ADIS DRUG PROFILE

Drugs 2011; 71 (16): 2179-2192
0012-6667/11/0016-2179/$55.55/0

Pegloticase
In Treatment-Refractory Chronic Gout

Katherine A. Lyseng-Williamson

Adis, a Wolters Kluwer Business, Auckland, New Zealand

Contents

Abstract

Intravenous pegloticase offers a novel approach to treating chronic gout refractory to conventional therapy. Pegloticase is a recombinant polyethylene glycol-conjugated form of uricase (a uric acid-specific enzyme lacking in humans) that catalyses the oxidation of uric acid to allantoin.

In randomized, placebo-controlled, double-blind, 6-month, phase III trials, intravenous pegloticase 8 mg every 2 or 4 weeks provided sustained reductions in plasma uric acid levels to less than the therapeutic target of 6 mg/dL in a substantial proportion of patients with chronic gout who were refractory to, or intolerant of, conventional urate-lowering therapy.

Pegloticase 8 mg every 2 weeks was associated with disease-modifying benefits relative to placebo, as shown by significant improvements from baseline in tophi resolution, frequency of gout flares and tender joint count, and clinically relevant and statistically significant improvements from baseline in health-related quality-of-life parameters related to disability, pain and physical function. Pegloticase 8 mg every 4 weeks was also significantly more effective than placebo with regard to most, but not all, of these endpoints.

Preliminary data from an open-label extension of the phase III trials indicate that long-term treatment with pegloticase 8 mg every 2 or 4 weeks may maintain plasma uric acid normalization in patients who experienced a sustained uric acid response during the phase III trials.

The most common serious adverse events associated with pegloticase are gout flares, infusion reactions and anaphylaxis. In addition, exacerbation of pre-existing congestive heart failure was reported in 2% of patients receiving pegloticase 8 mg every 2 weeks in the phase III trials.

Features and properties of pegloticase (KRYSTEXXA®)	
Indication	
Treatment of chronic gout in adult patients refractory to conventional therapy	
Mechanism of action	
Uric acid-specific enzyme that catalyses the oxidation of uric acid to allantoin, thereby lowering serum uric acid levels	
Dosage and administration	
Dose	8 mg (uricase protein)
Route of administration	Intravenous infusion over ≥2 h
Frequency of administration	Every 2 wk
Pharmacokinetic profile (following infusions of pegloticase 4 or 8 mg every 2 wk, or 8 or 12 mg every 4 wk for 12 wk, in 41 patients with refractory chronic gout)	
Median maximum serum concentrations (C_{max})	0.80–5.96 μg/mL
Time to C_{max}	Within 24 h
Systemic clearance	≈0.01 L/h
Median terminal elimination half-life	≈11–12 days
Most common (incidence ≥5%) treatment-emergent adverse events in 85 patients receiving pegloticase 8 mg every 2 wk in pooled clinical trials	
Gout flares (77% of patients), infusion reactions (26%), nausea (12%), contusion or ecchymosis (11%), nasopharyngitis (7%), constipation (6%), chest pain (6%), anaphylaxis (5%) and vomiting (5%)	

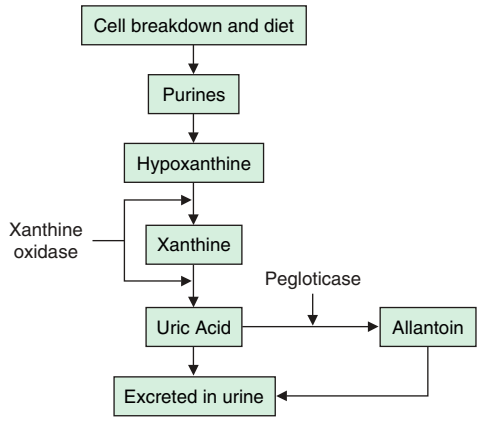

Fig. 1. Simplified diagram of purine metabolism in humans and the site of action of pegloticase.[1-3]

Gout is a common and increasingly prevalent type of arthritis caused by chronic hyperuricaemia and the formation of pro-inflammatory monosodium urate (MSU) crystals in joints.[1,2] Increased levels of uric acid, which exists primarily as the urate anion at physiological pH, are predominantly (≈90%) caused by conditions that result in the underexcretion of uric acid by the kidney.[1] Conditions that result in increased production of uric acid may also result in hyperuricaemia.

In humans, uric acid is the end product of the metabolism of purines, which are produced from the breakdown of nucleic acids (figure 1).[1-3] Metabolism of purines to uric acid involves catalysation by the rate-limiting enzyme xanthine oxidase. In most mammals, uric acid undergoes further metabolism by uricase (urate oxidase) to allantoin. As humans lack uricase, they have higher plasma urate levels than most mammals, and when these levels are greater than the solubility limit of ≈7 mg/dL, MSU crystals may be deposited in tissues and joints.[1-3] These crystals are pro-inflammatory stimuli that result in intense acute (i.e. gout flares) or sustained inflammatory responses.[1] Patients with untreated or inadequately treated acute gout can develop chronic gout, which is characterized by joint inflammation and destruction, persistent pain and the development of tophi (MSU crystals surrounded by chronic mononuclear and giant-cell reactions).[1,2,4] Chronic gout, especially refractory chronic gout, is associated with reductions in functional status, impairment of health-related quality of life (HR-QOL) and a significant economic burden through absence from work and treatment-related costs.[1,2,4]

The management of chronic gout primarily involves maintenance treatment with urate-lowering therapies, as symptomatic treatment with anti-inflammatory agents (e.g. (NSAIDs, colchicine and corticosteroids) does not affect urate levels.[1,2] A target urate level of <6 mg/dL is generally recommended to prevent or limit new crystals from forming and to encourage existing crystals to dissolve, thereby preventing gout flares and other consequences of hyperuricaemia (e.g. tophi, urate nephropathy and urolithiasis). Allopurinol and febuxostat inhibit xanthine oxidase, thus reducing the formation of uric acid. Uricosuric agents (e.g. probenecid, sulfinpyrazone and benzbromarone), which increase the renal excretion of urate, are generally considered of lesser importance when there is concomitant renal dysfunction. When used, uricosuric agents are concomitant with xanthine oxidase inhibitors. There are concerns regarding the safety of the uricosuric agents, particularly with regard to sulfinpyrazone and benzbromarone.[1,2,5]

