to withdrawal from the trials was liver function test abnormalities, with seven patients receiving febuxostat 120 mg/day and five patients receiving febuxostat 80 mg/day discontinuing treatment compared with one patient receiving fixed-dose allopurinol (300 mg/day). A higher incidence of gout flares with febuxostat (particularly 120 mg/day) during initial prophylaxis with colchicine or naproxen may lead to compliance issues in the short term, although the RCT evidence suggests that the incidence of gout flares may be reduced by starting at lower doses of febuxostat.

2.3 Statements from professional/patient groups and nominated experts

The population in which febuxostat has been tested in trials is likely to be different from that seen in UK primary care settings, where the use of this drug would be greatest. Notably, very few patients managed in the UK primary care setting have tophaceous gout. However, there are no reasons to believe that the results for other outcomes (including effects on sUA levels and recurrence of gout) are not generalisable to the UK population. The available clinical effectiveness evidence indicates that febuxostat is superior to the standard dose of 300 mg/day allopurinol in reducing sUA levels. However, in clinical trials comparing two doses of febuxostat (80 and 120 mg/day) with 300 mg/day allopurinol, almost half of the patients on the higher 120 mg/day dose did not reach the therapeutic target of sUA levels of below 6.0 mg/100 ml after 1 year of treatment.

It is therefore unclear what the approach should be with patients who fail to reach the target therapeutic sUA levels on 120 mg/day febuxostat. The use of a fixed dose of allopurinol of 300 mg/day does reflect common UK GP practice, even though recommendations in the EULAR and BSR guidelines are to use an escalating dose of allopurinol, titrated against sUA levels, up to a maximum dose of 900 mg/day depending on renal function.

Current evidence does not support any inference on the clinical effectiveness of febuxostat in comparison with doses of allopurinol titrated up to 900 mg/day or on the effect of titrating the dose of febuxostat. Although febuxostat was superior to allopurinol in reducing sUA levels, the RCTs did not show beneficial effects on the recurrence of gout over the first year of use. An apparent benefit was found in post hoc analysis of the trial results in the final 4 weeks of follow-up, but in the early follow-up periods the patients receiving febuxostat had more attacks of recurrent gout than those in the allopurinol group. This may be because of co-prescription of NSAIDS or colchicine for the

first few months of treatment, which is similar to the way in which allopurinol is used.

One clinical specialist was of the opinion that, since febuxostat does not appear to be superior to allopurinol in reducing recurrent gout, its use over the short term should be restricted to patients who have failed to achieve an adequate reduction in sUA levels to below 0.36 mmol/l (or 6 mg/100 ml) on a full dose of allopurinol or who are unable to tolerate allopurinol.

Generally, adverse effects of febuxostat do not seem to be a problem. In the one-year FACT trial, four participants in the febuxostat groups died compared with none in the allopurinol group, although this difference was not statistically significant and the cause of death was not thought to be directly attributable to the febuxostat. In addition, there were more dropouts and more abnormal liver function tests in patients on the higher 120 mg/day dose of febuxostat (12 patients on febuxostat compared with one patient on allopurinol). The higher dose of febuxostat also led to more exacerbations of acute flares of gout; these adverse events could result in a decreased quality of life, although this was not measured directly in the RCTs.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer submitted an economic model comparing febuxostat with allopurinol given continuously. For descriptions of the model structure and assumptions, see MS pp. 102 - 109 and ERG report pp. 50 - 57.

Base-case economic analyses presented as incremental cost-effectiveness ratios (ICERs) in the MS are shown in table 5. The results are based on 1-year and 2-year time horizons. See the MS (pages 126–131) and the ERG report (pages 63–65) for further details.

