Final appraisal determination

Pegloticase for treating severe debilitating chronic tophaceous gout

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

1 Guidance

1.1 Pegloticase is not recommended within its marketing authorisation, that is, for treating severe debilitating chronic tophaceous gout in adults who may also have erosive joint involvement and in whom xanthine oxidase inhibitors at the maximum medically appropriate dose have failed to normalise serum uric acid, or for whom these medicines are contraindicated.

1.2 People currently receiving pegloticase that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Pegloticase (Krystexxa, Savient Pharmaceuticals), is a polyethylene glycol conjugate of a recombinant enzyme uricase, also known as urate oxidase. It catalyses the oxidation of uric acid to allantoin, which is water soluble and can be excreted in urine, resulting in lowered serum uric acid levels. It is administered by intravenous infusion.
2.2 Pegloticase has a UK marketing authorisation for: ‘The treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalise serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose, or for whom these medicines are contraindicated.’

2.3 The most commonly occurring adverse reactions include: infusion-related reactions, gout flare, nausea, dermatitis, urticaria, pruritus, skin irritation, dry skin, anaphylaxis, influenza-like illness, joint swelling, vomiting and hyperglycaemia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The acquisition cost of a single vial containing 8 mg of pegloticase concentrate for 1 infusion is £1770 (cost from manufacturer’s submission; excludes VAT). The average cost of a course of 6 months’ treatment is £23,010. 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 pegloticase and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer’s submission presented evidence on clinical effectiveness from 2 phase III trials (C0405 and C0406) and an open-label extension study (C0407). The trials C0405 and C0406 were identical, randomised, double-blind, placebo-controlled, multicentre, 3-armed trials of 6 months’ duration conducted in the USA and Canada (C0405) and the USA and Mexico (C0406). The trial patients were 18 years or older, had a baseline serum uric acid level of at least 480 micromol/litre and at least 1 of the following...
criteria: 3 or more self-reported gout flares during the previous 18 months; 1 or more tophi; and gouty arthropathy (clinical or radiographic evidence of joint damage due to gout). Patients also had to either have a contraindication to treatment with allopurinol or their uric acid levels must have failed to normalise despite 3 or more months of treatment with the maximum medically appropriate allopurinol dose (determined by the treating doctor). Exclusion criteria were glucose-6-phosphate dehydrogenase (G6PD) deficiency, previous treatment with a uricase-containing drug, pregnancy, unstable angina, uncontrolled hypertension (blood pressure higher than 150/95 mmHg) or cardiac arrhythmia, uncompensated congestive heart failure, renal dialysis, or solid organ transplant. Intravenous pegloticase 8 mg every 2 weeks and intravenous pegloticase 8 mg every 4 weeks were compared with placebo. During the trial all patients received prophylaxis against gout flare with colchicine or a non-steroidal anti-inflammatory drug (NSAID), which started 1 week before the first infusion of pegloticase and continued throughout the trial. Patients also received prophylaxis against infusion-related reactions with 60 mg oral fexofenadine the evening before each infusion, 60 mg oral fexofenadine and 1 g oral paracetamol the morning of the infusion and intravenous hydrocortisone 200 mg immediately before each infusion. Only the results from patients receiving pegloticase 8 mg every 2 weeks were included for the estimate of efficacy in the submission.

3.2 The primary outcome was the proportion of patients whose plasma uric acid level responded to treatment in each pegloticase treatment group compared with treated with placebo. Plasma uric acid level was measured at baseline and 2 and 24 hours after the first infusion, before each 2-weekly infusion, and at 5 additional pre-specified time points in month 3 and month 6 (2 hours, 1 day and
7 days after the week 9 and week 21 infusions and 2 hours and 7 days after the week 11 and week 23 infusions). In the trials, a responder was defined as a patient with a plasma uric acid level below 360 micromol/litre for at least 80% of the time, measured during months 3 and 6.

3.3 Secondary outcomes were assessed at baseline, week 13, week 19 and week 25 and included resolution of tophi (defined as a 100% decrease in area of at least 1 out of up to 7 pre-specified target tophus without progression or appearance of a new tophus), the number of patients experiencing gout flares (incidence) and the number of flares per patient (frequency) during months 1–3 and 4–6, improvement in tender and swollen joint count, improvement in quality of life (SF-36) and improvement in functional status (’Health assessment questionnaire’ [HAQ] disability index and the HAQ pain scale). Tophi resolution was measured in each patient with tophi at baseline by tracking up to 5 measurable tophi and 2 additional tophi using serial, quantitative digital photographs, which were evaluated by an independent rheumatologist who was blinded to the patients’ treatment.

3.4 A total of 225 patients (109 in C0405 and 116 in C0406) were randomised to the 3 trial groups (pegloticase every 2 weeks or every 4 weeks, or placebo) in a 2:2:1 ratio. All urate-lowering, clinical efficacy, and tolerability analyses (except deaths) were carried out on a modified intent-to-treat population (n=212; 104 in C0405 and 108 in C0406) comprising all randomised patients who received at least 1 infusion. Baseline characteristics were similar across the trials and treatment groups except for chronic kidney disease (defined as a creatinine clearance below 60 ml/min), which was markedly lower in the placebo group in C0406 (13%) than in the intervention groups in both the trials and the placebo group in
C0405 (28–33%). Metabolic and cardiovascular disorders were also common. More than 80% of trial patients had cardiovascular comorbidities.

3.5 Plasma uric acid levels normalised within 24 hours of the first infusion for all patients receiving pegloticase. But over time some patients lost the urate-lowering response whereas others maintained a uric acid level under 360 micromol/litre throughout the trials. The number of responders in the treatment arms receiving 8 mg pegloticase every 2 weeks (responders defined as patients whose plasma uric acid level is under 360 micromol/litre for at least 80% of the time during months 3 and 6) was 20 out of 43 patients (47%) in C0405 and 16 out of 42 patients (38%) in C0406. There was no response in patients treated with placebo. The proportions of responders were statistically significantly different between pegloticase and placebo arms for both trials (p<0.001 for C0405 and p=0.001 for C0406). They were also statistically significantly different in the pooled analysis (36/85 [42%] for patients receiving 8 mg pegloticase every 2 weeks compared with 0/43 [0%] for patients receiving placebo, p<0.001).

3.6 Several pre-specified subgroup analyses were presented by the manufacturer, including stratifications according to gender, age, body mass index, disease duration, and presence or absence of tophi. The manufacturer stated that no clear pattern or trend was observed for the primary outcomes in these groups.

3.7 The results of the secondary outcomes were presented as pooled data from the pegloticase every 2 weeks arms of the 2 trials. Resolution of tophi was measured in patients with tophi at baseline as defined in section 3.3. Approximately 73% (62/85) of patients in the pegloticase every 2 weeks treatment group had tophi at baseline compared with 67% (29/43) in the placebo group. The
results were reported in patients with evaluable tophi and the proportion with complete resolution at month 6 was statistically significantly higher in the pegloticase treatment group than in the placebo group (21/52 [40%] and 2/27 [7%] respectively, p=0.002). The incidence of gout flares increased in the pegloticase treatment group compared with the placebo treatment group during the first 3 months of treatment (64/85 [75%] and 23/43 [53%] respectively, p=0.02). But with continued treatment, statistically significant reductions in the proportion of patients with flares during months 4 to 6 were seen in the pegloticase treatment group compared with placebo (28/69 [41%] and 29/43 [67%] respectively, p=0.007).

Similarly, during the first 3 months of treatment, flare frequency (number of flares per patient) was statistically significantly higher (p=0.001) in the pegloticase treatment group (mean 2.3, standard deviation [SD] 2.1) than in the placebo group (mean 1.2, SD 1.6). During months 4 to 6 there were fewer flares per person in the pegloticase group (mean 0.8, SD 1.2) than in the placebo group (mean 1.3, SD 1.5) but this was not statistically significant (p=0.06).

3.8 Patients in the pegloticase group also had fewer tender and swollen joints at the final visit than at baseline than patients in the placebo group. The reduction in the average number of tender joints was statistically significant in the pegloticase group compared with the placebo group (−7.4 and −1.2 respectively, p=0.01). There was also a greater reduction in the number of swollen joints in the pegloticase group than in the placebo group but this was not statistically significant (−5.5 and −2.6 respectively, p=0.18).

3.9 Patient-reported outcomes were also reported to be improved with pegloticase. There were statistically significant changes from baseline in HAQ disability index scores and SF-36 physical
component summary (PCS) scores and the changes met or exceeded the established minimum clinically important differences.

3.10 HAQ disability index was measured by administering a survey consisting of 20 questions about various physical activities, including activities of daily living. The patients were asked to score their functional ability from 0 (no difficulty) to 3 (unable to do without help or use of aids). The individual scores were averaged to obtain a final score between 0 and 3. The mean change in the HAQ disability index scores from 1–3 months to the final visit in the pegloticase group was −0.22 (SD 0.64) compared with 0.02 (SD 0.41) for the placebo group. This was statistically significant (p=0.01). The minimum clinically important difference reported in the literature on the HAQ disability index for inflammatory arthritis is 0.22.

3.11 The HAQ pain score was measured on a visual analogue scale from 0 (no pain) to 100 mm (worst pain). The pain score at baseline was lower in the pegloticase group (44.2 [SD 27.7]) than in the placebo group (53.9 [SD 28.1]) although the difference was not statistically significant (p=0.07). The reduction in pain score in the pegloticase group at the final visit was −11.4 (SD 33.8), which was greater than the minimum clinically important difference for inflammatory arthritis reported in the literature (0.10) as well as statistically significantly better (p=0.03) than the change in the placebo group (1.4 [SD 30.0]).

3.12 The patients in the pegloticase treatment group with data at the final visit also had improvements in their SF-36 PCS scores that were statistically significantly better than placebo (p=0.01).

3.13 Secondary outcomes were also presented for plasma uric acid responders compared with non-responders. Compared with non-
responders, the responder group had a higher proportion of patients with complete tophus response, a numerically greater reduction in the number of swollen or tender joints and greater improvement in mean HAQ pain and SF-36 PCS scores. On the other hand, incidence and frequency of flares were consistently higher in responders compared with non-responders during months 1–3 and months 4–6. The manufacturer submitted data with confidentiality restrictions and values are therefore not presented here.