However, in some patients with chronic gout, treatment with xanthine oxidase inhibitors and other conventional therapies may not be sufficiently effective, or may be poorly tolerated or contraindicated.[1,2,5] In addition, conventional urate-lowering therapies do not lead to rapid resolution of tophi, with tophi generally continuing to persist during years of treatment.[6] To meet these unmet medical needs, new urate-lowering agents that target other parts of the purine metabolism pathway are needed. Pegloticase (KRYSTEXXA®),[7] the first approved polyethylene glycol (PEG)-conjugated uricase, enables the degradation of uric acid to allantoin (figure 1). Pegloticase consists of 8 mg of recombinant mammalian uricase protein conjugated with 24 mg of 10 kDa monomethoxy PEG, providing a soluble, bioavailable enzymatic agent with reduced immunogenicity to uricase and a longer half-life than unmodified uricase.[3] Doses of pegloticase are expressed as the weight of uricase protein.

This article provides an overview of the pharmacological properties, therapeutic efficacy and

tolerability of pegloticase in the treatment of chronic gout refractory to conventional therapy.

Medical literature (including published and unpublished data) on the use of pegloticase in gout was identified by searching databases for studies published since 1996 (including MEDLINE and EMBASE), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 13 October 2011.

1. Pharmacological Profile

Data presented in this section are primarily derived from two open-label pharmacokinetic-pharmacodynamic studies of intravenous pegloticase.[8,9] In a single-dose phase I study, 24 patients with symptomatic gout received pegloticase 0.5, 1, 2, 4, 8 or 12 mg.[8] In a multiple-dose phase II study, 41 patients with refractory chronic gout were randomized to receive pegloticase in one of four dosage groups (4 or 8 mg every 2 weeks, or 8 or 12 mg every 4 weeks) for 12–14 weeks.[9] Some pharmacodynamic results from two phase III trials in patients with chronic gout refractory to conventional treatment[10] are also presented; clinical results of these trials are discussed in section 2. Additional data from these trials are derived from the manufacturer's summary of prescribing information[7] and the US FDA reviews of pegloticase.[11]

Mechanism of Action

- Pegloticase is a recombinant PEG-conjugated form of the mammalian enzyme uricase, a uric acid-specific enzyme lacking in humans.[7,11] Pegloticase catalyses the oxidation of uric acid to allantoin (figure 1), thereby reducing serum uric acid levels. Allantoin, an inert purine metabolite, is 5–10 times more soluble than uric acid, and is more readily eliminated by the kidneys.
- When serum uric acid levels are reduced sufficiently below their solubility limit (≈7 mg/dL), existing accumulations of MSU crystals are brought into solution. Once in solution, urate can be enzymatically converted to allantoin by pegloticase and excreted from the body, reducing serum uric acid and, over time, helping to alleviate the signs and symptoms of gout.[7] Of note, the initiation of any urate-lowering therapy causes changes in serum uric acid levels that result in the mobilization of urate from tissue deposits, which is generally associated with a transient increase in the incidence of gout flares.[1,7]

Pharmacodynamic Parameters

- In a proof-of-principle study using a mouse model of severe gout,[12] pegylated mammalian uricase had greater bioavailability and was markedly more effective in reducing urate levels in uricase-deficient mice than unmodified uricase.
- The onset of activity of pegloticase is rapid in patients with gout.[7-9] Following infusion of single-dose pegloticase 4–12 mg, mean plasma urate levels decreased from 11.1 mg/dL at baseline to <2 mg/dL within 24 hours, and by a maximum of 10.2 mg/dL within 24–72 hours.[8] In all treatment groups in the multiple-dose study, mean plasma urate levels were reduced from 8.7 mg/dL at baseline to ≤6 mg/dL within 6 hours of the first pegloticase infusion; maximal suppression of plasma urate was achieved within 24 hours of each dose.[9] In the 24 hours after infusion of the first dose in the phase III trials,[10] mean plasma uric acid levels were 0.7 mg/dL in patients receiving pegloticase 8 mg and were 8.2 mg/dL in patients receiving placebo.[7]
- The plasma uricase activity of pegloticase is maintained for several weeks after infusion,[8,9] with increasing doses of pegloticase appearing to be associated with increases in the duration of urate-lowering response.[7] During the entire 21-day post-infusion period of the single-dose study, pegloticase 4, 8 and 12 mg was associated with area under the curve (AUC) values for plasma urate levels that were equivalent to maintaining constant plasma urate levels of 4.7, 1.2 and 2.7 mg/dL, respectively.[8] Likewise, over the entire multiple-dose study (including the 28-day follow-up period), mean plasma urate levels were reduced from baseline by 38–86% across all treatment groups,

and ranged from 1.42 to 4.12 mg/dL.[9] Although mean plasma urate levels increased between pegloticase infusions, they remained below the therapeutic target of 6 mg/dL in all but the group receiving pegloticase 4 mg every 2 weeks.

