

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Febuxostat for the management of hyperuricaemia in people with gout

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 Febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol (as defined in section 1.2) or for whom allopurinol is contraindicated.
- 1.2 For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation.
- 1.3 People currently receiving febuxostat should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Febuxostat (Adenuric, Ipsen) is a non-purine selective inhibitor of xanthine oxidase that achieves its therapeutic effects by decreasing the serum uric acid concentration. Febuxostat has a marketing authorisation for the treatment of chronic hyperuricaemia in conditions where urate/uric acid deposition has already occurred (including a history or the presence of tophi and/or gouty arthritis).

- 2.2 The most common side effects associated with febuxostat are diarrhoea, nausea, headache, liver function test abnormalities and rash. Uncommon side effects include fatigue, oedema, dizziness, altered sense of taste, increase in blood amylase, decrease in platelet count, increase in blood creatinine, and arthralgia. Rare side effects include nervousness, insomnia, asthenia and renal insufficiency. The summary of product characteristics (SPC) states that treatment with febuxostat is not recommended for people with ischaemic heart disease or congestive heart failure. For full details of side effects and contraindications, see the SPC.
- 2.3 The recommended dose of febuxostat is 80 mg once daily. If the person's serum uric acid concentration is above 6 mg/100 ml (360 µmol/l) after 2–4 weeks of treatment with 80 mg once daily, febuxostat 120 mg once daily may be considered. The price for febuxostat 80 mg and 120 mg is £0.87 per tablet. Annual treatment costs are approximately £318. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of febuxostat and a review of this submission by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer's decision problem specified febuxostat (80 mg or 120 mg once daily) as the intervention of interest in a population of adults with hyperuricaemia in gout. The comparator specified by the manufacturer was fixed-dose allopurinol (300 mg once daily). The manufacturer did not present comparisons with alternative comparators such as sulphinpyrazone, benzbromarone, probenecid or combinations of these treatments. The health outcomes considered included serum uric acid concentration, gout flare rates, reduction in size of tophi, and health-related quality of life. The

results of the economic evaluation were expressed as incremental cost per quality-adjusted life year (QALY) over a time horizon of 2 years.

- 3.2 The manufacturer presented evidence on the clinical effectiveness of febuxostat from three randomised controlled trials (RCTs): the FACT trial, the APEX trial and the TMX-00-004 study. The FACT trial was a 52-week, phase III, multi-arm, randomised, double-blind, parallel-group trial that compared febuxostat 80 mg/day (n = 257), febuxostat 120 mg/day (n = 251) and allopurinol 300 mg/day (n = 254). The APEX trial was a 28-week, phase III, multi-arm, randomised, double-blind trial that compared febuxostat 80 mg/day (n = 267), febuxostat 120 mg/day (n = 269), febuxostat 240 mg/day (n = 134), allopurinol 300 or 100 mg/day (n = 268) and placebo (n = 134). The reduced dose of allopurinol (100 mg/day) in the APEX trial was used for 10 patients with renal impairment. In the APEX and FACT trials, colchicine and naproxen (a non-steroidal anti-inflammatory drug [NSAID]) were given as prophylaxis for treatment-initiated gout flares during the first 8 weeks of treatment. The TMX-00-004 study was a 4-week, phase II (dose–response), multicentre, randomised, double-blind, parallel-group trial that compared febuxostat 40 mg/day (n = 37), febuxostat 80 mg/day (n = 40), febuxostat 120 mg/day (n = 38) and placebo (n = 38).
- 3.3 Supplementary data in support of the clinical effectiveness of febuxostat were provided by the manufacturer from two open-label extension studies. The EXCEL trial is an ongoing open-label extension study that enrolled a subset of patients (n = 735) from the APEX and FACT trials. The EXCEL study compared febuxostat 80 mg/day (n = 299), febuxostat 120 mg/day (n = 291) and allopurinol 300 or 100 mg/day (n = 145). The FOCUS trial was a 5-year, open-label, non-controlled extension study that enrolled

patients (n = 116) who completed the TMX-00-004 study. The FOCUS study evaluated febuxostat 80 mg/day, with dose titration to lower (40 mg/day) or higher (120 mg/day) doses permitted between weeks 4 and 28.