3.14 The safety data presented by the manufacturer were from a pooled analysis of adverse events reported in patients in the pegloticase 8 mg every 2 weeks groups in the 2 phase III trials (C0405 and C0406), and long-term safety data from an open-label extension study (C0407). The pooled analysis showed that serious adverse events were more frequent (24%) in patients in the pegloticase group than in the placebo group (12%). Similarly, the rate of adverse events leading to discontinuation was 18% in the pegloticase group and 2% in the placebo group. The most commonly reported adverse events were gout flare (76% in the pegloticase group and 81% in the placebo group), infusion-related reactions (26% in the pegloticase group and 5% in the placebo group – despite prophylaxis against infusion-related reactions), headache (9% in the pegloticase group and 9% in the placebo group), and nausea (12% in the pegloticase group and 2% in the placebo group). The manufacturer stated that most infusion-related reactions (91%) were after a loss of treatment response (plasma uric acid levels greater than 360 micromol/litre). Anti-pegloticase antibodies were detected in 89% of patients receiving pegloticase in the 2 phase III trials. The manufacturer stated that 39% of patients had developed anti-pegloticase antibodies at a concentration that had potential clinical consequences (for example
loss of responsiveness or increased risk of infusion-related reactions). In response to consultation, the manufacturer reported a post-hoc analysis which indicated that if the stopping rule specified in the summary of product characteristics (that treatment should be discontinued if 2 consecutive serum uric acid levels are above 6 mg/dl) had been applied during the trials (C0405, C0406) the proportion of infusion reactions in patients receiving pegloticase every 2 weeks would have decreased from 26% to 14%. The manufacturer stated that post-marketing surveillance data from the USA suggested that the number of infusion reactions and anaphylaxis in clinical practice is 61% lower than in patients receiving pegloticase every 2 weeks in the trials (C0405, C0406) (Malamet et al. 2012).

3.15 In response to clarification questions, the manufacturer stated that all patients who completed C0405 or C0406 were invited to participate in the open-label extension study C0407 of up to 30 months’ duration. The primary objective of the open-label extension study was to assess the long-term safety of pegloticase. A secondary objective was to evaluate the treatment effects of pegloticase in patients who continued to receive active treatment from the phase III trials and in those originally randomised to placebo, and the duration of benefit. Outcomes included the plasma and serum uric acid response, tophus response, incidence and frequency of gout flares, swollen joint count, tender joint count, SF-36, HAQ and ‘clinical global assessment of disease activity’.

3.16 A total of 151 patients entered the open-label extension study (C0407). Of these patients, 57 had received pegloticase 8 mg every 2 weeks, 53 had received pegloticase 8 mg every 4 weeks, and 39 patients had received placebo in the previous trials. Two patients (3%) who had previously received pegloticase 8 mg
every 4 weeks selected the option of not receiving any further pegloticase but participated in the study for observation only. Twenty-three out of 39 patients who had received placebo in previous trials opted for pegloticase 8 mg every 2 weeks and the remaining 16 received pegloticase 8 mg every 4 weeks in the open-label extension study (C0407).

3.17 Overall safety observations in the open-label extension were consistent with those reported in the 2 phase III trials, suggesting no cumulative risk with continued exposure to pegloticase. Gout flare was the most commonly reported adverse event, occurring in 71% of patients. But the overall percentage of patients with gout flare decreased throughout the study, particularly in the responders to pegloticase treatment group. Infusion-related reactions were the second most commonly reported adverse events. Infusion-related reactions were less frequent in pegloticase responders. There were 4 deaths in the open-label extension study: 1 from sepsis while receiving pegloticase and 3 from cellulitis/sepsis, pneumonia and worsening of myelodysplastic disorder. A total of 51 (34%) patients had serious adverse events across all treatment groups. Of these, 13 were considered to be possibly or probably related to pegloticase, 11 were infusion-related reactions, 1 was nephrolithiasis (a kidney stone) and 1 was skin necrosis. The remainder were considered unlikely to be related to the study drug and were consistent with the high degree of pre-existing comorbidities and polypharmacy.

3.18 A completed non-randomised, non-controlled, open-label, multicentre re-exposure trial (C0409) that was not included in the manufacturer’s submission was identified by the ERG. The manufacturer provided a brief synopsis of this trial in response to clarification questions. This small trial evaluated efficacy and safety
outcomes in 7 patients who were re-exposed to a 24-week course of pegloticase after a treatment break of at least 1 year. Further information on this trial was marked academic in confidence and therefore is not presented here.

3.19 Pre-planned subgroup analyses of the individual phase III trials (C0405 and C0406) and of the pooled data for treatment responders were undertaken by the manufacturer according to sex, age (55 years or younger, older than 55 years), body mass index (30 kg/m² or less, more than 30 kg/m²), absence or presence of tophi, disease duration (less than 5 years, 5 years or more), and baseline HAQ disability index score (1 or less, more than 1) creatinine clearance (less than 50 ml/min, 50 ml/min or more), and antibody status. The manufacturer stated that results for the pooled data did not indicate any clear pattern or trend of improved efficacy in any subgroup.

3.20 For health economic analysis the manufacturer submitted a de novo model comparing pegloticase with best supportive care in patients with chronic gout refractory to xanthine oxidase inhibitors. The model was based on a decision tree coupled with a Markov model for extrapolation to the 20-year base-case time horizon. There are 4 health states in the Markov model based on patients’ serum uric acid levels: below 360 micromol/litre, 360 or higher but below 480 micromol/litre, 480 or higher but below 600 micromol/litre and 600 micromol/litre or higher. Death is also included as a Markov state in the model.

3.21 In the manufacturer’s model, patients receiving pegloticase were separated into ‘responder’, ‘non-responder’ and ‘non-completer’ groups.
• Responders were defined in the manufacturer’s submission as people whose serum uric acid levels were maintained at or below 360 micromol/litre. These patients were assumed to gain the most clinical benefit from pegloticase. After the treatment course with pegloticase (lasting a maximum of 6 months in the base-case analysis), patients were switched to maintenance treatment with either allopurinol or febuxostat. Based on the trial data for response rate (60%) among patients who continue with pegloticase (68%), the manufacturer estimated that 40.8% of the cohort would be classified as responders.

• Non-responders were defined as those who discontinue pegloticase treatment because serum uric acid levels exceed the limit set out in the summary of product characteristics: ‘increase to above 360 micromol/litre on 2 consecutive observations’. In the base-case analysis, patients were assumed to be identified as non-responders after 2 months of pegloticase treatment. These patients, estimated to be 27.2% of the original cohort, were switched to best supportive care. Based on the clinical trial data, it was assumed that these patients still got some clinical benefit.

• The non-completer group was defined in the manufacturer’s submission as ‘patients who are non-persistent to pegloticase treatment’, but subsequently the manufacturer clarified that this included patients who did not complete the full 6-month treatment course for any reason, primarily because of adverse events, but also because of other reasons such as the patient disliking intravenous administration. These patients were assumed to not gain any clinical benefit from pegloticase treatment although pegloticase treatment costs are incurred. In the base-case analysis, it was assumed that a non-completer could be identified after 1 month of pegloticase treatment. In the
3.22 The manufacturer modelled the best supportive care arm on clinical data from patients receiving placebo in the clinical trials. The model assumed that all patients who respond to pegloticase treatment will progress to maintenance treatment with either allopurinol (70%) or febuxostat (30%). Discontinuation of maintenance treatment was modelled with data derived from an observational study of allopurinol (Annemans et al. 2008) and from a randomised trial of febuxostat (EXCEL). Patients who discontinued maintenance treatment were switched to best supportive care. It was assumed that maintenance treatment was effective in maintaining the serum uric acid levels achieved by pegloticase treatment, and that on discontinuing maintenance treatment serum uric acid levels returned to baseline levels. The probability of discontinuing maintenance treatment, and therefore progressing to best supportive care, was modelled using a constant hazard for febuxostat, and a decreasing hazard for allopurinol. The rate of discontinuation for febuxostat was derived by taking the average proportion who had stopped treatment at the end of the 2-year EXCEL trial across the 2 doses (80 mg/day and 120 mg/day) and assuming a constant hazard (exponential survival curve) to convert this proportion to a monthly rate of 1.3%, which is equivalent to an annual rate of 14%. The rate of discontinuation for allopurinol was derived by fitting a Weibull survival curve to retrospective 2-year observational data from 7443 UK patients with chronic gout, of whom 89% were receiving allopurinol. In the economic model, the manufacturer stated that a Weibull curve was fitted to the second year of data from the trial to reflect long-term persistence (patients
who continue to take their medication long term), as opposed to persistence from the start of treatment.

3.23 The baseline characteristics of the modelled population were defined according to age (56 years), serum uric acid level (9.6 mg/dl; equivalent to 576 micromol/litre) and baseline utility values (0.6) based on the baseline demographic characteristics of the 2 phase III trials. No natural disease progression was modelled because tophaceous gout was considered the final stage of gout.

3.24 Each of the responder, non-responder and non-completer groups has a distinct set of health states with no transitions allowed between the groups. For each of these groups, the model has health states defined according to the treatment being given and the serum uric acid level at that time point. In the comparator arm, all patients receive best supportive care for the duration of the model so the health states are defined solely according to serum uric acid level.

3.25 The model estimated the distribution of patients across the 4 serum uric acid levels by assuming a normal distribution around the mean serum uric acid level for each group in the pegloticase arm (responders, non-responders, non-completers) and for the comparator arm population as a whole. Transitions to death are possible at any time and do not depend on the treatment being given or the patient’s serum uric acid level and are therefore the same across the whole population of the model. The manufacturer described the mortality used in the model as being UK-specific.

3.26 Treatment effectiveness is captured within the model by changes in 4 patient-related outcomes: serum uric acid level, quality of life, frequency of flares and tophi resolution. Patient-level data were available from the 2 phase III trials (C0405 and C0406) for all
3.27 In the model, serum uric acid levels in responders were based on data from the pegloticase arm for the first 6 months and then maintained at 0.17 mg/dl (equivalent to 10.2 micromol/litre) during maintenance treatment. After patients discontinued maintenance treatment, serum uric acid levels were based on trial data from the pegloticase non-responder group for months 6 to 12 of the model and on the baseline level for the whole trial cohort for the remainder of the model up to 20 years (base-case time horizon). Serum uric acid levels in non-responders were based on data from non-responders in the pegloticase arm of the trials for 2 months and then on data from the placebo arms of the 2 phase III trials for the remaining 4 months once the patients have progressed to best supportive care. Serum uric acid levels in non-completers were based on data from the placebo arms of the 2 phase III trials for the full 6 months. The baseline serum uric acid level was modelled beyond 6 months for non-responder and non-completer patients.

3.28 Frequency of flares in the pegloticase arm was based directly on trial outcomes in the first 6 months for responders receiving pegloticase. Frequency of flares in the pegloticase non-responder group was based on trial data from non-responders for 2 months and then estimated from the serum uric acid level once the non-responders progressed to best supportive care. Frequency of flares in the pegloticase non-completer group was based on trial data from the placebo arm for 1 month and then on the serum uric acid level once the non-completers progress to best supportive care. Frequency of flares for patients receiving best supportive care in
the comparator arm in the first 6 months was derived directly from the trial data and later was based on the serum uric acid level.