Table 5 Summary of results of base-case economic analysis

Economic analyses	Total costs	Incremental costs	Total QALYs	Incremental QALYs	ICER
1-year time horizon					
Allopurinol (300 mg/day)	£1,314[a]		0.709		
Febuxostat (80 and 120 mg/day; pooled)	£1,592[b]	£278	0.726	0.017	£16,574
2-year time horizon					
Allopurinol (300 mg/day)	£2,605		1.395		
Febuxostat (80 and 120 mg/day; pooled)	£3,146	£540	1.430	0.035	£15,565
a: the manufacturer states that the anticipated price of febuxostat is £0.87 per day b: the price of allopurinol is £0.065 per day					

The results of the probabilistic sensitivity analysis presented in the MS are shown in table 6. Cost-effectiveness acceptability curves presented in the MS showed that the probability that febuxostat 80 mg/day (titrated to 120 mg/day where appropriate) had an ICER lower than £20,000 per QALY gained compared with fixed-dose allopurinol was 63%.

Table 6 Summary of results of probabilistic sensitivity analysis

	Cost	Lower 95% CI	Upper 95% CI	QALY	Lower 95% CI	Upper 95% CI
Allopurinol (300 mg/day)	£2,606	£2,102	£3,223	1.399	1.291	1.510
Febuxostat (80 and 120 mg/day; pooled)	£3,145	£2,612	£3,770	1.432	1.346	1.510
Incremental	£539	£347	£776	0.033	-0.017	0.083
ICER	£16,324	£6,281	£239,928	-	-	-

A number of univariate sensitivity analyses were presented in the MS to investigate the effects of changing the time horizon of the model, the protective effect of colchicine prophylaxis, discount rates, the assumed cost of febuxostat, the disutility associated with increments in sUA levels, and the proportion of patients with sUA levels below 360 µmol/l (6 mg/100 ml) between 4 and 24 months of treatment with febuxostat. The results of these

sensitivity analyses showed that the key drivers of the economic results were: (1) the assumed cost of febuxostat (the anticipated price is £0.87 per day), (2) the disutility associated with each increment in sUA levels and (3) the proportion of patients with sUA levels below 360 µmol/l (6 mg/100 ml) between 4 and 24 months of treatment with febuxostat.

In the manufacturer's model, QALYs are generated from two sources: a reduction in the number of flares and a reduction in sUA levels. Both patients not experiencing a flare and patients experiencing a flare used the EQ-5D instrument to identify both their current health state, and also what health state they thought they would be in if they were or were not currently experiencing a flare. The mean difference was re-expressed as a disutility of [redacted] per flare. A bivariate analysis of observational data (n = 415) showed no significant association between sUA levels and EQ-5D score. However, a multivariate analysis showed a significant association when controlling for employment status and gender. A linear relationship was assumed, and it was estimated that utility decreases by a value of [redacted] for each increase in sUA level (see pages 106-107 of the MS and pages 54-55 of the ERG report for details).

3.2 Evidence Review Group comments

The ERG expressed 'serious' concerns about the cost-effectiveness analyses undertaken, primarily in relation to the model structure and the strategies compared. The ERG noted that the natural history of hyperuricaemic patients with gout who did not receive treatment was not modelled, and hence no inference can be made of the cost effectiveness of febuxostat in comparison with no treatment. In addition, no data were provided on the likely sUA levels of patients who receive no treatment, and the model assumes full treatment compliance and usage over the time horizon modelled. However, evidence from the open-label EXCEL trial reports show 'low' continuation rates with all treatments. A randomised subset of the EXCEL trial showed that 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. Thus assuming full treatment compliance and usage over the time horizon could potentially bias the economic results in favour of febuxostat.

The ERG requested in a clarification letter 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 unfeasible because of a lack of clinical data. Nonetheless, the ERG asserts that appropriate modelling assumptions could have been made for this analysis. Even though there are no data to inform assumptions of how the efficacy of a treatment may vary depending on prior treatments, a base-case analysis assuming constant efficacy irrespective of prior treatments or the position of a sUA lowering agent in the treatment sequence would have been informative. The ERG highlighted that the economic model and analysis presented was not appropriate for determining the most cost effective way to use febuxostat in the treatment of patients with gout.

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 sUA levels on the basis of a multivariate analysis of data obtained from an Intercontinental Marketing Services (IMS) report on a health economic assessment of febuxostat in the management of gout. However, the 'multivariate analysis' referred to appears to be the same as a bivariate analysis that investigates the relationship between sUA levels and odds of gout flares occurring (the p values of the two analyses were identical).