- 3.4 Although summaries of the clinical evidence from the respective trials were provided by the manufacturer, the main evidence presented in support of the clinical effectiveness of febuxostat was based on pooled data from the APEX and FACT trials. This evidence was not in the form of a meta-analysis of the separate studies. It involved adding together the number of events observed for each treatment group across the trials and dividing the results by the total number of patients in the combined treatment group.
- 3.5 The manufacturer's 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 the serum uric acid concentration to target therapeutic levels (of below 6 mg/100 ml) at the last three visits and at the final visit. Febuxostat at either dose was also significantly more effective ($p \leq 0.05$) than fixed-dose allopurinol (300 mg/day) at lowering the serum uric acid concentration from baseline levels at the final visit. No statistically significant differences were observed with febuxostat 80 mg/day compared with 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, when statistically significantly greater reductions in primary tophus size from baseline were observed with febuxostat 120 mg/day than with allopurinol.

- 3.6 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 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 whose serum uric acid concentration fell below the target level of 5 mg/100 ml was higher ($p \leq 0.05$) among those receiving febuxostat than among those receiving fixed-dose allopurinol. No subgroup analyses were conducted for patients with renal impairment or those whose condition did not respond to allopurinol.
- 3.7 Results from the EXCEL extension study showed that a higher proportion of 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. In addition, no data were provided on withdrawals because of gout flares, adverse events or lack of response to treatment.
- 3.8 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 guidelines) and the

European League Against Rheumatism (EULAR guidelines), 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 the RCT comparisons with fixed-dose allopurinol. However, the ERG noted that dose titration of allopurinol is rarely carried out in routine clinical practice.

- 3.9 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 results of the meta-analysis showed that the probability of reaching therapeutic targets for serum uric acid concentration was statistically significantly higher for patients receiving febuxostat (80 or 120 mg/day) than for those receiving fixed-dose allopurinol (300 mg/day). The ERG's meta-analysis also showed that a higher proportion of patients receiving febuxostat needed treatment for gout flares (both during prophylaxis [weeks 1–8] and after prophylaxis [weeks 9–52]) compared with those receiving fixed-dose allopurinol. For the febuxostat 80 mg/day group this difference was not statistically significant ($p > 0.18$), but for the 120 mg/day febuxostat group it was ($p < 0.05$).
- 3.10 The manufacturer's submission presented an analysis of the cost effectiveness of febuxostat in comparison with fixed-dose allopurinol. A decision-tree model was provided to estimate the cost and health outcomes for patients with gout after initiation of urate-

lowering therapy with febuxostat 80 mg or 120 mg daily, or allopurinol 300 mg daily. The model had a time horizon of up to 2 years. The time horizon was based on 1-year trial data and a further 1 year of extrapolation, and was extended to 5 years in sensitivity analyses. A mixed cohort of men and women with gout and a baseline serum uric acid concentration of 80 mg/100 ml or above entered the model after initiation of urate-lowering therapy. The model was split into two time periods: an initial period of 3 months, during which patients may or may not experience a treatment-initiated flare, and a treatment maintenance period from 4 to 24 months.

- 3.11 The results of the economic analysis were presented as incremental costs per QALY gained for febuxostat in comparison with fixed-dose allopurinol. The base-case economic analysis using pooled clinical data over a 1-year time horizon comparing febuxostat (80 mg/day and 120 mg/day) with fixed-dose allopurinol of 300 mg/day produced an incremental cost-effectiveness ratio (ICER) of £16,574 per QALY gained. An alternative base-case analysis based on a 2-year time horizon produced an ICER of £15,565 per QALY gained. The manufacturer presented the results of a probabilistic sensitivity analysis that gave a mean ICER of £16,324 per QALY gained (95% confidence interval [CI] £6281 to £239,928 per QALY). The cost-effectiveness acceptability curve reported 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%.
- 3.12 The manufacturer presented a number of univariate sensitivity analyses to evaluate the impact of changing the following variables: 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 serum uric acid concentration; and the proportion of patients with a serum uric acid concentration below 360 $\mu\text{mol/l}$ (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 model were: (1) the assumed cost of febuxostat; (2) the disutility associated with each increment in serum uric acid concentration; and (3) the proportion of patients with a serum uric acid concentration below 360 $\mu\text{mol/l}$ (6 mg/100 ml) between 4 and 24 months of treatment with febuxostat. The base-case ICER remained stable over time when extrapolating to a 5-year time horizon. In the base-case analysis, gout flare rates were reduced by 78% in the first 3 months by assuming that patients received 3 months of prophylaxis with colchicine. Setting the reduction in gout flares because of prophylaxis to 0% increased the ICER to £18,826. Discounting had only a marginal effect on the ICER. The manufacturer presented an additional economic analysis after consultation on the appraisal consultation document. This compared febuxostat with a no-treatment (placebo) option over a 2-year time horizon using clinical data from the placebo arm in the APEX trial. The results of the economic analysis gave an ICER of £3727 per QALY gained for a comparison of febuxostat against a no-treatment option.