3.29 Tophi resolution was assumed to increase linearly over the first 6 months to the level seen at month 6 in the pooled data of the 2 key trials. The resolution of tophi achieved during pegloticase treatment was assumed to be maintained in 100% of responders and 50% of non-responders for the entire time horizon of the model (20 years). For non-completers and patients in the best supportive care arm of the model tophi resolution achieved at 6 months in the pooled analysis of the placebo arms of the trials was modelled and maintained for the entire time horizon of the model.

3.30 Utility estimates for the first 6 months were based on SF-6D utilities derived from the SF-36 data collected in the pegloticase phase III trials and validated against the EQ-5D. Modelled utility values were corrected for differences in baseline utility of different patient groups. No disutilities associated with adverse drug reactions were included in the model. The manufacturer said this was because utility data for the entire duration of pegloticase treatment in the model were collected in the trial, and therefore the disutilities associated with adverse effects would already be captured.

3.31 In the manufacturer’s model, long-term utilities were based on estimates derived from Febuxostat for the management of hyperuricaemia in people with gout (NICE technology appraisal guidance 164) and Scottish Medicines Consortium guidance (637/10) on febuxostat. These values were based on a European observational study in chronic gout patients with health-related quality of life and utility measured by EQ-5D and utilities for each serum uric acid level state derived by regression analysis. The utility values applied in the model after 6 months (and in some patients before 6 months, for instance in non-responders after
2 months and in non-completers after 1 month) were based on a combination of serum uric acid level, frequency of flares and tophi resolution.

3.32 The acquisition cost of pegloticase used in the model was £1770 for a single vial containing 8 mg of concentrate. Other costs included the costs of intravenous drug administration (assumed to be the cost of 3.5 hours of nursing time), prophylaxis for acute gout flares and infusion-related reactions, adverse event costs, refractory chronic gout management, treatment for acute flares, and tophus surgery. Resource use for the management of severe debilitating refractory chronic gout according to serum uric acid level was estimated by a survey of 6 clinical experts and an in-depth interview with a clinician. Drug costs incurred for prophylaxis for acute gout flares and infusion-related reactions, adverse event costs, refractory chronic gout management costs and the cost of treating acute flares were based on costs in the ‘British national formulary’ (BNF) 63. All other resource use cost was estimated using NHS reference costs and Healthcare Resource Groups for 2010–11. The resource use for 2 adverse drug effects (infusion-related reactions and vomiting) was modelled for the pegloticase arm and assumed to be 0 for best supportive care, which was assumed to consist of standard medical care with NSAIDs, colchicine and corticosteroids but no urate-lowering treatment. However, a cost for drug treatment associated with the best supportive care comparator was not included in the economic model in the original submission. The cost used in the model of managing an episode of acute flare was £295 based on Scottish Medicines Consortium guidance (637/10) on febuxostat.

3.33 In the manufacturer’s submission the base-case incremental cost-effectiveness ratio (ICER) for pegloticase compared with best
supportive care was £29,946 per quality-adjusted life year (QALY) gained based on incremental costs of £9466 and an estimated QALY gain of 0.316. The ICER generated by probabilistic analysis was £29,833 (after correction by the ERG for an error identified in the computer program used to run the probabilistic sensitivity analysis).

3.34 The deterministic sensitivity analyses conducted by the manufacturer showed that the cost effectiveness of pegloticase was particularly sensitive to changes in baseline levels of serum uric acid, the disutility associated with higher serum uric acid levels and patients’ age. The sensitivity analyses also showed that the disutility associated with higher serum uric acid levels is a significant driver of cost effectiveness, which is important given the significant uncertainty about this assumption. The cost-effectiveness results were also fairly sensitive to changes in the utility value for patients with serum uric acid levels under the target value and the baseline utility value. The cost-effectiveness results were also moderately sensitive to the parameter values for treatment efficacy and persistence with pegloticase treatment.

3.35 The scenario analyses showed the sensitivity of the ICER to several structural changes in the model’s clinical pathways. The most sensitive variables were related to how long patients receive pegloticase for and how soon non-responders stop treatment with pegloticase. ICERs in the scenario analyses for pegloticase compared with best supportive care ranged from £19,817 per QALY gained (assuming a pegloticase treatment duration of 5 months instead of 6 months as in the base case) to £38,025 per QALY gained (assuming that non-completers would be identified after 3 months instead of 1 month as in the base case).
At the clarification stage, several assumptions in the manufacturer’s model were questioned. The model assumed that all patients who responded to pegloticase treatment will progress to maintenance treatment with either allopurinol (70%) or febuxostat (30%). However, the ERG stated that this treatment sequence would not have been appropriate for patients in whom conventional urate-lowering therapies are contraindicated or not tolerated. Furthermore the ERG was concerned that the model did not include any drug costs for best supportive care. In response to clarification the manufacturer submitted a revised model in which

- After pegloticase treatment, 10% of the responders were assumed to switch to best supportive care, instead of maintenance treatment with xanthine oxidase inhibitors.

- Drug costs for best supportive care were included. Best supportive care treatment was considered to consist of a combination of an NSAID, colchicine and corticosteroids.

The deterministic results for this revised base-case analysis (hereafter referred to as the revised base-case’) showed an incremental cost of £9452 and incremental QALY of 0.305 for pegloticase compared with best supportive care, resulting in a revised ICER of £31,027 compared to £29,946 per QALY gained in the original base case. A probabilistic sensitivity analysis (after correcting for an error identified in the computer program used to run the probabilistic sensitivity analysis) of 10,000 samples using the revised assumptions yielded a mean ICER of £31,031 per QALY gained (incremental cost of £9491 and a QALY gain of 0.306). The ERG explored other assumptions in its exploratory analyses (see sections 3.40-3.51) and all these analyses, including ERG’s preferred scenario (see section 3.46), were based on this revised model.
The ERG was satisfied that all available phase III trials were included in the submission but noted that in the 2 phase III trials a higher proportion of patients in the pegloticase every 2 weeks arms had dropped out at the end of the study (30% in C0405 and 28% in C0406) than in the placebo arms (5% in C0405 and 13% in C0406). The ERG stated that the manufacturer did not explain or adjust for the imbalances in these drop-out rates, particularly in the patients who dropped out because of adverse events in both trials.

The ERG highlighted the manufacturer’s approach of pooling data from the 2 phase III trials and pointed out that simple pooling of data may yield counterintuitive or false results and that a meta-analysis would have been a better approach to combining the results of the 2 trials. The ERG performed a fixed and random effects exploratory meta-analysis for plasma uric acid responder status and tophi resolution. These outcomes were selected because plasma uric acid responder status was the primary efficacy outcome and tophi resolution was a key driver in the cost-effectiveness model. The results from the ERG’s meta-analysis showed that plasma uric acid response was significantly greater in the pegloticase 8 mg every 2 weeks treatment group compared with the placebo group (relative risk [RR]=18.99, 95% confidence interval [CI] 2.69 to 133.94). Similarly, the results for tophus resolution favoured the pegloticase 8 mg every 2 weeks group compared with the placebo group (RR=4.57, 95% CI 1.35 to 15.45). The ERG stated that the software used to perform exploratory meta-analysis automatically applied a correction of 0.5 to the placebo arms of both trials if no events were observed and noted that this may introduce uncertainty to the results.

The ERG also highlighted that the impact of repeated courses of pegloticase on uric acid levels, secondary outcomes,
immunogenicity and adverse events was not clear from the manufacturer’s submission. It stated that limited evidence from the small re-exposure trial (C0409) suggested that there was an immune response against pegloticase in most of the re-exposed patients, resulting in loss of efficacy and infusion-related reactions. The ERG also stated that it was not clear whether the benefits of pegloticase would be maintained after pegloticase treatment stopped or whether maintenance treatment with other urate-lowering drugs would be successful in maintaining low uric acid levels and other benefits in the long term. During consultation, the manufacturer referred to an observational study (Prez-Ruiz et al. 2012) which, according to the manufacturer, supported the assumption of long-term maintenance of benefits with xanthine oxidase inhibitors. The ERG commented that it could be inferred from the study that if long-term treatment with allopurinol or febuxostat successfully maintains a low serum uric acid level, then incidences of flares may decrease. But the study did not provide any evidence that these drugs (allopurinol or febuxostat) can regain effectiveness in patients who had been previously refractory at the maximum medically appropriate doses. The ERG also noted that this study indicated that attributes of the pegloticase target population (such as, presence of tophi, high serum uric acid level, multiple joint involvement and poor renal function) may be associated with increased risk of gout recurrence.

3.40 The ERG questioned several assumptions in the manufacturer’s economic model. It noted that in the 2 key trials, it took up to 4 months for all patients who eventually lost response or withdrew from pegloticase to be identified, however the model assumed that non-responders can be identified after 2 months of pegloticase treatment. Additionally, the ERG stated that the group termed ‘non-completers’ by the manufacturer would be difficult to identify in
clinical practice. It also noted the assumption that non-completers could be identified in the first month of treatment was arbitrary because there were no data on time to stopping treatment from the trials.

3.41 The ERG suggested that an alternative modelling approach could have classified each non-completer patient as a non-responder and incorporated their outcomes within the mean result for non-responders. This would have been a more accurate reflection of the trials. The ERG conducted an exploratory deterministic analysis on the revised model using these assumptions, which involves assuming persistence with pegloticase to be 100% and a response rate of 42%, which was the rate observed in the pooled analysis of the 2 phase III trials. This increased the revised base-case ICER from £31,027 to £32,492 per QALY gained. The ERG noted that the manufacturer’s model assumed that each year 2% of patients undergo surgery to remove their tophi. The ERG conducted an exploratory sensitivity analysis removing tophi surgery from the model and stated that this had a marginal impact on the ICER and that tophi surgery is not a significant driver of cost-effectiveness.

3.42 The ERG noted that published data from modified intention-to-treat analysis of the trials were not used to calculate the clinical effectiveness in the model, and that there was additional analysis of the trial data to inform the health economic model. Primary end points in the trials were based on plasma uric acid level but in the economic model they were based on serum uric acid level. However, the ERG noted that plasma and serum uric acid levels had a degree of correlation and that serum uric acid levels would likely be used in clinical practice. The ERG agreed that long-term maintenance of serum uric acid levels below 360 micromol/litre could be expected to result in clinically meaningful changes in
patient-related outcomes, although it noted that the British Society for Rheumatology guideline recommended maintaining serum uric acid levels below 300 micromol/litre.

3.43 The ERG commented that the mortality applied in the model was not weighted according to the gender distribution of people with gout. This will have underestimated mortality because male-specific mortality is higher for all age groups over 55 years and gout is more prevalent in men. The ERG also noted that gout has been reported to be an independent risk factor for all-cause and cardiovascular mortality in the literature and it is reasonable to expect mortality in the modelled population to be higher than that for the general population of the UK. The manufacturer had stated that no data were available on mortality in people with severe debilitating chronic tophaceous gout in the UK. The ERG conducted an exploratory analysis in which the mortality risk was doubled to assess whether mortality was a significant driver of cost effectiveness. The result from this exploratory analysis increased the revised base-case ICER from £31,027 to £33,793 per QALY gained.