The significance of the correlation between sUA levels and the number of gout flares disappears in the manufacturer's 'multivariate analysis' when other significant covariates from the bivariate analysis are controlled for. The ERG argues that a true multivariate analysis, in which a backward stepwise analysis is carried out, should be presented. The ERG also expressed concerns about discarded data points from the datasets used in the analysis showing a relationship between sUA levels and gout flares. The ERG noted that a relationship, that is not necessarily linear, between sUA levels and number of gout flares may still be found with more appropriate analysis and larger or different datasets and would be consistent with clinical advice.

The ERG highlighted that since the relationship between sUA levels and number of gout flares is a key driver of the economic results presented by the manufacturer, uncertainty about the relationship translates into uncertainty about the ICER estimates presented by the manufacturer. The ERG considers that this uncertainty has not been adequately investigated in the manufacturer's probabilistic sensitivity analysis. The ERG noted that the manufacturer's probabilistic sensitivity analysis samples the number of gout flares in the subgroup of patients with sUA levels of 6 mg/100 ml or below and assumes a constant proportional increase in the number of flares in patients with sUA levels above 6 mg/100 ml. A similar sampling procedure is applied to the proportions of patients in the different categories of sUA levels; only the percentage of patients in the subgroup with sUA levels of 6 mg/100 ml or below is sampled, with the remaining patients divided among the remaining categories using fixed proportions. The assumption of a fixed proportionate change in both of these cases leads to an underestimation of the uncertainty in the economic models.

3.3 Further considerations following premeeting briefing teleconference

The impact of time horizon used in the economic evaluation (2 years, which was extended to 5 years in a deterministic sensitivity analysis) may be an issue for consideration. An extension of the model's time horizon to 5 years did not significantly affect the results of the economic analysis. This effect of extending the model's time horizon on the economic results seems predictable, as it was assumed in the model that the improvement in sUA levels achieved at 1 year will continue to the 2-year time horizon, after which there were no treatment benefits accrued. In addition, it is notable that sUA levels achieved after 3 months are assumed to persist until month 24, yet no consideration was given to the long-term benefits of avoiding flares and maintaining a lowered sUA level. In addition, it is notable that no allowance was made for the possibility that the impact of treatment may decline over time, and no treatment stopping rules were provided.

4 Authors

Ebenezer Tetteh and Helen Chung, with input from the Lead Team (John Cairns and Lynn Field).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:

- Stevenson M, Pandor A. Febuxostat for the management of hyperuricaemia in patients with gout, March 2008.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Ipsen, UK

II Professional/specialist, patient/carer and other groups:

- Arthritis Care
- British Society for Rheumatology
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists

C Additional references used:

European Medicines Agency Committee for Medicinal Products for Human Use Summary of positive opinion for febuxostat (accessed 23 April 2008 at http://www.emea.europa.eu/pdfs/human/opinion/Adenuric_8075108en.pdf)