- 3.13 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 people with hyperuricaemia in gout who did not receive treatment was not modelled, and hence no inference could be made of the cost effectiveness of febuxostat compared 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, first-line therapy. The ERG asserted that appropriate modelling assumptions could have been made to allow some exploratory analysis.

- 3.14 The ERG noted that no data were provided on the likely serum uric acid concentrations 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/day febuxostat and 10% for 120 mg/day 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 results of the economic analysis in favour of febuxostat.

- 3.15 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 and FACT 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 the two 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 number of 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.
- 3.16 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 a lower serum uric acid concentration 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 had not been adequately investigated. In an exploratory analysis provided by the ERG, removing the 'chronic utility gain' associated with lower serum uric acid concentration increased the base-case ICER to £81,000 per QALY gained over a 2-year time horizon. A similar analysis gave an ICER of £696,000 per QALY gained over a 1-year time horizon, and an ICER of £150,000 per QALY gained over a 5-year time horizon.

- 3.17 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of febuxostat for the management of hyperuricaemia in people with gout, having considered evidence on the nature of the condition and the value placed on the benefits of febuxostat by people with chronic hyperuricaemia in conditions where uric acid deposition has already occurred (including a history or the presence of tophi and/or gouty arthritis), those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.2 The Committee discussed the decision problem presented in the manufacturer's submission. It noted that the manufacturer had initially 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 because of intolerance or lack of response), and include benzbromarone, sulphinyprazole and probenecid, all of which have limitations such as limited availability, adverse effects and poor effectiveness. The Committee was, however, persuaded that these options need not be considered as routine or best-practice comparators.

- 4.3 The Committee discussed the possible use of febuxostat as an alternative to allopurinol as first-line therapy; that is, where allopurinol is tolerated and not contraindicated. It identified that it has been established in clinical practice (as set out in BSR and EULAR guidelines) that allopurinol is most effective when given in a titrated regimen depending on the serum uric acid concentration. The Committee heard that even though many GPs limit their prescribing of allopurinol to a fixed dose of 300 mg/day, this is not best practice, particularly in the subset of people with gout for whom febuxostat might be considered. The Committee concluded that up-titrated allopurinol (to a maximum of 900 mg/day) should be considered as the best-practice comparator for febuxostat.
- 4.4 The Committee also discussed the outcome measures used. 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 a high serum uric acid concentration, but that comparatively few people present with clinical symptoms related to gout. However, although it noted that there remained some uncertainty about the relationship between serum uric acid concentration and clinical benefits (such as gout flare control, renal impairment and reduction in tophi size and

number), the Committee was persuaded that a reduction in the serum uric acid concentration below the 'saturation point' (approximately 6 mg/100 ml) was necessary to avoid precipitation of uric acid crystals in tissues in the long term. Additionally, although the association between serum uric acid concentration and symptoms of gout is complex and not completely understood, the Committee concluded that it was reasonable to assume that a relationship with symptoms is likely above a serum uric acid concentration of 6 mg/100 ml.

- 4.5 The Committee discussed the evidence for the clinical effectiveness of febuxostat, and specifically the 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.
- 4.6 The Committee noted that in the main comparative trials, fixed-dose allopurinol was found to effectively reduce the serum uric acid concentration below the saturation point of 6 mg/100 ml in a substantial proportion of patients. The Committee accepted that febuxostat is more effective at reducing serum uric acid concentration than fixed-dose allopurinol. The Committee also agreed that it was plausible that a reduction in serum uric acid concentration was associated with a reduction of gout symptoms,

However, it concluded that the benefits of febuxostat compared with allopurinol (using a fully titrated dosing schedule) in improving clinical outcomes, such as gout flare control, reduction in tophi size and number, and avoidance of joint and organ damage as a result of urate deposition in the longer term, had not been clearly demonstrated.

4.7 The Committee discussed the observation that the proportion of people with recurrent gout flares needing treatment was higher in the febuxostat arm than in the allopurinol arm of the APEX and FACT RCTs, although the number of gout flares declined over time. It heard from the clinical specialists that this phenomenon is seen 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 having a more pronounced effect. The Committee accepted this explanation and noted that an initial rise in clinical gout flares can be mitigated with the use of prophylaxis with an NSAID or colchicine. Nevertheless, it concluded that, where they remain, these initial flares are of clinical importance.