- In the multiple-dose study, pegloticase 8 mg every 2 weeks was the dosage that appeared to provide the most favourable responses to treatment.[9] This treatment group had the highest (87.5%) proportion of patients with a response (defined as a plasma urate level ≤6 mg/dL for at least 80% of the study period; primary endpoint), the least pronounced increases in mean plasma urate levels between doses, and the highest (91.9%) proportion of time with a response. However, between-group differences in these parameters were not significant, largely because of the small sample size.[9] Of note, administration of pegloticase 8 mg every 2 or 4 weeks for 12 weeks was also associated with rapid resolution of tophi in two patients.[13]
- Single infusions of pegloticase 4–12 mg were also effective in lowering urate levels in urine.[8] During the 21-day post-infusion period of the single-dose study, spot urine samples indicated that there were marked reductions in the uric acid : creatinine ratio, which occurred in parallel with reductions in plasma uric acid concentrations.[8]
- As with all therapeutic proteins, there is a potential for immunogenicity with pegloticase.[7] Anti-pegloticase antibodies were developed by 92% of patients receiving pegloticase 8 mg every 2 weeks and 28% of patients receiving placebo; anti-PEG antibodies were detected in 42% of pegloticase recipients.[7] Most of the anti-pegloticase antibodies appeared to be directed against PEG, with only a small proportion directed against uricase.[11] The proportion of placebo recipients who developed anti-pegloticase antibodies is consistent with the previously reported prevalence of antiPEG antibodies in the healthy blood donor population of ≈22–25%.[14]
- The presence of anti-pegloticase antibodies was associated with a decrease in the exposure and elimination half-life of pegloticase.[9,11] However, only high titres of anti-pegloticase antibodies (>1 : 2430) were associated with a failure to maintain normalized urate levels (see section 2) and a higher incidence of infusion reactions (see section 3).[7]
- Interactions between pegloticase and other drugs have not been formally studied.[7] The effect that the development of anti-PEG antibodies and anti-pegloticase antibodies will have on the response of patients to other PEG-containing therapies is not currently known.[7]

Pharmacokinetic Parameters

- Maximum serum concentrations (C_{max}) of pegloticase (based on measurements of plasma uricase activity) were dose proportional following a single infusion of pegloticase 0.5–12 mg.[8] Up to 8 mg of pegloticase, the AUC for plasma uricase activity and plasma uric acid levels were inversely related to one another and were dose proportional.[8] The volume of distribution of pegloticase was ≈5–10 L.
- Across all dosage regimens in the multiple-dose study, median C_{max} values of pegloticase were 0.80–5.96 μg/mL (i.e. after the first or last infusion of pegloticase 4 or 8 mg every 2 weeks, or 8 or 12 mg every 4 weeks), and were reached within 24 hours after administration.[11] Throughout the duration of the trial, clearance was constant at ≈0.01 L/h.[11]
- In patients receiving the approved dosage of pegloticase 8 mg every 2 weeks, median pegloticase C_{max} values were 2.95 (range 1.98–4.81) μg/mL after the first infusion, and 5.96 (range 2.87–8.89) μg/mL after the sixth infusion.[11]
- Administration of pegloticase every 2 weeks may result in a degree of accumulation of the drug.[9] Compared with the first dose, mean pegloticase serum concentrations were higher after the sixth dose in patients receiving pegloticase 8 mg every 2 weeks, but were comparable after the third dose in patients receiving pegloticase 8 mg every 4 weeks.[9]
- The terminal elimination half-life ($t_{½}$) of uricase is prolonged by PEG-conjugation of the enzyme, and is highly variable.[8,9] In the single-dose study,[8] the mean $t_{½}$ of pegloticase in serum was 9.2 days (range 6.4–13.8 days). After the first and last infusion in the multiple-dose study,[9] the median

$t_{½}$ of pegloticase in serum was 12.04 (range ≈7.54–16.79) days and 11.17 (range ≈3.88–39.17) days, respectively. In comparison, the $t_{½}$ of rasburicase (a non-PEG-conjugated uricase) is 15.7–22.5 hours.[15]

- The clearance and volume of distribution of pegloticase were influenced by body surface area and anti-pegloticase antibodies,[7] but its pharmacokinetic profile was not affected by age, sex, body weight and creatinine clearance.[7] The effects of renal or hepatic impairment on the pharmacokinetics of pegloticase have not been formally studied.

2. Therapeutic Efficacy

Randomized, Double-Blind, Phase III Trials

The efficacy of intravenous pegloticase 8 mg every 2 or 4 weeks for 6 months in the treatment of chronic gout refractory to conventional treatment has been evaluated in two replicate, randomized, double-blind, placebo-controlled, multicentre, North American phase III trials (trial C0405 and trial C0406; reported together in one paper).[10] Table I describes the methodology of these trials.[10]

There were no significant differences in baseline characteristics between trials or between treatment groups (i.e. pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks, and placebo).[10] Across the treatment groups in the two trials (n = 212), mean patient age was 53.8–58.2 years, 69.8–91.5% of patients were male, mean body mass index (BMI) was 31–35 and 43–70% of patients were obese (BMI ≥30). At baseline, the mean duration of gout was 12–16 years, mean serum uric acid levels were 9.4–10.4 mg/dL and tophi were present in 65–79% of patients. Most patients had co-morbid conditions; 78–88% of patients had one or more cardiovascular condition or risk factor, and 13–33% had chronic kidney disease (defined as an estimated creatinine clearance <60 mL/min).

- Pegloticase was significantly more effective in providing sustained reductions in plasma uric acid levels to below target levels than placebo.[10] The proportions of patients who achieved the primary endpoint of a response (defined as plasma uric acid levels <6 mg/dL for ≥80% of the time during months 3 and 6) was significantly ($p \leq 0.001$) greater with pegloticase 8 mg every 2 weeks than with placebo in the individual trials (47% vs 0% in trial C0405, and 38% vs 0% in trial C0406), and when the results of the trials were pooled (42% vs 0%) [figure 2].
- Pegloticase 8 mg every 4 weeks was also significantly more effective than placebo with regard to the proportion of patients who responded to treatment in trials C0405 (20% vs 0%; $p = 0.04$) and C0406 (49% vs 0%; $p < 0.001$), as well as in the pooled trials (35% vs 0%; $p < 0.001$) [figure 2].[10]
- In patients who responded to pegloticase 8 mg every 2 or 4 weeks, mean plasma uric acid levels were markedly below the target level of 6.0 mg/dL at each 2-week timepoint throughout the 6-month trial.[10] However, 72 of 74 pegloticase recipients who lost urate-lowering efficacy prior to trial completion or withdrawal did so by month 4. In patients who did not sustain plasma uric acid levels <6.0 mg/dL throughout the trial, mean plasma uric acid levels were below the target level at all timepoints up to and including week 10, but not at any time point thereafter, in the pegloticase 8 mg every 2 weeks group, and were below the target level at weeks 1 and 3, but not for the majority of subsequent measurements, in the pegloticase 8 mg every 4 weeks group.[10]
- Anti-pegloticase antibodies were detected in 134 (89%) of 150 evaluable patients receiving pegloticase 8 mg every 2 or 4 weeks.[10] However, only high anti-pegloticase antibody titres (>1 : 2430) were associated with a failure to maintain pegloticase-induced normalization of uric acid. A urate-lowering response to therapy was maintained in only 2% (1 of 52) of patients with high anti-pegloticase antibody titres at any time during the study compared with 63% (52 of 82) of patients who remained in the study for ≥2 months and never had a high anti-pegloticase antibody titre.[10] In a *post hoc* analysis,[10] there was a significant ($p < 0.001$) difference between response rates in patients with and without high antibody titres.