3.44 The ERG was concerned about the assumption that resource use would be greater in patients with a higher serum uric acid level over and above the difference determined by gout flares. It therefore conducted an exploratory analysis in which resource use for patients with a serum uric acid level over 360 micromol/litre was set to the same value as for those with a level under 360 micromol/litre. It also assumed that the number of rheumatology visits associated with pegloticase treatment would be reduced to 3 (from 5 in the manufacturer’s model) in year 1 and none thereafter, but assumed that 2 visits would be needed even for patients classified as non-responders or non-completers, giving a net reduction in the cost of
3.45 The ERG also noted that limited details were available about the methods used to derive the relationship between serum uric acid level and utility in the model beyond 6 months, which were based on data from guidance on Febuxostat for the management of hyperuricaemia in people with gout (NICE technology appraisal guidance 164). The ERG noted that the relationship between serum uric acid level and underlying utility was considered uncertain by the Appraisal Committee during appraisal of NICE technology appraisal guidance 164. The ERG had concerns that the method for calculating utility from a combination of serum uric acid level, frequency of flares and tophi resolution may result in quality of life improvements being ‘double counted’ because all 3 are likely to be correlated in an individual. For example, tophi resolution is likely to be correlated with low serum uric acid levels, but the model assumes that the probability of having tophi resolution is the same irrespective of the serum uric acid level, and applies a utility benefit for both tophi resolution and low serum uric acid levels. The ERG stated there was a similar risk of ‘double counting’ when capturing the benefits of reduced flares and lower serum uric acid level, because the frequency of flares is assumed to be related to the serum uric acid level but in the model both are treated as independent factors in determining utility. This type of ‘double counting’ was more problematic because both utility gains were applied to all patients from 6 months and to patients in the pegloticase arm of the model who receive best supportive care before 6 months. The ERG conducted an exploratory analysis.
assuming that utility benefits are driven exclusively by the frequency of flares and the resolution of tophi and not directly by the serum uric acid level. This had a considerable effect on the incremental QALY gained from pegloticase treatment, which decreased to 0.230 from the 0.305 in the manufacturer’s revised base case and increased the ICER to £41,118 per QALY gained.

3.46 The ERG described the scenario combining the alternative assumptions about utility gains with alternative assumptions about resource use (see sections 3.44–3.45) as its preferred scenario. This scenario incorporated the following changes to the manufacturer’s revised base case:

- No disutility for higher serum uric acid levels.
- A disutility of 0.076 for patients with tophi compared with those without.
- A utility of 0.68 for patients with tophi (and without flares).
- No increased resource use for higher serum uric acid levels.
- No additional rheumatology visits for pegloticase treatment after year 1.
- Rheumatology visits for starting and stopping treatment in non-responders and non-completers.

In this scenario (the ERG’s preferred exploratory analysis), pegloticase was associated with an incremental cost of £12,492 and an incremental QALY gain of 0.230 when compared with best supportive care, resulting in an ICER of £54,345 per QALY gained. This ICER was still associated with many uncertainties about the structural assumptions in the model.

3.47 The ERG was concerned that the duration of pegloticase treatment in the non-completer group could be more than the 1 month assumed in the manufacturer’s revised base case. It conducted a
further exploratory analysis assuming treatment duration of 3 months for this group before switching to best supportive care. This resulted in a substantial increase in the incremental cost from £12,492 to £15,084 and a marginal increase in the incremental QALY gains from 0.230 to 0.226, giving an ICER of £66,696 per QALY gained. In response to consultation, the manufacturer stated that data from a post-marketing retrospective survey of 50 rheumatologists in the USA indicated that the average number of vials used for non-completers was 2.5 vials, corresponding to treatment duration of just over 1 month. The ERG stated that though this survey had some limitations around external validity and quality of reporting, it was reasonable to assume that the duration of pegloticase treatment in the non-completer group would be 1 month.

3.48 The ERG was concerned that the length of time on treatment for patients who showed a response in clinical practice could be greater than the 6 months assumed in the model. It stated that the summary of product characteristics did not limit treatment to 6 months but also acknowledged the lack of data to support long-term treatment. The ERG also noted that in the open-label extension study patients were allowed to continue pegloticase treatment for up to a maximum of 30 months (2.5 years). The combined data from the 2 key trials (C0405 and C0406) and the open-label extension study (C0407) indicated that the duration of pegloticase treatment for responders is much longer than 6 months. The ERG stated that, based on exploratory analysis, an assumption of prolonged duration of pegloticase treatment in the responders would result in a substantial increase in the incremental cost but a marginal increase in the incremental QALY gained, giving a considerably higher ICER than that of the ERG’s preferred exploratory analysis of £54,345 per QALY gained. In response to
consultation, the manufacturer stressed that duration of treatment with pegloticase in responders was unlikely to exceed 6 months. It said that this was supported by results from a post-marketing retrospective survey of rheumatologists in the USA, which indicated that ‘therapeutic goal’ (not specified) was achieved in responders with an average of 6.2 vials. As before (see section 3.47), the ERG highlighted issues around the study design, external validity and quality of reporting in the post-marketing survey, stating that while a 6-month duration of pegloticase in responders seemed plausible based on these data, there was no possibility of it being less than 6 months.

3.49 The economic model assumes that the benefits of pegloticase treatment in responders during the 6-month treatment period can be maintained in the long term by treatment with allopurinol or febuxostat. The ERG considered that this was uncertain because there was no direct evidence on persistence with either allopurinol or febuxostat in the population receiving maintenance treatment in the economic model (patients with severe debilitating chronic tophaceous gout who had not responded to or are intolerant of xanthine oxidase inhibitors and who had responded to treatment with pegloticase). The ERG noted that in the manufacturer’s original model 34% of the incremental QALY gains were accrued more than 10 years after starting pegloticase treatment. The ERG considered that the extrapolation of benefits over such a long period was a significant area of uncertainty because no direct evidence had been presented by the manufacturer to show that the serum uric acid levels after response to pegloticase treatment can be maintained by treatment with allopurinol or febuxostat treatment in the long term. The ERG conducted an exploratory analysis assuming no effect of long-term xanthine oxidase inhibitor (allopurinol, febuxostat) treatment in maintaining lower serum uric
acid levels after pegloticase treatment. It indicated that it would substantially decrease the incremental QALY gained and so increase the ICER above the £54,345 per QALY gained in the ERG’s preferred exploratory analysis.

3.50 The ERG also had concerns about the survival model used to extrapolate persistence with allopurinol, and noted that in the scenario analysis the ICER was sensitive to the rate of discontinuation of allopurinol. The ERG noted that an alternative approach to modelling allopurinol persistence could be a Weibull fit for all the 2-year data available from the UK observational study (Annemans et al. 2008) as opposed to the Weibull fit for only the second year data, as in the original model. Sensitivity analysis conducted by the manufacturer at the clarification stage using this approach increased the ICER from the revised base-case of £31,027 to £37,981 per QALY gained. The ERG conducted similar exploratory analysis for the ERG’s preferred scenario (ICER £54,345 per QALY gained) and it resulted in an increased ICER of £55,529 per QALY gained. In response to consultation, the manufacturer presented indirect evidence from 3 observational studies (Harrold et al. 2009, Riedel et al. 2004 and Solomon et al. 2008) to support the hypothesis that the pegloticase target population (older people with tophaceous gout and comorbidities who are receiving treatment from a gout specialist) have greater adherence to urate-lowering therapy than the general gout population. The ERG agreed that the indirect evidence presented by the manufacturer supported this hypothesis.

3.51 The ERG also conducted subgroup analyses to assess the difference in ICER for patients unable to take maintenance treatment (with allopurinol or febuxostat) because of intolerance or contraindication and for those who can take maintenance
treatment. In the manufacturer’s revised base case, in patients unable to take maintenance treatment with xanthine oxidase inhibitors, pegloticase was associated with an ICER of £60,793 per QALY gained compared with best supportive care, while in patients who could take maintenance treatment the ICER was £28,922 per QALY gained. Similarly, for the ERG’s preferred exploratory analysis, in patients unable to take maintenance treatment with xanthine oxidase inhibitors, pegloticase was associated with an ICER of £62,961 per QALY gained compared with best supportive care, but for patients who could take maintenance treatment the ICER was £53,517 per QALY gained.

Additional analyses submitted by the manufacturer during consultation

3.52 During consultation, the manufacturer submitted another revised base case model, reducing the association between serum uric acid level and utility gain to 50% of the estimate in the original submission (hereafter referred to as the ‘revised base-case at consultation’). The manufacturer acknowledged the lack of robust evidence on the precise relationship between serum uric acid level and disutility from symptoms and sequelae other than flares and tophi, but stated that a plausible relationship between them had been previously recognised in Feboxostat for the management of hyperuricaemia in people with gout (NICE technology appraisal guidance 164). The manufacturer further justified this relationship by stating that pegloticase significantly improves the consequences of severe gout other than tophi and flares, for example tender and swollen joints (see sections 3.8–3.12), and referenced 2 studies (Whelton et al. 2013 and Wang et al. 2012) that demonstrated a beneficial effect of lower serum uric acid on renal function in patients with renal insufficiency.
This revised base-case at consultation resulted in an incremental cost of £9452 and an estimated QALY gain of 0.267 for pegloticase compared with best supportive care, with an ICER of £35,447 per QALY gained. The manufacturer also provided 6 scenario analyses around the revised base-case at consultation. Restricting the use of pegloticase in patients who can take long-term xanthine oxidase inhibitor (allopurinol or febuxostat) maintenance therapy and assuming no flares in the patients on maintenance therapy would decrease the ICER to £33,374 and £32,592 per QALY gained respectively. However, reducing the association between resource use and serum uric acid level, assuming an increased treatment duration for non-completers (with or without assuming some benefits), would increase the ICER to between £37,968 and £40,488 per QALY gained. Assuming a day-care cost (£248) for pegloticase administration instead of the cost of 3.5 hours of nursing time (£92) would increase the incremental cost of pegloticase from £9452 to £10,477 and the revised base-case ICER at consultation from £35,447 to £39,293 per QALY gained.

The manufacturer also presented probabilistic sensitivity analyses for this revised base-case and scenario analysis presented at consultation. For the revised base case, the probability of pegloticase being cost effective was 5.3% at a threshold of £30,000 per QALY gained. The probability of pegloticase being cost effective increased to 23.6% in the scenario in which it was assumed that responders on maintenance therapy did not have any flares.