4.8 The Committee considered the adverse effects associated with febuxostat in comparison with fixed-dose allopurinol. In particular, it noted that there were a higher number 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 completeness in reporting, despite requests for clarification. However, it was noted that no dose–response relationship between these events and increasing doses of febuxostat had been observed in RCTs. The Committee also noted

that the marketing authorisation for febuxostat carries special warnings and precautions that preclude its use in patients with ischaemic heart disease or congestive heart failure.

4.9 The Committee discussed the economic model presented by the manufacturer, initially covering only the use of febuxostat as an alternative to first-line allopurinol therapy, and the ERG's subsequent critique. It had a number of concerns with the model structure and parameter assumptions in the model. The Committee was concerned 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 manufacturer did not consider that it could include up-titrated allopurinol as a comparator in the current model. The Committee concluded that the manufacturer's ICER calculation for febuxostat compared with fixed-dose allopurinol, having failed to consider up-titrated allopurinol, was a substantial underestimate.

4.10 The Committee 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. It understood that this was the case for febuxostat, and that its place in the pathway of care was preferentially as second-line treatment after allopurinol. It was mindful that the ERG had requested modelling of sequential use when patients progress to the need for alternative treatments (following lack of response to allopurinol treatment) or no-treatment options, and that the manufacturer had declined the request on the basis of lack of evidence. The Committee noted that these shortcomings of the manufacturer's model were too great for the ERG to be able to rectify and offer an alternative ICER. It also noted that the manufacturer had subsequently offered to model sequential

treatment strategies, but that it estimated that this would take between 4 and 6 months.

4.11 The Committee discussed the relationship assumed in the manufacturer's model between serum uric acid concentration, frequency of gout flares and how this may translate into improvements in long-term health-related quality of life. The Committee noted clarification from the manufacturer that the estimated relationship was non-linear. The Committee considered the ERG's concerns about the validity of the 'multivariate analysis' from which this assumption was derived. It noted the ERG's critique that this was based on a dataset from which some data points had been selectively excluded. The Committee also considered the statements from the clinical specialists that although a relationship between serum uric acid concentration above the saturation point and both frequency of gout flares and long-term adverse outcomes of gout is plausible, the strength and nature of the relationship is not clearly understood. The Committee concluded that there remained some uncertainty about the relationship between absolute serum uric acid concentration and gout symptoms in general, and that this was an additional source of uncertainty in the estimation of the incremental QALYs gained.

4.12 The Committee discussed the exploratory analysis by the ERG of the incremental QALY gain associated with the effect of lowering the serum uric acid concentration. The overall incremental QALY gain (0.032) included both the incremental QALY gain from the avoidance of gout flares and the 'chronic utility gain' from the prevention of gout-related symptoms. This is much higher than the overall incremental QALY gain (0.006) obtained from including the avoidance of gout flares alone. The impact of this difference on the final ICER was proportionately substantial. The Committee noted

that removing the component of incremental QALY gain associated with the 'chronic utility gain' from lowering serum uric acid concentration increased the ICER from the base case from £15,000 to £81,000 per QALY gained over a 2-year time horizon. It considered, however, that uncertainty about the strength and nature of the relationship between serum uric acid concentration, gout flares and utility gain added to the uncertainties surrounding the manufacturer's base case. Although the Committee was persuaded that removal of the 'chronic utility gain' would lead to an underestimation of the long-term clinical benefits of febuxostat treatment, it considered that the true base-case ICER, even when compared with fixed-dose allopurinol, would be within a wide range of between £15,000 and £81,000 per QALY gained.

4.13 The Committee then considered how improvements in health-related quality of life obtained with febuxostat had been estimated. The Committee discussed clarifications received from the manufacturer that estimates reported in the submission were based on utility decrements associated with the acute effects of gout flares and on a 'chronic utility gain' associated with the benefits of a lower serum uric acid concentration and of the avoidance of gout-related symptoms such as tophi, joint erosion and renal complications. It noted that this had been reported in the manufacturer's submission on the basis of a separate analysis in which a direct and continuous relationship between utility and serum uric acid concentration had been assumed. The Committee remained concerned (as described in section 4.11) that although this relationship was plausible, evidence supporting it was uncertain and not clearly established.