Table I. Overview of the methodology of two replicate, randomized, double-blind, placebo-controlled, multicentre, phase III trials evaluating the efficacy of intravenous pegloticase in the treatment of adults (age ≥18 y) with chronic gout refractory to conventional treatment. The two trials (C0405 and C0406) are reported together,[10] and were conducted in North America (US, Canada and Mexico). All interventions were infused intravenously over at least 2 h[a]

Pt inclusion/exclusion criteria	
Inclusion	Baseline serum uric acid level ≥8 mg/dL Symptomatic gout with at least one of the following: at least three gout flares in the previous 18 mo; at least one tophus; gouty arthropathy in at least one joint (i.e. clinical or radiological joint damage due to gout) Plus one of the following: self-reported medical contraindication to allopurinol; or medical history of failure to normalize uric acid levels to <6 mg/dL with at least 3 mo of allopurinol at the maximum medically appropriate dose as determined by the treating physician
Exclusion	Glucose-6-phosphate dehydrogenase deficiency, prior treatment with uricase-containing agent, unstable or uncontrolled cardiovascular disease (including unstable angina pectoris, uncontrolled hypertension [blood pressure >150/95 mmHg], uncontrolled arrhythmia, or uncompensated congestive heart failure), renal dialysis, solid organ transplant, pregnancy
Trial design	
Timeline	Wk 0: washout period for pts receiving urate-lowering medication at screening Wk 1–23: randomized interventions (pegloticase and/or placebo) administered every 2 wk for a total of 12 infusions Wk 25: final study visit
Randomized interventions (no. of pts in mITT pop.)	Pegloticase 8 mg every 2 wk (85 [43 in trial C0405 and 42 in trial C0406]) Pegloticase 8 mg every 4 wk[b] (84 [41 in trial C0405 and 43 in trial C0406]) Placebo every 2 wk (43 [20 in trial C0405 and 23 in trial C0406])
Prophylactic treatment	To prevent infusion-related reactions: oral fexofenadine 60 mg the evening before and morning of the infusion; paracetamol (acetaminophen) 1000 mg the morning of the infusion; and intravenous hydrocortisone 200 mg immediately before each infusion To prevent gout flares: analgesic doses of NSAIDs or colchicine 0.6 mg once or twice daily (unless contraindicated or not tolerated) initiated ≥1 wk prior to the first infusion and continued throughout the trial[c]
Prespecified efficacy endpoints and assessment methods	
Primary endpoint (analysed separately for each trial)	Proportion of pts who achieved a response (defined as plasma uric acid levels of <6 mg/dL for ≥80% of the time during mo 3 and 6 [i.e. period from wk 9 infusion to just before wk 13 infusion, from wk 21 infusion to wk 25, respectively]) Pts who withdrew before the wk 25 visit were classified as nonresponders Plasma uric acid levels were measured: prior to the first infusion (baseline) and 2 and 24 h after the first infusion; prior to each subsequent infusion; 2 h, 1 d and 7 d after the wk 9 and wk 21 infusions; and 2 h and 7 d after the wk 11 and wk 23 infusions
Secondary endpoints (analysed using pooled data from both trials)	Gout-related endpoints: tophus resolution (proportion of pts with complete resolution of at least one tophus with no new or progressive tophi); proportion of pts with gout flares (for periods of mo 1–3 and mo 4–6); number of gout flares per pt (for periods of mo 1–3 and mo 4–6); reductions from baseline in the no. of tender joints and the no. of swollen joints per pt Health-related quality-of-life endpoints: changes from baseline in HAQ disability index score, HAQ pain score, SF-36 physical component summary score Assessed prior to the first infusion (baseline) and at the wk 13, wk 19 and wk 25 visits

a In pts with infusion reactions, investigators were able to slow the rate or stop the infusion and restart at a slower rate; both of these led to some pts receiving their drug over a period >2 h.

b Pts received alternate infusions of pegloticase and placebo at successive 2 wk infusions.

c Any gout flares that occurred were also treated according to protocol-defined flare management.

HAQ = Health Assessment Questionnaire; **mITT pop.** = modified intent-to-treat population (i.e. all randomized pts who received at least one infusion); **pt(s)** = patient(s); **SF-36** = Medical Outcomes Study Short Form 36.