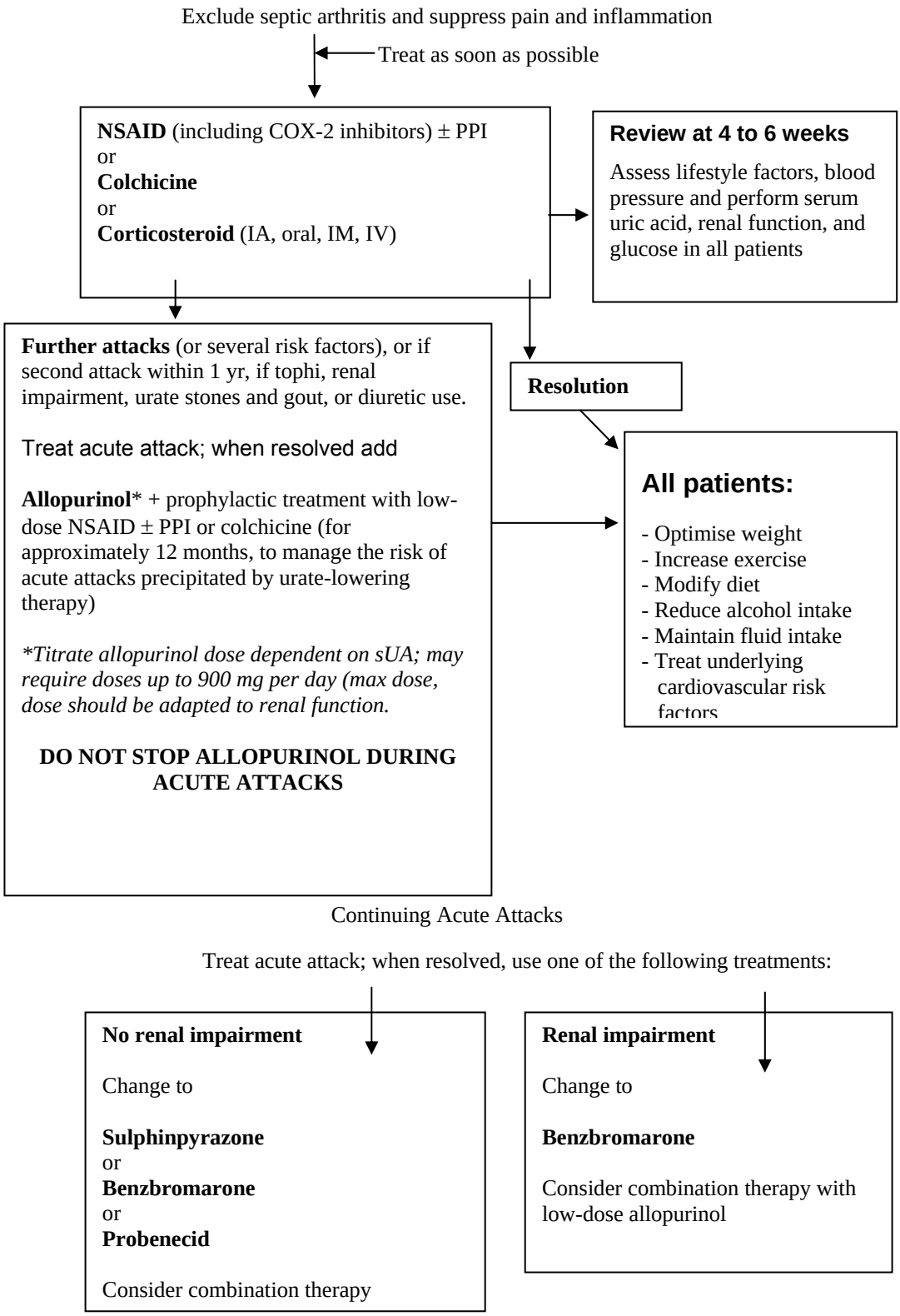
British Society of Rheumatology and British Health Professionals in Rheumatology (BSR) and European League Against Rheumatism (EULAR) guidelines (see appendix B)

Appendix B: BSR and EULAR guidelines

British Health Professionals in Rheumatology (BSR) guidelines for the management of recurrent, intercritical and chronic gout

	Recommendation
1	Serum uric acid should be lowered and maintained below 300 µmol/l (5 mg/100 ml) by pharmacological treatment in patients with gouty arthritis and/or tophi and in uncomplicated gout if one or more additional gout attacks occur within 1 year.
2	Specific treatment should be considered and begun as soon as the acute gout attack has resolved in patients with visible gouty tophi, patients with renal insufficiency (raised plasma creatinine, creatinine clearance, or glomerular filtration rate less than 80 ml per minute), patients with uric acid stones and gout, and patients who need to continue to take diuretics. Treatment with uric acid-lowering drug therapy should not begin until 1 to 2 weeks after inflammation has resolved in all patients with acute or subacute gout.
3	Allopurinol is the first-line treatment in uncomplicated gout patients with more than one attack per year and in gout patients with comorbidity. The starting dose for allopurinol is 50 to 100 mg daily, which is increased by 50-mg to 100-mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (serum uric acid < 300 µmol/l) is reached (the maximum dose is 900 mg). Doses of allopurinol should be lowered according to renal function in all patients with a reduction in estimated glomerular filtration rate, including normal, elderly subjects.
4	Uricosuric agents (sulphinpyrazone with normal renal function and benzbromarone with mild or moderate renal insufficiency) should be used only as second-line drugs in the chronic treatment of gout, in those patients producing and underexcreting a normal or reduced amount of urate, and in those patients resistant to or intolerant of allopurinol.
5	Colchicine should be given for up to 6 months following initiation of long-term treatment with allopurinol or uricosuric drugs. In patients who cannot tolerate colchicine, an NSAID or COX-2 inhibitor can be substituted, provided there are no contraindications, but the treatment duration for the NSAID or COX-2 inhibitor should be limited to 6 weeks.