4.14 The Committee also considered that the difference in quality of life between experiencing a gout 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's duration was an overestimate. On the other hand, it heard from a patient expert that the assumption that gout flares last 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 additionally that published research studies have reported a number of anomalous responses, such as better overall health when experiencing a flare than when not, and 'perfect' health during a flare.

- 4.15 The Committee discussed the time horizons used in the manufacturer's model. It thought that for this chronic illness that requires life-long therapy, a lifetime time horizon would have been appropriate. The Committee further took into account evidence from the APEX and FACT trials 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 results of the economic analysis in favour of febuxostat. It was, however, mindful of conflicting evidence from the EXCEL trial that patients on febuxostat were more likely to continue treatment. 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 a marginal impact 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.

4.16 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 in cost between febuxostat and allopurinol), and the costs saved by avoiding treatment costs associated with any gout 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 (although this may be offset by the cost savings from the long-term benefits of alleviating gout symptoms).

4.17 The Committee discussed the results of a second economic analysis presented by the manufacturer showing that a comparison between febuxostat and a no-treatment (placebo) option gave an ICER of £3727 per QALY gained over a 2-year time horizon. It considered that this estimate was also subject to substantial uncertainty, given the concerns discussed above regarding the approach taken by the manufacturer in the economic analysis. The Committee considered, however, that given that the option of titrated allopurinol was obviously not available for the treatment of people who are intolerant of allopurinol or for whom allopurinol is contraindicated, the ICER of febuxostat in these groups of patients was very likely to be at an acceptable level, despite the degree of uncertainty because of lack of evidence.

4.18 The Committee further discussed the use of febuxostat in cases where treatment goals were not achieved with allopurinol. The Committee considered that there is no evidence, and no basic pharmacodynamic reason, to suppose that febuxostat would confer any benefit for patients in whom up-titrated allopurinol has failed to

lower the serum uric acid concentration below the 'saturation point'. Thus the Committee considered that febuxostat could be recommended as a treatment option in people with chronic hyperuricaemia and symptomatic gout who are intolerant of allopurinol (defined as adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation), or for whom allopurinol is contraindicated (for instance in cases of severe renal impairment or interactions with other medications).

- 4.19 Overall, the Committee concluded that although febuxostat had been shown to be more effective than fixed-dose allopurinol in lowering serum uric acid concentration, it had not been shown to be clinically or cost effective compared with the more appropriate comparator of allopurinol up-titrated in accordance with established best clinical practice. However, it concluded that febuxostat should be recommended as an option for the management of chronic hyperuricaemia in gout for people who are intolerant of allopurinol (defined as adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation), or for whom allopurinol is contraindicated.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals, normally within 3 months from the date that NICE publishes the guidance.

Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6 Review of guidance

6.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

6.2 The guidance on this technology will be considered for review in August 2011.

David Barnett
Chair, Appraisal Committee
August 2008

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor Stirling Bryan

Head, Department of Health Economics, University of Birmingham

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Charkravarty

Director, External Relations, Procter and Gamble Health Care, Europe

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Ms Lynn Field

Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler

Professor of Surgical Education, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mrs Barbara Greggains

Lay member

Mr Sanjay Gupta

Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Mr Terence Lewis

Lay member

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology, University of Southampton

Dr Neil Milner

General Medical Practitioner, Tramways Medical Centre, Sheffield

Dr Rubin Minhas

General Practitioner, Coronary Heart Disease Clinical Lead, Medway PCT

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent PCT

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula College of Medicine and Dentistry, University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

B ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ebenezer Tetteh

Technical Lead

Helen Chung

Technical Adviser

Natalie Bemrose

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the 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 The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also had the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Ipsen

II Professional/specialist and patient/carer groups:

- Arthritis Care
- Kidney Research UK
- South Asian Health Foundation
- Royal College of Physicians
- Royal College of Pathologists
- Royal College of Nursing
- Royal College of General Practitioners
- Primary Care Rheumatology Society
- British Society for Rheumatology

III Other consultees:

- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- NHS Quality Improvement Scotland

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on febuxostat by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Paramit Chowdhury, Consultant Nephrologist, Guy's and St Thomas' (nominated by the Royal College of Physicians) – clinical specialist
- Dr Paul Collinson, Consultant Chemical Pathologist, St George's Hospital, London (nominated by the Royal College of Pathologists) – clinical specialist
- Professor Michael Doherty, Professor of Rheumatology, University of Nottingham (nominated by the British Society for Rheumatology) – clinical specialist
- Mr Iain Phillips (nominated by the UK Gout Society) – patient expert