- The incidence of gout flares during the first few months of pegloticase therapy was higher than with placebo, but decreased with continued treatment.[10] During months 1 to 3 of the trials, patients in both of the pegloticase groups had significantly ($p < 0.05$) higher rates of gout flares

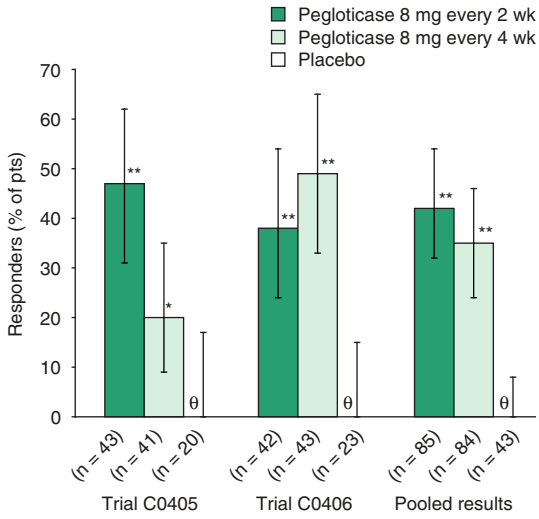

Fig. 2. Efficacy of intravenous pegloticase 8 mg every 2 or 4 wk for 6 mo in reducing plasma uric acid levels in adults with chronic gout refractory to conventional treatment. Proportion of patients (pts) who responded to treatment (defined as plasma uric acid levels <6 mg/dL for ≥80% of the time during mo 3 and 6; primary endpoint) in two replicate, randomized, double-blind, placebo-controlled, phase III trials (trials C0405 and C0406) and a pooled analysis.[10] Error bars represent 95% confidence intervals. θ indicates zero; * $p = 0.04$, ** $p \leq 0.001$ vs placebo.

and mean number of gout flares per patient than those in the placebo group (table II).[10] However, over the next 3 months, the proportion of patients with gout flares was significantly lower in the group receiving pegloticase 8 mg every 2 weeks than in the group receiving placebo (table II).[10]

- Pegloticase 8 mg every 2 or 4 weeks was significantly more effective than placebo with regard to some of the other secondary chronic gout-related endpoints.[10] Of the patients with one or more tophi at baseline, a significantly greater proportion of patients receiving pegloticase 8 mg every 2 weeks than placebo recipients had complete tophus resolution (defined as complete resolution of one or more tophi with no new or progressive tophi by the final visit) [table II]. Pegloticase 8 mg every 2 or 4 weeks was significantly more effective than placebo with regard to the change in baseline in the mean number of tender joints, but not the swollen joints, per patient (table II).[10]
- HR-QOL parameters improved to a significantly greater extent with pegloticase 8 mg every 2 or 4 weeks than with placebo.[10] Clinically relevant and statistically significant ($p \leq 0.01$) improvements from baseline in Health Assessment Questionnaire (HAQ) disability index score and Medical Outcomes Study Short Form 36 (SF-36) physical component summary score were shown in both pegloticase groups (table III).[10] Pegloticase 8 mg every 2 weeks recipients also reported significant ($p = 0.03$) improvements from baseline in HAQ visual analogue scale (VAS) pain scores.
- Pegloticase 8 mg every 2 or 4 weeks also improved other pain and patient global assessments of the effects of gout from baseline to a significantly greater extent than placebo.[16] In pooled data reported in a validation study of pain and patient global scales in chronic gout,[16] pegloticase recipients had significantly ($p < 0.0001$) greater

Table II. Effect of intravenous pegloticase 8 mg every 2 or 4 wk for 6 mo on secondary gout-related outcome in adults with chronic gout refractory to conventional treatment. Pooled results of two replicate, randomized, double-blind, phase III trials[10]

Treatment group	% of pts with flare		Mean no. of flares/pt		Tophus	Mean TJC/pt		Mean SJC/pt	
(no. of evaluable pts)	mo 1–3	mo 4–6	mo 1–3	mo 4–6	resolution[a] (% of pts)	b/l	change from b/l	b/l	change from b/l
Pegloticase 8 mg every 2 wk (52–85)	75*	41**	2.3***	0.8	40**	11.7	–7.4**	8.9	–5.5
Pegloticase 8 mg every 4 wk (52–84)	81**	57	2.7***	1.5	21	11.1	–6.1*	10.1	–5.1
Placebo (27–43)	53	67	1.2	1.3	7	14.1	–1.2	13.2	–2.6

a Defined as the complete resolution of at least one tophus with no new or progressive tophi. The effect of treatment on tophi was assessed methodologically using standardized digital photography, image analysis and a central reader blinded to treatment assignment.

b/l = baseline; **pt** = patient; **SJC** = swollen joint count; **TJC** = tender joint count; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs placebo.

Table III. Effect of intravenous pegloticase 8 mg every 2 or 4 wk for 6 mo on secondary health-related quality-of-life outcomes in adults with chronic gout refractory to conventional treatment. Pooled results of two replicate, randomized, double-blind, phase III trials[10]

Treatment group	HAQ disability index score[a]		HAQ VAS pain score[b]		SF-36 PCS score[c]	
(no. of evaluable pts)	b/l	change from b/l	b/l	change from b/l	b/l	change from b/l
Pegloticase 8 mg every 2 wk (77–84)	1.10	–0.22**[d]	44.2	–11.4*[d]	35.2	4.4**[d]
Pegloticase 8 mg every 4 wk (77–84)	1.21	–0.20**[d]	45.1	–6.9	33.3	4.9**[d]
Placebo (43)	1.24	0.02	53.9	1.4	31.0	–0.3

a Total score ranges from 0 (no disability) to 3 (severe disability); a decrease in score indicates improvement. In pts with rheumatoid arthritis, the MCID is a between-group difference of 0.22 points.[17]

b Assessed using a VAS from 0 (best) to 100 (worst); a decrease in score indicates improvement. In pts with rheumatoid arthritis, the MCID is ≈10 points.[18]

c Mean score is 50 with a standard deviation of 10; an increase in score indicates improvement. In pts with rheumatoid arthritis, the MCID is 2.5 points.[17]

d Meets or exceeds the MCID.

b/l = baseline; **HAQ** = Health Assessment Questionnaire; **MCID** = minimum clinically important difference; **pts** = patients; **SF-36 PCS** = Medical Outcomes Study Short Form 36 physical component summary score; **VAS** = visual analogue scale; * $p = 0.03$, ** $p \leq 0.01$ vs placebo.

improvements from baseline than placebo recipients in SF-36 bodily pain scores (14.6 vs –0.04 points; total score ranges from 0 to 100, with an increase in score indicating improvement) and in a patient global assessment of the effect of gout (–9.3 vs 3.4 points; assessed using a VAS from 0 to 100, where a decrease in score indicates improvement). Of note, the validation study indicated that SF-36 bodily pain, patient global VAS and VAS pain are valid outcome measures in patients with refractory chronic gout.[16]

Long-Term Treatment

Preliminary data are available for an open-label extension study of pegloticase (available as an abstract plus poster).[19] Of the 157 patients who completed one of the two randomized, double-blind, phase III trials, 151 patients (96%) enrolled in the extension study and chose to receive either active drug (pegloticase 8 mg every 2 weeks [n = 82] or pegloticase 8 mg every 4 weeks [n = 67]) or observation only (n = 2). The choice of treatment was made without knowledge of the randomized treatment group or response to treatment during the phase III trials.[19] Data for 140, 121 and 95 patients are available for ≥6, ≥12 and ≥18 months of pegloticase treatment during the phase III plus extension studies, respectively.