BSR treatment algorithm for gout management



European League Against Rheumatism (EULAR) guidelines

In 2006, the EULAR task force was formed to develop evidence-based recommendations for the management of gout. This multidisciplinary group, representing 13 European countries, consisted of 19 rheumatologists and one expert in evidence-based medicine.

The EULAR guidelines (see table below) differ from the BSR treatment guidelines in following ways:

- The goal of gout treatment is to reduce and maintain serum uric acid levels at or lower than 360 µmol/l (6 mg/dl), eliminate gout flares, and resolve tophi.
- Conventional recommended treatments for gout also include probenecid in addition to NSAIDs, steroids, colchicine, allopurinol, benzbromarone, and sulphinpyrazone.
- Specific patient populations may require more aggressive treatment, with combination treatment in those patients with high baseline serum uric acid levels (greater than 540 µmol/l [9 mg/dl]), in elderly patients, and in patients with tophi.
- EULAR recommend the xanthine oxidase inhibitor allopurinol as an appropriate urate-lowering therapy; in cases of allopurinol toxicity, another xanthine oxidase inhibitor or a uricosuric agent are considered alternative options. Probenecid and sulphinpyrazone are suggested as suitable uricosuric agents in patients with normal renal function, and benzbromarone can be used in patients with mild to moderate renal impairment.

EULAR guidelines for the management of gout

	Recommendation
1	Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to (a) specific risk factors (levels of serum uric acid, previous attacks, radiographic signs); (b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout); and (c) general risk factors (age, gender, obesity, alcohol consumption, urate-elevating drugs, drug interactions, and comorbidity).
2	Patient education and appropriate lifestyle advice regarding weight loss, if obese; diet; and reduced alcohol (especially beer) are core aspects of management.
3	Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity, and smoking should be addressed as an important part of the gout management program.
4	Oral colchicine and/or NSAIDs are first-line agents for systemic treatment of acute attacks. In the absence of contraindications, an NSAID is a convenient and well-accepted option.
5	High doses of colchicine lead to side effects; low doses (for example, 0.5 mg three times daily) may be sufficient for some patients with acute gout.
6	Intra-articular aspiration or injection of long-acting steroids is an effective and safe treatment for an acute attack.
7	Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout.
8	The therapeutic goal of urate-lowering therapy is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (≤ 360 μmol/l).
9	Allopurinol is an appropriate long-term urate-lowering therapy. It should be started at a low dose (e.g., 100 mg daily) and increased by 100 mg every 2 to 4 weeks, if required. The dose must be adjusted in patients with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitisation (the latter is an option only in patients with a mild rash).
10	Uricosuric agents, such as probenecid and sulphinpyrazone, can be used as an alternative to allopurinol in patients with normal renal function but are relatively contraindicated in patients with urolithiasis. Benzbromarone can be used in patients with mild to moderate renal insufficiency on a named-patient basis but carries a small risk of hepatotoxicity.
11	Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by the use of colchicine (0.5 mg to 1 mg daily) and/or an NSAID (with gastroprotection, if indicated).
12	When gout is associated with diuretic therapy, stop the diuretic if possible. For hypertension, consider the use of losartan, and for hyperlipidaemia consider using fenofibrate (both drugs have modest uricosuric effects).