In its critique of the manufacturer’s revised base-case model at consultation, (see section 3.52), the ERG identified that a new relationship between tophi status and utility had been included. In this revised model, as the utility per serum uric acid level is
reduced, the difference between those with and without tophi resolution was maintained by introducing a separate relationship between tophi resolution and utility, which increased in proportion to the decrease in the association between serum uric acid level and utility. The ERG stated that without this additional assumption on tophi resolution and utility, the manufacturer’s revised ICER at consultation would increase from £35,447 to £55,949 per QALY gained. The ERG highlighted that the manufacturer’s revised base-case assumption at consultation was a half-way position between their previous assumption and the ERG’s preferred assumption, and that this decision was not based on any evidence. The ERG stated that the evidence base available to support the relationships between utility and serum uric acid level, and tophi resolution and estimation of the size of the correlation between them was weak.

3.56 The ERG also commented on the plausibility of scenario analyses presented by the manufacturer around its revised base case at consultation. The ERG agreed with the manufacturer that the treatment duration in non-completers and resource use with intravenous administration of pegloticase used in the original model, that is, equal to the cost of 3.5 hours of nursing time, seemed plausible. It commented that restricting the use of pegloticase in patients who can take long-term xanthine oxidase inhibitor maintenance therapy may not be practical and the assumption of no flares in the patients on maintenance therapy is based on indirect evidence and from a population who may not be representative of the population likely to receive pegloticase. The ERG also questioned the use of extrapolated data (between the tophi benefits in pegloticase responders and the tophi benefits in those receiving placebo) to calculate benefit in the non-completers when trial data were available. The ERG commented that the assumption that the resource use associated with above-target...
serum uric acid level was reduced by 50% of the resource use assumed previously was not evidence-based.

3.57 Full details of all the evidence are in the manufacturer’s submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pegloticase having considered evidence on the nature of severe debilitating chronic tophaceous gout and the value placed on the benefits of pegloticase by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee discussed the natural history of gout. It heard from the clinical specialist that gout is characterised by intermittent and painful attacks of arthritis, known as acute gout flares. Flares appear when a high level of uric acid leads to formation of monosodium urate crystals, which can accumulate and release into the joints causing inflammation. The flares are self-limiting and followed by an asymptomatic period. The Committee heard from the patient expert that flares can be very painful and can seriously affect people’s daily life. The Committee also heard from the clinical specialist that if the uric acid level in the blood remains persistently high, the patient may develop tophi, caused by a build-up of urate crystals in the skin and in or around joints. This deposition is usually painless but may limit joint function. The subcutaneous tophi may ulcerate and could be painful and cosmetically unacceptable to many patients. If left untreated the disease may
progress to joint destruction, resulting in considerable pain and progressive loss of mobility and function. The Committee noted the manufacturer’s comment at consultation that severe debilitating chronic tophaceous gout is the most extreme form of gout, which is refractory to current therapies, and affects a small number of people who may also have multiple comorbidities. The Committee concluded that chronic tophaceous gout can be a severe and debilitating condition, which has a considerable effect on the quality of life of the people with the condition.

4.3 The Committee discussed the current care for people with severe debilitating chronic tophaceous gout. The Committee heard from the clinical specialist that xanthine oxidase inhibitors (mainly allopurinol or febuxostat) are used for treating gout. The Committee heard that allopurinol is used as a first-line urate-lowering treatment for gout. It heard from the clinical specialist that initial urate-lowering treatment leads to more gout flares shortly after treatment is started but that the frequency is usually reduced after some time on treatment. The clinical specialist explained that the initial increased frequency of flares may lead to under-use of allopurinol. The clinical specialist explained further that in clinical practice, some patients may be considered allopurinol-intolerant, without attempts to desensitise the patient or titrate the dose of allopurinol up to the maximum dose. The Committee heard that the main reasons for referral to secondary care are diagnostic uncertainty, failure to escalate the dose of urate-lowering drugs and increased flares associated with initiation of allopurinol treatment. The Committee agreed that, in practice, treatment of chronic tophaceous gout is not clinically optimal.

4.4 The Committee discussed the place of pegloticase in the clinical pathway of care for people with severe debilitating chronic
tocurious gout. It heard from the clinical specialist that lowering uric acid is central to the treatment of gout. Lower uric acid reduces the severity and frequency of further episodes of flares, reduces the deposition of urate crystals in the skin, and protects joints from damage. The Committee noted that the population for this appraisal was narrower than that originally specified in the NICE scope, that is, adults with hyperuricaemia and symptomatic gout whose disease is refractory to conventional urate-lowering therapy or in whom conventional urate-lowering therapy is contraindicated or not tolerated, and that this was in line with the marketing authorisation for pegloticase which limits its use to treating severe debilitating chronic tophaceous gout. The Committee noted that in this small group of patients the disease becomes resistant to urate-lowering treatment, which results in persistently high levels of uric acid, even when receiving the maximum tolerated dose of allopurinol. It also noted that there are some patients who cannot take allopurinol because of contraindication or intolerance and for whom NICE recommended febuxostat. The Committee heard from the clinical specialist that pegloticase would be used late in the treatment pathway after unsuccessful response to all other treatments. The Committee also noted that the manufacturer estimated that around 2700 patients would be eligible to receive pegloticase in England and Wales. The Committee noted the manufacturer’s comment at consultation that pegloticase was associated with ‘debulking’, that is, a rapid reduction in urate burden in the tissues to the point at which oral urate-lowering drugs could effectively maintain low uric acid levels and prevent recurrence of the symptoms and sequelae of gout. The Committee was aware that the population in the observational studies provided to support this concept of ‘debulking’ was different from the pegloticase target population. However, the Committee was persuaded that rapidly achieving
target serum uric acid level is likely to be associated with speedy tophus dissolution in people with chronic tophaceous gout.

4.5 The Committee discussed the decision problem addressed in the manufacturer’s submission. The Committee was aware that the comparators listed in the scope were febuxostat and best supportive care. The Committee noted that the manufacturer submitted evidence comparing pegloticase with best supportive care but not with febuxostat. The Committee noted the manufacturer’s explanation that patients whose symptoms were controlled using xanthine oxidase inhibitors would not be eligible for treatment with pegloticase, in line with the marketing authorisation. The Committee concluded that pegloticase would be an option for people whose uric acid levels have failed to normalise with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose or for whom xanthine oxidase inhibitors were contraindicated. The Committee was therefore satisfied that best supportive care was an appropriate comparator for pegloticase in people whose serum uric acid level has failed to normalise after treatment with xanthine oxidase inhibitors.

4.6 The Committee discussed the generalisability of the 2 phase III trials to the UK population. It noted that the mean age of patients in the trial was 56 years but heard from the Evidence Review Group (ERG) that the average age of men with gout in UK practice was around 10 years older. The clinical specialist also stated that in women the average age of disease onset is even older. The Committee noted that the manufacturer’s submission was not explicit about whether trial participants had previously received true optimised care with allopurinol. However, it did consider the disease severity at baseline in the trial to be representative of patients for whom treatment with pegloticase would be considered
in UK practice. The Committee concluded that it was uncertain whether patients in the trials represented people whose previous treatment with an optimised titration of allopurinol had failed to bring serum uric acid levels down to normal, but was persuaded that overall the trial is largely generalisable to the UK patient population.

4.7 The Committee discussed the manufacturer’s analysis of the trial results. It noted that the manufacturer had presented a pooled analysis of the 2 phase III trials but that the ERG had expressed concerns that simple pooled analyses may give counterintuitive results. The Committee discussed the ERG’s exploratory meta-analysis and noted that it yielded similar results (see section 3.38). The Committee was also aware of difficulties in carrying out a meta-analysis when some arms of the trials have zero event rates, as was the case in the pegloticase trials. The Committee concluded that, although a simple pooled analysis is generally not a robust method for combining results from 2 trials, it was acceptable for the Committee’s deliberation because the results of the meta-analysis were not substantially different from the pooled analysis, and because there was methodological uncertainty in the meta-analysis (see section 3.38).

4.8 The Committee discussed the results of the 2 phase III trials and the pooled analysis. It noted that plasma uric acid levels normalised within 24 hours of the first infusion in all patients receiving pegloticase. But over time some patients lost the urate-lowering response and as a result the proportion of patients who had a response (as defined in the trial protocols) was 47% in trial C0405, 38% in trial C0406 and 42% in the pooled analysis. The Committee also noted that no patients in placebo arms had a persistently lower level of plasma uric acid and that this difference was statistically
significant. The Committee concluded that with pegloticase treatment a significant proportion of patients had a decrease in plasma uric acid level, which continued over the trial (6 months) and extension study period (30 months).

4.9 The Committee discussed the evidence relating to gouty flares during treatment with pegloticase. It noted a higher incidence of flares during the initial 3 months of treatment in patients treated with pegloticase, whether they had a response to pegloticase or not, than in patients treated with placebo. The Committee was concerned that in the initial 3 months of the trial an average patient receiving pegloticase had almost twice as many flares as a patient receiving placebo. The Committee heard from the clinical specialist that this is an expected reaction to any urate-lowering treatment because a lower level of uric acid can lead to urate crystals starting to dissolve, which in turn leads to an increase in flares. The Committee discussed whether there is any difference in the severity of flares caused by the disease process and those induced by the treatment. The Committee heard from the patient expert that in his experience flares during the initial stages of urate-lowering treatment were similar to subsequent ones. The Committee also noted that in the 3 months after the initial period, the number of patients with flares and the number of flares per patient were lower in patients receiving pegloticase than in patients receiving placebo. The Committee concluded that the initial risk of increased flares does not negate the effectiveness of pegloticase.

4.10 The Committee discussed the results for other secondary outcomes, including patient-reported outcomes. The Committee noted that a significantly higher proportion of patients who had tophi at baseline in the pegloticase treatment group had complete resolution at 6 months. The Committee also noted that patients in
the pegloticase group had significantly fewer tender joints at the final visit than patients in the placebo group. The Committee discussed the results of patient-reported outcomes and agreed that treatment with pegloticase was associated with favourable outcomes compared with placebo, and that the difference was statistically significant in most cases. The Committee concluded that pegloticase has been proved to be effective in resolving tophi, and in improving the overall wellbeing of patients who continued receiving it in the trials.