In addition, data for up to 2.4 years (125 weeks) for some endpoints are available for a subgroup of 19 patients in the extension study who received pegloticase 8 mg every 2 weeks in the phase III trials and throughout the extension study, and who were responders in both the phase III and open-label studies (available as an abstract).[20] The rationale for this subgroup assessment was to understand the potential effects in patients who received the labelled dose of pegloticase 8 mg every 2 weeks, and in whom it would have been appropriate to continue treatment based on the label guidelines (see section 4), as uric acid levels were maintained at <6 mg/dL.[20]

- Patients with a sustained uric acid response during the phase III trials continued to experience normalization of plasma uric acid levels with pegloticase 8 mg every 2 or 4 weeks during the 6-month extension trial.[19] Of the 59 patients in the extension trial who had consistent plasma uric acid levels of <6 mg/dL in the phase III trials, 50 patients had sustained uric acid normalization during a minimum of 18 months of continued pegloticase treatment.[19]
- Continued treatment with pegloticase 8 mg every 2 or 4 weeks resulted in the resolution of tophi.[19] In addition to the 32 patients who had complete tophus resolution (defined as a complete resolution of one or more tophi with no new or progressive tophi) in the phase III trials, 20 pa-

tients (including 12 who had received pegloticase in both the phase III and extension studies) had their first complete tophus resolution during the extension study. Progression of tophi occurred in three patients without a sustained plasma uric response.[19]

- Sustained or further improvements in other chronic gout-related outcomes were associated with long-term treatment with pegloticase 8 mg every 2 or 4 weeks.[19] The progressive decrease in the frequency of gout flares that was seen after the initial 3 months of pegloticase treatment in the phase III trials continued during the extension study. The reduction from baseline in the number of tender joints and improvements in patient-reported HR-QOL assessments (i.e. HAQ disability index, SF-36 physical component summary and HAQ pain scores) that were shown in the phase III trials were sustained or improved further in the extension study.[19]
- Prolonged treatment with pegloticase 8 mg every 2 weeks also maintained its efficacy in the subgroup of responders to pegloticase 8 mg every 2 weeks.[20] Uric acid levels continued to be normalized for >2 years in 84% of patients. Relative to baseline (i.e. the beginning of the randomized trials), there were significant ($p < 0.05$) decreases in the mean number of weekly gout flares per patient, as well as in the mean number of tender and swollen joints throughout the extension study. At week 50 of continued treatment, 78% of individual tophi had completely resolved ($p < 0.006$), with similar results shown at weeks 78 and 102. The clinically relevant improvements in HR-QOL measures that were shown during the phase III trials also persisted or improved further.[20]

3. Tolerability and Safety

This section reviews the tolerability profile of intravenous pegloticase in patients with refractory chronic gout, focusing on descriptive pooled data from the phase III[10] and open-label extension[19] trials discussed in section 2. The report of the phase III trials included a *post hoc* adjudicated review assessing deaths, the Anti-Platelet Trialists' Collaboration (APTC) composite endpoint[21] and non-APTC serious cardiovascular events. Additional pooled data from these trials were derived from the manufacturer's prescribing information[7] and a *post hoc* analysis (available as an abstract).[22]

Randomized, Double-Blind, Phase III Trials

- Treatment-emergent adverse events were reported in almost all patients in the pooled phase III trials (94%, 100% and 95% of patients in the pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks and placebo groups, respectively).[10] The corresponding proportions of patients with serious treatment-emergent adverse events was 24%, 23% and 12%, and that discontinued the trial because of adverse events was 18%, 19% and 2%. In the pegloticase groups, the most common reason for treatment discontinuation was infusion-related reaction (10% and 13% of patients in the pegloticase 8 mg every 2 or 4 weeks groups, respectively).[10]
- Gout flare was the most common adverse event in all treatment groups, occurring in 76%, 85% and 81% of patients in the pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks and placebo groups, respectively, during the 6-month trials.[10] See section 2 for a more detailed discussion of the incidence of gout flares.
- Infusion-related reactions were the second most common adverse event associated with pegloticase treatment, in spite of all patients receiving pretreatment with antihistamines, corticosteroids and paracetamol (acetaminophen) to prevent such reactions.[7,10] The release of various mediators, such as cytokines, is thought to be involved in the development of infusion reactions.[7] The manufacturer's prescribing information[7] contains a boxed warning concerning the risk of anaphylaxis and infusion reactions, and recommendations for prophylactic treatment, monitoring and adjustments or discontinuation of pegloticase infusion if such reactions occur (see section 4).
- In the pooled phase III trials, infusion reactions were reported in 26% of pegloticase 8 mg every 2 weeks recipients compared with 5% of placebo recipients (figure 3); 41% of patients receiving pegloticase 8 mg every 4 weeks experienced infusion reactions.[10] The reported frequency of

these reactions may be underestimated, as the pre-treatment regimen may have blunted or obscured their signs and symptoms.[7] Infusion reactions most commonly manifested as urticaria (frequency of 10.6%), chest discomfort (9.5%), chest pain (9.5%), erythema (9.5%), pruritus (9.5%) and dyspnoea (7.1%), occurred at any time during the course of treatment (≈3% occurred with the first infusion) and the majority (91%) occurred during the time of infusion.[7] Slowing the rate of infusion, or stopping the infusion and restarting it at a slower rate reduced the manifestation of some infusion reactions. Infusion reactions were considered serious in 5% and 8% of patients receiving pegloticase 8 mg every 2 or 4 weeks, respectively.[10]