4.11 The Committee discussed the adverse events associated with pegloticase. The Committee noted that at the end of the 2 trials around a third of patients in the pegloticase every 2 weeks arm had withdrawn from the trials. The Committee noted the ERG’s concerns that a substantially greater number of patients had left the trials before completion in the pegloticase arm compared with the placebo arm. The Committee noted that the primary reason was adverse events, including infusion reactions and anaphylaxis. In the trials around 90% of patients had an increased titre of anti-pegloticase antibodies; the incidence of anaphylaxis was associated with a high titre of anti-pegloticase antibodies. The Committee heard from the manufacturer that rising antibody titre was also associated with the loss of urate-lowering response. The Committee also noted that the manufacturer’s submission stated that most of the infusion-related reactions were after a loss of treatment response (plasma uric acid levels greater than 360 micromol/litre). It considered the results from the manufacturer’s post-hoc analysis, which confirmed that the proportion of patients with infusion reactions in the trials would have declined from 26% to 14%, with efficacy remaining unchanged, if the stopping rule in the summary of product characteristics had been applied in the trials. The Committee was
aware that post-marketing surveillance data from the USA, submitted by the manufacturer in response to consultation, also suggested that infusion reactions were lower in clinical practice than in the trials. However, it noted comments from the manufacturer and the ERG that these data were limited by the voluntary nature of adverse event reporting and the relatively short data collection period. The Committee noted the manufacturer’s clarification that the rate of anaphylaxis, which was very likely to have been reported completely in post-marketing surveillance, remained the same as in the trial. The Committee was concerned that incidence of infusion reactions may not have been completely reported in post-marketing surveillance. In addition, the Committee also noted that according to the summary of product characteristics for pegloticase, there was greater risk of infusion reactions in people with a body weight of more than 100 kg and heard from the ERG that approximately 10–15% of gout patients in the UK would weigh more than 100 kg. The Committee was aware of the manufacturer’s assertion during consultation that patients at this extreme stage of gout who have severe pain and may be at risk of joint destruction would be willing to accept greater risks associated with treatment than those in earlier stages of the disease. However, the Committee also noted concerns from a patient organisation about the reported increased risk of acute flare, infusion-related reactions, and progressive loss of efficacy associated with pegloticase treatment. The Committee concluded that treatment with pegloticase is associated with a risk of infusion reactions and anaphylaxis.

4.12 The Committee also discussed whether the potential immunogenicity of pegloticase may also result in other immune-complex diseases. It heard from the manufacturer that there was no evidence available to suggest this. The Committee was also
concerned that antibodies against pegloticase may cross-react with other drugs and heard from the manufacturer that pegloticase may cross-react with other drugs containing a polyethylene glycol moiety. The Committee concluded that long-term safety data for pegloticase, including data from the post-marketing 5-year observation study being carried out in the European Union by the manufacturer, would be useful to address these concerns.

4.13 The Committee discussed re-treatment with pegloticase in patients who had responded earlier after a treatment break, and whether potential immunogenicity may affect it. The Committee noted the results of a very small re-exposure study (n=7) and noted that the summary of product characteristics states that patients receiving pegloticase treatment after an interruption of more than 4 weeks may have a higher risk of infusion-related reactions, including anaphylaxis. The Committee concluded that, because of the limited availability of data on efficacy, and the risk of serious adverse reactions from immunogenicity, re-treatment with pegloticase would be limited in clinical practice.

4.14 The Committee considered the optimum duration of pegloticase treatment in patients with severe debilitating chronic tophaceous gout. It noted that the summary of product characteristics states that duration of treatment should be based on ‘maintenance of response and clinical judgement’. The Committee discussed that although the clinical trials were 6 months long, patients were invited to participate in a long-term open-label extension study. The Committee noted that the patients were given the choice of receiving pegloticase or participating in the study to observe the long-term effect of pegloticase. Nearly all patients (97%) who had received pegloticase every 2 weeks chose to continue receiving it. The combined data from the trials and the open-label extension
study suggest an average treatment duration of approximately 2 years in people whose serum uric acid level responded to pegloticase. The Committee discussed the manufacturer’s comment at consultation that in clinical practice duration of treatment is not expected to be longer than 6 months. This was based on clinical opinion as well as a retrospective survey of rheumatologists in the USA. The Committee noted the ERG’s concerns about the study design, quality of reporting and external validity of this survey. The Committee also questioned whether it would be reasonable to stop treatment at 6 months in patients who are responding and tolerating it well, especially when there are no other treatment options available and re-treatment after a break in of therapy is not considered safe (see section 4.13). It also noted the comment from the British Society of Rheumatology that continuing pegloticase beyond 6 months in responders is possible in clinical practice. The Committee noted that data from clinical trials proved the effectiveness of pegloticase treatment for 6 months, but it was not persuaded that duration of treatment with pegloticase in responders would be limited to 6 months. The Committee concluded that in clinical practice duration of treatment might be substantially longer than 6 months.

**Cost effectiveness**

4.15 The Committee considered the manufacturer’s economic models, the assumptions on which the parameters in the model were based, and the critique and exploratory analyses performed by the ERG. The Committee also took into account the manufacturer’s revised model and additional evidence submitted during consultation and the ERG critique of these additional analyses. The Committee discussed whether the model accurately reflects the natural history of the disease. The Committee was concerned that Markov states based on the serum uric acid level may not have
captured the progressive joint destruction seen in severe debilitating chronic tophaceous gout. The Committee heard from the ERG that a proportion of the modelled population has joint involvement at baseline. The Committee concluded that the structure of the manufacturer’s model was acceptable but noted that there is uncertainty about the structural assumptions of the model (see sections 3.40, 3.43, 3.44 and 3.45).

4.16 The Committee discussed the structural assumptions used in the model. It noted that the rate of mortality of the general population was used (see section 3.43) without taking into account the increased risk of death in the patients eligible to receive pegloticase. The Committee discussed that mortality derived from the general population may underestimate the mortality rate for patients with gout. The clinical specialist clarified that increased cardiovascular mortality has been reported in patients with gout. The Committee also discussed whether a different mortality rate should have been used for men and women. It heard from the clinical specialist that around 25% of people treated for gout are women, who are also generally older at the time of presentation. However, the Committee heard from the ERG that mortality does not seem to be a major driver of the incremental cost-effectiveness ratio (ICER). The Committee noted that applying a 10% increase in mortality would have a minimal effect on the revised base-case ICER; applying a 100% increase would increase the manufacturer’s revised base-case ICER from £31,000 per quality-adjusted life year (QALY) gained to around £34,000 per QALY gained. The Committee concluded that although disease-specific values for mortality are desirable, in this instance the ICERs were not affected in a substantial way.
4.17 The Committee noted that in the model patients classified as non-responders (who discontinue pegloticase treatment because serum uric acid levels exceed the limit of 360 micromol/litre on 2 consecutive observations) and non-completers (those who discontinue the treatment for any reason except lack of response) stop treatment with pegloticase and move to best supportive care. For patients classified as non-responders, pegloticase treatment was assumed to stop after 2 months and patients classified as non-completers stopped treatment after 1 month. The Committee noted the ERG’s comment that some trial data on patients who discontinued pegloticase treatment (provided as academic in confidence and therefore not shown here) suggested that a 1-month duration of treatment in this group is an underestimate. However, the Committee also noted comments at consultation from the British Society of Rheumatologists that non-completers were defined as those who are intolerant to pegloticase or intravenous infusions, and that it would be possible to identify them within 1 to 2 months of treatment starting. The Committee also noted that data presented by the manufacturer from a retrospective survey of US rheumatologists reported that on average non-completers were treated for just over 1 month. The Committee concluded that despite the limitations of these data, a 1-month duration of pegloticase treatment for the non-completer population is plausible.

4.18 The Committee considered the modelling of the clinical-effectiveness data. The Committee noted the ERG’s comment that in the manufacturer’s base case 34% of the incremental QALY gains were accrued more than 10 years after pegloticase treatment (see section 3.49) but that data on the effectiveness of pegloticase was available only for the first 6 months. The model submitted by the manufacturer, however, assumes that all benefits gained in the first 6 months of pegloticase treatment would be sustained by
maintenance treatment with allopurinol or febuxostat. At clarification stage, the revised model submitted by the manufacturer assumed that all but 10% of patients who respond to pegloticase will receive maintenance treatment with allopurinol or febuxostat, an assumption that the Committee did not find plausible given that these treatments had lost effectiveness in patients who received pegloticase in earlier lines of therapy. The Committee discussed the study (Perez-Ruiz et al. 2011) provided by the manufacturer in response to consultation to support the assumption that benefits of pegloticase therapy could be maintained by long-term treatment with allopurinol or febuxostat. The Committee noted the ERG’s comments that, while the study provided indirect evidence that if serum uric acid is maintained successfully at a low level by long-term treatment with febuxostat or allopurinol, then flares should not recur, it does not support the hypothesis that xanthine oxidase inhibitors could be effective in a patient population in which they had lost effectiveness previously. The Committee also noted that this study indicated that the presence of tophi, higher serum uric acid level, multiple joint involvement and poorer renal function were associated with a higher risk of gout recurrence. The Committee agreed that these are clinical features of the pegloticase target population, and therefore the risk of gout recurring in this population after achieving the target serum uric acid level may be higher than in patients who have less severe gout. The Committee concluded that there is substantial uncertainty about the long-term benefits of treatment assumed in the model, and therefore the ICER for pegloticase is likely to be substantially higher than that presented in the manufacturer’s revised base case of £31,000 per QALY gained.

4.19 The Committee also discussed the modelling of long-term utility values after treatment with pegloticase. The Committee noted that,
to estimate long-term utilities, the manufacturer had applied the relationship between serum uric acid level and utility used in *Febuxostat for the management of hyperuricaemia in people with gout* (NICE technology appraisal guidance 164). The Committee noted that the manufacturer presented limited information on the methodology and that the ERG was not able to comment on the robustness of the data (see section 3.45). It also noted that the Committee that appraised febuxostat was not convinced by the robustness of the method used to derive the relationship between utility and serum uric acid level as outlined in section 4.11 of NICE technology appraisal guidance 164. The Committee was also concerned about the direct applicability of this relationship to people who would have received treatment with pegloticase, because the data on which this relationship is based were collected in a different population (patients who were responding to xanthine oxidase inhibitors). The Committee noted that the utility values applied in the pegloticase model after 6 months (and in some patients before 6 months, for instance in non-responders after 2 months and in non-completers after 1 month) were based on 3 outcomes: serum uric acid level, frequency of flares and tophi resolution. The Committee heard from the ERG that frequency of flares was a function of serum uric acid level and that using both is ‘double counting’ the benefits of lowered serum uric acid level. The Committee discussed whether lower serum uric acid levels benefit quality of life in any way other than through fewer flares and the resolution of tophi. The Committee heard from the clinical specialist that serum uric acid level is a biochemical marker and should not have been assumed to improve quality of life separately from the effect on flares and tophi, and noted that this was supported by the Royal College of Pathologists consultation comments. The Committee discussed consultation comments from the manufacturer, which suggested that there are benefits associated
with lower serum uric acid level other than its effect on flares and tophi. The Committee considered that while it was possible that a low level of serum uric acid could have an impact on other systems, for example cardiovascular or renal functioning, it was not possible to assess the effects of this separately, particularly in a population with multiple comorbidities. The Committee noted that there was no additional evidence to establish benefits from other symptoms and sequelae. The Committee also learned that in the trials, the term ‘complete resolution’ did not mean these patients would be free from all tophi (see section 3.3) although trial data for complete resolution were modelled as ‘patients without tophi’ and attributed higher utility gain than those with tophi, therefore perhaps overestimating the utility gain with tophi resolution. The Committee noted that there was substantial uncertainty in the long-term utility values used in the manufacturer’s model and concluded that the ERG’s exploratory analysis, which assumed utility based solely on the frequency of flares and resolution of tophi, increasing the revised base-case ICER from £31,000 to £41,000 per QALY gained, was more plausible.

4.20 The Committee discussed resource use in the model. The Committee noted that administration costs in the manufacturer’s model were calculated using an assumption of 3.5 hours of nursing time per infusion, based on clinical opinion. The Committee heard from the clinical specialist that because of the risk of anaphylactic reactions, it would be reasonable that pegloticase infusion would be administered on a day-case basis with the associated additional cost. The Committee took into account comments from the manufacturer and the British Society of Rheumatology, received during consultation, that an estimate of 3.5 hours would be appropriate. The Committee also noted that the summary of product characteristics for pegloticase states that infusion...
administration time should not be less than 2 hours and patients should be closely monitored for at least 1 hour after the end of infusion. However, the Committee was aware that, from the NHS perspective, 3.5 hours would be coded as a day case and therefore incorporating day-case costs remained appropriate. The Committee noted that incorporating a day-case cost would increase the incremental cost of pegloticase by approximately £1000 (see section 3.53). The Committee concluded that administration costs in the model were underestimated and a more accurate estimate would increase the ICER per QALY gained.

4.21 The Committee discussed long-term resource use in the manufacturer’s model. The Committee did not consider resource use would be greater with higher serum uric acid levels over and above that associated with gout flares. The Committee noted the manufacturer’s comment that 27% of patients in the trial did not have tophi and had other symptoms and sequelae of long-term high serum uric acid levels. In UK clinical practice these patients were likely to be referred to a rheumatologist despite having no tophi. However, the Committee was not persuaded that a biochemical marker (serum uric acid) could be assumed to have a direct effect on resource other than its clinical consequence, which is already captured in the increased incidence of flares outcome. The Committee concluded that the alternative assumption about resource use (independently of the assumption of benefit; see section 3.44) in the ERG’s exploratory analysis was appropriate, noting that this increased the revised base-case ICER from £31,000 to £41,000 per QALY gained.

4.22 The Committee discussed the ERG’s exploratory analyses. The Committee noted the ERG’s preferred exploratory scenario, which assumed that utility benefits are driven solely by flare frequency
and tophi resolution and not by serum uric acid levels directly. The ERG’s preferred exploratory scenario also incorporated changes to resource use (see section 3.46). Combined, these changes resulted in an ICER of £54,000 per QALY gained. The Committee further noted that there was still considerable uncertainty in the robustness of this ICER because:

- The duration of treatment with pegloticase in patients who have a response to pegloticase is likely to be more than 6 months.
- Long-term maintenance therapy with allopurinol may not maintain the lower serum uric acid level.
- The cost for pegloticase infusion is likely to be coded as a day case instead of 3.5 hours of nursing time.

The Committee concluded that the ICER for pegloticase compared with best supportive care was likely to be greater than £54,000 per QALY gained.

4.23 The Committee considered the effect of a longer duration of treatment than the 6 months assumed in the model in patients who have a response to pegloticase (see section 4.14). The Committee noted that a longer treatment duration increased the incremental cost but the QALY increased only marginally so the ICER was likely to increase. The Committee concluded that duration of treatment in patients who have a response to pegloticase was a major driver of the ICER, which had been underestimated, and the most plausible ICER would be higher than £54,000 per QALY gained.

4.24 The Committee was aware that in the manufacturer’s model, it was assumed that the benefits from pegloticase treatment would be maintained with xanthine oxidase inhibitors (allopurinol or febuxostat) even after stopping pegloticase. The Committee considered the effect on the ICER of assuming no continued
benefit after stopping pegloticase that is, assuming that maintenance treatment with xanthine oxidase inhibitors does not maintain the low serum uric acid levels achieved with pegloticase treatment. The Committee noted that this would decrease the incremental QALY gain and increase the incremental cost, so increasing the ICER. The Committee then discussed long-term persistence with allopurinol in the model. The Committee noted the ERG’s alternative exploratory approach to modelling allopurinol persistence after pegloticase, which applied a Weibull fit for all the 2-year data available from the UK observational study (Annemans et al. 2008) instead of a Weibull fit for only the second-year data, as in the manufacturer’s model. It noted that this increased the ERG’s preferred exploratory scenario ICER from £54,000 to £56,000 per QALY gained. The Committee was not convinced this was a more relevant assumption, and accepted the manufacturer’s comment that there was a positive correlation between age and adherence to therapy in chronic gout patients, also noting that the target population for pegloticase was older, therefore implying adherence would be better. However, it concluded that the lack of long-term effectiveness data for allopurinol and febuxostat in patients who had been treated with pegloticase increased uncertainty in the estimation of the ICER.

4.25 The Committee discussed the additional evidence and revised base-case assumptions submitted by the manufacturer during consultation. The Committee noted that these revised analyses assumed an association between low serum uric acid level and utility that was half the assumption used in the original submission. The Committee noted that this new assumption was not based on robust evidence and maintained its preference for a scenario assuming no association between serum uric acid level and utility gain over and above that estimated by flare frequency and tophi.
resolution (see section 4.21). The Committee also heard from the ERG that a new relationship between tophi status and utility had been introduced in manufacturer’s revised model, which increased linearly as the relationship between serum uric acid and utility decreased. The Committee was aware that the ERG’s preferred exploratory scenario already included a constant utility difference between people with and without tophi. The Committee heard that in the model considered at the first Committee meeting the relationship between serum uric acid and utility was found to indirectly produce a utility difference of 0.076 between patients with and without tophi, but in the manufacturer’s revised model at consultation, as the utility per serum uric acid level reduced, the utility difference between those with and without tophi was maintained by introducing a separate relationship between tophi resolution and utility. The Committee noted that these revised assumptions were not based on robust evidence. The Committee therefore concluded that the additional ICERs (base case of £35,000 per QALY gained and scenario analyses, ranging from £33,000 to £40,000 per QALY gained) presented by the manufacturer in response to consultation could not be accepted.

4.26 The Committee noted that the most plausible ICER considered at the first meeting was in excess of £66,000 per QALY gained. The Committee recalled that this ICER incorporated an assumption of longer treatment duration of 3 months rather than 1 month in non-completers, along with the other assumptions driving the ERG’s preferred exploratory scenario (see section 3.46-3.47). Uncertainties around the duration of treatment in responders, effectiveness and persistence of maintenance treatment, higher resource use in administration of pegloticase were expected to drive the ICER higher. However, following comments received during consultation, the Committee accepted that a 1 month
treatment duration in non-completers is plausible (see section 4.21), and the Committee concluded that an ICER of £54,000 per QALY gained, which incorporated this assumption, would be an appropriate starting point for discussion on the most plausible ICER. The Committee then noted that though persistence with allopurinol maintenance treatment after pegloticase is likely to be high (see section 4.24), other uncertainties such as longer duration of treatment in responders (see section 4.23), uncertain effectiveness of xanthine oxidase inhibitors maintenance treatment after pegloticase in responders (see section 4.24) and higher resource use associated with pegloticase administration (see section 4.20) remained and would increase the ICER in excess of £54,000 per QALY gained.

4.27 Having carefully considered all the evidence submitted by the manufacturer, the manufacturer’s base case and revised base-case models and the ERG exploratory analyses, the Committee concluded that there was considerable uncertainty around the estimation of the ICER for pegloticase and that the most plausible ICER would be in excess of £54,000 per QALY gained. The Committee concluded that pegloticase has not been shown to be a cost-effective use of NHS resources in people with severe debilitating chronic tophaceous gout and that therefore pegloticase could not be recommended.

4.28 The Committee discussed whether there were any equality issues to be considered in this appraisal. It considered the potential equality issues identified in the scoping consultation and through the course of the appraisal. The Committee heard that pegloticase is contraindicated in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency and that this enzyme deficiency is more common among people of African or Mediterranean family
origin. The Committee agreed that this was not an equality issue because pegloticase is contraindicated in people with G6PD deficiency because of a high risk of adverse reaction, not because of family origin. The Committee also discussed comments received from a patient organisation that frequent hospital admissions for infusions would amount to an equality issue because it creates a significant barrier for people with limited mobility. The Committee heard that because of the considerable risk of anaphylaxis, pegloticase can only be given in a facility equipped to deal with serious adverse events. It concluded that the draft recommendations do not differentially affect either group of people and concluded that this was not an equality issue as defined in the current equality and diversity legislation.

4.29 The Committee noted the manufacturer’s statement that pegloticase is the first treatment option for patients with severe debilitating chronic tophaceous gout whose serum uric acid level has failed to normalise despite treatment with xanthine oxidase inhibitors. The Committee also noted the manufacturer’s comments in response to consultation that the QALY gain estimated does not take account of the severity of the condition, the lack of alternative treatment options and the benefits pegloticase can bring to patients who can effectively become non-severe gout patients and can be treated with lower cost maintenance therapy. However, the Committee was not presented with a case substantiated by data to show the potential of pegloticase to make a significant and substantial impact on health-related benefits or that it adds demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure presented in the economic model.
### Summary of Appraisal Committee’s key conclusions

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: Pegloticase for treating severe debilitating chronic tophaceous gout</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
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<tr>
<td>The Committee concluded that pegloticase effectively lowers plasma uric acid levels for a significant proportion of patients with severe debilitating chronic tophaceous gout. However, the Committee noted the risk of infusion reactions and anaphylaxis.</td>
<td>4.8, 4.11,</td>
<td></td>
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<td>The Committee concluded that the most plausible ICER was likely to be greater than £54,000 per QALY gained given the uncertainties around the assumptions in the manufacturer’s analyses such as a longer duration of treatment in responders; uncertain effectiveness of xanthine oxidase inhibitors maintenance treatment and also higher resource use associated with pegloticase administration. It therefore concluded that pegloticase has not been shown to be a cost-effective use of NHS resources in people with severe debilitating chronic tophaceous gout and that therefore pegloticase could not be recommended.</td>
<td>4.22, 4.26, 4.27</td>
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**Current practice**

| | The Committee acknowledged that chronic tophaceous gout can be a severe and debilitating condition, which has a considerable effect on the quality of life of the people with the condition. |
| Clinical need of patients, including the availability of alternative treatments | The Committee agreed that, in practice, treatment of chronic tophaceous gout is not clinically optimal. |
| | The Committee heard from the clinical specialist that pegloticase would be used late in the treatment pathway after unsuccessful response to all other treatments. |

**The technology**

| | The Committee concluded that with pegloticase treatment a significant proportion of patients had a decrease in plasma uric acid level, which continued over the trial and extension study period. |
| Proposed benefits of the technology | The Committee concluded that the initial risk of increased flare does not negate the effectiveness of pegloticase. |
| How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee concluded that pegloticase has |
been proved to be effective in resolving tophi, and in improving the overall wellbeing of patients who continued receiving it in the trials.