- Importantly, the risk of infusion reactions was higher in patients who had lost therapeutic response (i.e. those whose uric acid levels increased to >6 mg/dL, particularly when two consecutive levels were greater than this threshold).[7] Serum uric acid levels should be monitored prior to infusions, and consideration given to discontinuing treatment if levels are >6 mg/dL (see section 4).[7]
- The development of anti-pegloticase antibodies was associated with infusion reactions.[10] In the pooled phase III trials,[10] anti-pegloticase antibodies were detected in 134 (89%) of 150 evaluable patients receiving pegloticase every 2 or 4 weeks. The incidence of infusion reactions was significantly higher in 52 patients with high anti-pegloticase antibody titres (>1 : 2430) at any time during the study than in 84 patients who never had a high anti-pegloticase antibody titre (60% vs 19%; $p < 0.001$).
- Although antibody titres at the time of occurrence of the first infusion reaction were not reliable in predicting infusion reactions, a *post hoc* analysis indicated that a loss of plasma-urate lowering efficacy generally preceded the first infusion reaction. In patients with an infusion reaction, plasma uric acid levels were >6.0 mg/dL prior to the first infusion reaction in 20 of 22 patients (91%) receiving pegloticase 8 mg every 2 weeks, and 24 of 34 patients (71%) receiving pegloticase 8 mg every 4 weeks.[10]
- An infusion reaction that met the FDA criteria for anaphylaxis was retrospectively identified in 14 (5.1%) of 273 patients in the clinical trial programme of pegloticase.[7] The proportion of patients with anaphylaxis was 6.5%, 4.8% and 0% in the pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks and placebo groups, respectively, with anaphylaxis generally occurring within 2 hours after pegloticase infusion. In the phase III trials, anaphylaxis was reported in 5% of pegloticase 8 mg every 2 weeks recipients (figure 3).[7] The FDA clinical criteria for diagnosing anaphylaxis were skin or mucosal tissue involvement, plus either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to pegloticase or placebo infusion with no other identifiable cause (based on generally accepted anaphylaxis diagnostic criteria[23]).
- In patients receiving the clinically relevant dosage of pegloticase 8 mg every 2 weeks,[7] other treatment-emergent adverse events that were reported in ≥5% of patients were nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain and vomiting (figure 3).[7] Most

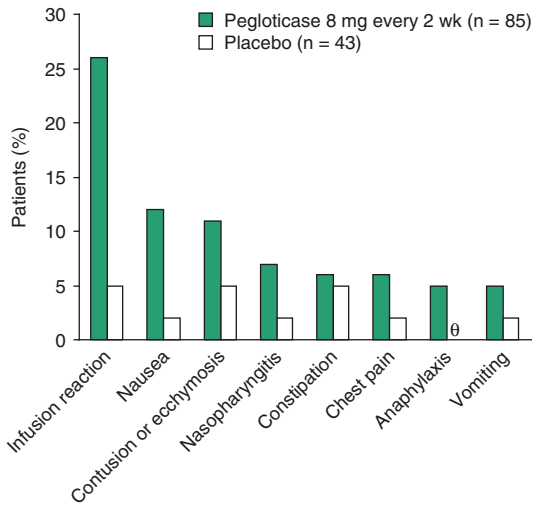

Fig. 3. Tolerability of intravenous pegloticase 8 mg every 2 wk in adults with chronic gout refractory to conventional treatment. Descriptive incidence of pooled treatment-emergent adverse events (with the exception of gout flares) that occurred in ≥5% of patients receiving pegloticase 8 mg every 2 wk or placebo in two replicate, randomized, double-blind, placebo-controlled, multicentre, 6 mo, phase III trials (as reported in the manufacturer's prescribing information).[7] Infusion reactions included any adverse events that occurred during or within 2 h of infusion. θ indicates zero.

occurrences of contusion or ecchymosis did not occur on the day of infusion and may be related to other factors such as the use of concomitant medications associated with these adverse events or insulin-dependent diabetes mellitus.[7]

Long-Term Treatment

- The tolerability and safety profiles of long-term treatment with pegloticase in the open-label extension study[19] were similar to those in the phase III trials.[10] At least one treatment-emergent adverse event was reported in 105 (95%) of the 110 patients in the safety population of the extension study.[19] Serious treatment-emergent adverse events (excluding serious infusion reactions) were reported in 22 (20%) patients. None of the three deaths that were reported during the extension trial were considered to be related to pegloticase treatment.[19]
- The most common treatment-emergent adverse events reported during the extension study were gout flare and infusion reactions; at least one gout flare or infusion reaction was experienced by 68% and 27% of recipients of pegloticase 8 mg every 2 or 4 weeks, respectively.[19] Serious infusion reactions were reported in three (2.7%) patients, and infusion reactions led to discontinuation of therapy in seven (6.7%) patients.[19]
- In patients who received pegloticase 8 mg every 2 weeks in the phase III trials and either pegloticase 8 mg every 2 or 4 weeks in the extension study (n = 57), other treatment-emergent adverse events that occurred in ≥5% of patients during the extension study included arthralgia (17.5% of patients), peripheral oedema (14.0% of patients), diarrhoea (12.3%), upper respiratory tract infection (10.5%), back pain (10.5%), sinusitis (10.5%), cough (10.5%), urinary tract infection (8.8%), fatigue (8.8%), headache (8.8%), chest pain (7.0%), rash (7.0%), skin ulcer (7.0%), pruritus (5.3%) and contusion (5.3%).[19]
- There was no evidence of cumulative immunogenicity or toxicological risk related to exposure to pegloticase in the extension study.[19] Of the 18% of patients entering the extension trial who had not developed anti-pegloticase antibodies during the phase III trials, only 20% developed antibodies during the extension study. No evidence of organ toxicity was shown in a comprehensive assessment of chemistry and haematological parameters.[19]