The Committee was not presented with a case substantiated by data to show the potential of pegloticase to make a significant and substantial impact on health-related benefits or that it adds demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure presented in the economic model.

<table>
<thead>
<tr>
<th>What is the position of the treatment in the pathway of care for the condition?</th>
<th>The Committee heard from the clinical specialist that pegloticase would be used late in the treatment pathway after unsuccessful response to all other treatments. The Committee concluded that pegloticase would be an option for people whose uric acid levels have failed to normalise with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose or for whom xanthine oxidase inhibitors were contraindicated.</th>
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<tr>
<td>Adverse reactions</td>
<td>The Committee noted concerns from a patient organisation about the reported increased risk of acute flare, infusion-related reactions, and progressive loss of efficacy associated with pegloticase treatment. It concluded that pegloticase treatment is associated with a risk of infusion reactions and anaphylaxis. The Committee was concerned that potential immunogenicity of pegloticase may also result in other immune-complex diseases and antibodies against pegloticase may cross-react with other drugs containing a polyethylene glycol moiety. The Committee concluded that long-term safety data for pegloticase, including data from the post-marketing 5-year observation study being carried out in the European Union by the manufacturer, would be useful to address these concerns. The Committee concluded that, because of the limited availability of data on efficacy, and the risk of serious adverse reactions from immunogenicity, re-treatment with pegloticase would be limited in clinical practice.</td>
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<tr>
<th><strong>Evidence for clinical effectiveness</strong></th>
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<tr>
<td><strong>Availability, nature and quality of evidence</strong></td>
<td>The Committee noted that the manufacturer had presented a pooled analysis of the 2 phase III trials but the ERG had expressed concerns that simple pooled analyses may give counterintuitive results. The Committee discussed that the ERG’s exploratory meta-analysis yielded similar results. The Committee concluded that, although a simple pooled analysis is generally not a robust method for combining results from 2 trials, it was acceptable for the Committee’s deliberation.</td>
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<tr>
<td><strong>Relevance to general clinical practice in the NHS</strong></td>
<td>The Committee discussed the generalisability of the 2 phase III trials to the UK population. The Committee concluded that it was uncertain whether patients in the trials represented people whose previous treatment with an optimised titration of allopurinol had failed to bring serum uric acid levels down to normal, but was persuaded that overall the trial is largely generalisable to the UK patient population.</td>
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<tr>
<td><strong>Uncertainties generated by the evidence</strong></td>
<td>The Committee was also concerned that antibodies against pegloticase may cross-react with other drugs and heard from the manufacturer that pegloticase may cross-react with other drugs containing a polyethylene glycol moiety. The Committee concluded that long-term safety data for pegloticase, including data from the post-marketing 5-year observation study being carried out in the European Union by the manufacturer, would be useful to address these concerns. The Committee considered the optimum duration of pegloticase treatment and concluded that in clinical practice treatment duration with pegloticase might be substantially longer than 6 months.</td>
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<tr>
<td><strong>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</strong></td>
<td>Several pre-specified subgroup analyses were presented by the manufacturer, including stratifications according to gender, age, body mass index, disease duration, and presence or absence of tophi. The manufacturer stated that no clear pattern or trend was observed for the primary outcomes in these groups.</td>
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<tr>
<td><strong>Estimate of the size of the clinical effectiveness including</strong></td>
<td>The Committee discussed the results of the 2 phase III trials and the pooled analysis. It noted that the proportion of patients who had a response</td>
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National Institute for Health and Care Excellence

Final appraisal determination – Pegloticase for treating severe debilitating chronic tophaceous gout

Issue date: May 2013
## Strength of supporting evidence

(as defined in the trial protocols) was 47% in trial C0405, 38% in trial C0406 and 42% in the pooled analysis. The Committee also noted that no patients in placebo arms had a persistently lower level of plasma uric acid and that this difference was statistically significant.

The Committee discussed the results for other secondary outcomes, including patient-reported outcomes. The Committee noted that treatment with pegloticase was associated with favourable outcomes compared with placebo.

The Committee discussed the evidence relating to gouty flares during treatment with pegloticase and noted a higher incidence of flares during the initial 3 months of treatment in patients treated with pegloticase, whether they had a response to pegloticase or not, than in patients treated with placebo. The Committee also noted that in the 3 months after the initial period, the number of patients with flares and the number of flares per patient were lower in patients receiving pegloticase compared with placebo. The Committee concluded that the initial risk of increased flares does not negate the effectiveness of pegloticase.

### Evidence for cost effectiveness

<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The Committee considered the manufacturer’s economic model, the assumptions on which the parameters in the model were based and the critique and exploratory analyses performed by the ERG. It concluded that the structure of the manufacturer’s model was acceptable but noted that there is uncertainty about the structural assumptions of the model. The Committee also took into account the manufacturer’s revised model and additional evidence submitted during consultation and the ERG critique of these additional analyses.</th>
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<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
<td>The Committee discussed that mortality derived from the general population may underestimate the mortality rate for patients with gout. The Committee concluded that although disease-specific values for mortality are desirable, in this instance the ICERs were not affected in a substantial way.</td>
</tr>
</tbody>
</table>
The Committee considered the modelling of the clinical-effectiveness data and noted the model assumes that all benefits gained in the first 6 months of pegloticase treatment would be sustained by maintenance treatment with allopurinol or febuxostat. The Committee discussed the study provided by the manufacturer in response to consultation to support the assumption that benefits of pegloticase therapy could be maintained by long-term treatment with allopurinol or febuxostat. The Committee concluded that there is substantial uncertainty about the long-term benefits of treatment assumed in the model.

The Committee noted that the utility values applied in the model were based on 3 outcomes: serum uric acid level, frequency of flares and tophi resolution. The Committee heard that frequency of flares was a function of serum uric acid level and that using both is ‘double counting’ the benefits of lowered serum uric acid level. The Committee heard that serum uric acid level is a biochemical marker and should not have been assumed to improve quality of life separately from the effect on flares and tophi. The Committee noted that there was no additional evidence to establish benefits from other symptoms and sequelae. It also learnt that in the trials, the term ‘complete resolution’ did not mean these patients would be free from all tophi although trial data for complete resolution were modelled as ‘patients without tophi’ and attributed higher utility gain than those with tophi, therefore perhaps overestimating the utility gain with tophi resolution.

Incorporation of health-related quality-of-life benefits and utility values

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

The Committee was not presented with a case substantiated by data to show that pegloticase adds demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure presented in the economic model.
<table>
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<th>Are there specific groups of people for whom the technology is particularly cost effective?</th>
<th>Not applicable</th>
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</table>
| What are the key drivers of cost effectiveness? | The Committee concluded that duration of treatment in patients who have a response to pegloticase was a major driver of the ICER, which had been underestimated.  
The Committee considered the effect of assuming no continued benefit after stopping pegloticase, that is, assuming that maintenance treatment with xanthine oxidase inhibitors does not maintain low serum uric acid levels. The Committee noted that this would decrease the incremental QALY gain and increase the incremental cost, so increasing the ICER. It concluded that the lack of long-term effectiveness data for allopurinol and febuxostat in patients who had been treated with pegloticase increased uncertainty in the estimation of the ICER.  
The deterministic sensitivity analyses conducted by the manufacturer showed that the cost effectiveness of pegloticase was particularly sensitive to changes in baseline levels of serum uric acid, the disutility associated with higher serum uric acid levels and patients’ age. The sensitivity analyses also showed that the disutility associated with higher serum uric acid levels is a significant driver of cost effectiveness. The cost-effectiveness results were also fairly sensitive to changes in the utility value for patients with serum uric acid levels under the target value and the baseline utility value. The cost-effectiveness results were also moderately sensitive to the parameter values for treatment efficacy and persistence with pegloticase treatment. | 4.23 4.24 3.34 |
| Most likely cost-effectiveness estimate (given as an ICER) | The Committee concluded that the most plausible ICER would be in excess of £54,000 per QALY gained. | 4.27 |

**Additional factors taken into account**

<table>
<thead>
<tr>
<th>Patient access schemes (PPRS)</th>
<th>Not applicable</th>
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<tr>
<td>End-of-life</td>
<td>Not applicable</td>
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</table>
### 5 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX](www.nice.org.uk/guidance/TAXXX) to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

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

| consideratinos and social value judgements | The Committee heard that G6PD deficiency is more common among people of African or Mediterranean family origin. The Committee agreed that this was not an equality issue because pegloticase is contraindicated in people with G6PD deficiency because of a high risk of adverse reaction, not because of family origin. The Committee also discussed comments that frequent hospital admissions for infusions would amount to an equality issue because it creates a significant barrier for people with limited mobility and noted that because of the considerable risk of anaphylaxis, pegloticase can only be given in a facility equipped to deal with serious adverse events. It concluded that the recommendations do not differentially affect either group of people and concluded that this was not an equality issue as defined in the current equality and diversity legislation. | 4.28 |
6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

- Febuxostat for the management of hyperuricaemia in people with gout.
  NICE technology appraisal guidance 164 (2008).

7 Review of guidance

7.1 The guidance on this technology will be considered for review in May 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens and Gary McVeigh
Chair and Vice-Chair, Appraisal Committee
May 2013
8 Appraisal Committee members and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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 Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Gary McVeigh
Vice Chair of Appraisal Committee C, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett
Director for Health Improvement and Medical Director, NHS Barnet, London
David Chandler
Lay Member

Dr Mary Cooke
Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Professor Peter Crome
Honorary Professor, Dept of Primary Care and Population Health, University College London

Dr Maria Dyban
General Practitioner, Kings Road Surgery, Glasgow

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford and Airedale Primary Care Trust

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Emily Lam
Lay Member

Dr Grant Maclaine
Director, Health Economics & Outcomes Research, BD, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Professor Eugene Milne
Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne
8.2 **NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Anwar Jilani**
Technical Lead
Raisa Sidhu and Pall Jonsson
Technical Advisers

Lori Farrar
Project Manager
Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health Related Research (ScHARR):

- Archer R, Davis S, Uttley L and Cantrell A. Pegloticase for the treatment of hyperuricaemia in people with symptomatic gout whose disease is refractory to conventional urate-lowering therapy, or in whom conventional urate-lowering therapy is contraindicated or not tolerated: A Single Technology Appraisal. ScHARR, University of Sheffield, 2012.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. 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 have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:
- Savient Pharmaceuticals

II Professional/specialist and patient/carer groups:
- UK Gout Society
- British Society for Rheumatology
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:
- Department of Health
- Welsh Government
IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Arthritis Research UK
- Warwick Evidence
- National Institute for Health Research Health Technology Assessment Programme

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

- Dr Edward Roddy, Clinical Senior Lecturer in Rheumatology and Consultant Rheumatologist, nominated by Arthritis Research UK – clinical specialist
- Jonathan Harris, nominated by UK Gout Society – patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Savient Pharmaceuticals