Cardiovascular Adverse Events

- In the review of deaths and cardiovascular events that occurred during and outside the treatment period in the phase III trials, seven deaths (four in the pegloticase groups and three in the placebo group) were reported. Two of these deaths in the pegloticase groups were attributed to APTC cardiovascular adverse events (one patient each with cardiac arrest and arrhythmia during treatment with pegloticase 8 mg every 2 weeks).[10] In addition to these two fatal APTC cardiovascular adverse events, one patient receiving pegloticase 8 mg every 4 weeks had a non-fatal APTC cardiovascular event (myocardial infarction). All three of these patients had four or more cardiovascular risk factors at baseline.[10]
- Serious non-APTC cardiovascular events (including chronic heart failure, arrhythmia, deep vein thrombosis, transient ischaemic attack, unstable angina and coronary revascularization) were reported in two (2.3%), six (7.1%) and no (0%) patients in the pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks and placebo groups, respectively, in the phase III trials.[10] All patients with these events had a prior history of cardiovascular disease; events were not clustered by event category or duration of pegloticase treatment.[10]
- Although the use of pegloticase in patients with congestive heart failure has not been formally studied, an exacerbation of their pre-existing congestive heart failure was reported in some pegloticase 8 mg every 2 weeks recipients in the clinical trial programme (two patients in the phase III trials and four patients in the extension study).[7] In the phase III trials, exacerbation of pre-existing congestive heart failure was not reported in any patients in the placebo group.[7]
- Pegloticase was not associated with prolongation of the QT interval.[22] In a *post hoc* investigation of pooled data from the phase III trials, the change from baseline in rate corrected

QT intervals was not significant in patients in the pegloticase 8 mg every 2 or 4 weeks groups.[22]

4. Dosage and Administration

In the US,[7] intravenous pegloticase 8 mg every 2 weeks is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy (i.e. chronic gout occurring in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dosage, or for whom these drugs are contraindicated). It should be infused over ≥2 hours.[7]

Dosage adjustments are not required in patients aged ≥65 years or in those with renal impairment (no overall differences in efficacy in these patient populations were observed in the controlled studies).[7] The only contraindication to the use of pegloticase is in patients with glucose-6-phosphate dehydrogenase deficiency; such patients are at risk of haemolysis and methaemoglobinaemia due to the production of hydrogen peroxide during the uricase catalysed conversion of urate to allantoin.[7]

As pegloticase is associated with a risk of anaphylaxis and infusion reactions during or after administration (boxed warning),[7] precautions should be taken to minimize the risk of these reactions, and to manage any reactions that may occur. Patients should receive antihistamines and corticosteroids prior to pegloticase infusion, pegloticase should be administered in a healthcare setting by providers prepared to manage anaphylaxis and infusion reactions, and patients should be monitored for an appropriate period of time (≈1 hour) after completion of the infusion. If an infusion reaction occurs during the administration of pegloticase, the rate of infusion should be slowed, or the infusion stopped and restarted at a slower rate.[7] As patients whose uric acid levels increase to >6 mg/dL (particularly if they have two consecutive increases to >6 mg/dL) have a higher risk of infusion reactions and anaphylaxis, serum uric acid levels should be monitored prior to infusions, and consideration should be given to discontinuing treatment if levels are >6 mg/dL.[7]

To reduce the likelihood of gout flares, which are frequently observed upon initiation of antihyperuricaemic therapy, patients should receive treatment with NSAIDs or colchicine starting at least 1 week before initiation of pegloticase therapy, and continuing for at least 6 months.[7] If a gout flare occurs during pegloticase therapy, the flare should be treatment appropriately, and pegloticase treatment does not need to be discontinued.

Caution and close monitoring is advised when pegloticase is administered to patients with preexisting congestive heart failure, as exacerbation of this condition has been experienced by some patients.

Local prescribing information should be consulted for further details on the use of pegloticase.

5. Pegloticase: Current Status

Intravenous pegloticase 8 mg every 2 weeks is approved for the treatment of chronic gout in adult patients refractory to conventional therapy in the US. It catalyses the oxidation of uric acid to allantoin, thereby lowering uric acid levels via a completely different mechanism of action than previously available urate-lowering or uricosuric agents.

In two randomized, placebo-controlled, double-blind, 6-month trials, pegloticase 8 mg every 2 weeks provided sustained reductions in plasma uric acid levels to <6 mg/dL in a substantial proportion of patients with chronic gout who were refractory to, or intolerant of, conventional urate-lowering therapy. Pegloticase 8 mg every 2 weeks was also associated with disease-modifying benefits, as shown by significant improvements from baseline in tophi resolution, the frequency of gout flares and number of tender joints relative to placebo. Improvements from baseline in HR-QOL parameters related to disability, pain and physical function were significantly greater with pegloticase 8 mg every 2 week than with placebo, and were clinically relevant. Although pegloticase 8 mg every 4 weeks was also significantly more effective than placebo with regard to most of these endpoints, it was not significantly more effective than placebo with regard to the major

secondary endpoint of tophi resolution, and was associated with numerically lower and less consistent effects on the primary endpoint of plasma uric acid levels than pegloticase 8 mg every 2 weeks. Preliminary data from an open-label extension of the phase III trials indicate that long-term treatment with pegloticase 8 mg every 2 or 4 weeks may maintain the urate-lowering normalization in patients who experienced a sustained uric acid response during the phase III trials.

With the exception of an expected increase in gout flares following the initiation of treatment with pegloticase, resolvable infusion reactions, including some cases of anaphylaxis, were the most common adverse events. The incidence of infusion reactions was numerically higher in patients receiving pegloticase 8 mg every 4 weeks than in those receiving pegloticase 8 mg every 2 weeks. As the risk of infusion reactions and anaphylaxis is greater in patients whose uric acid levels increase to >6 mg/dL (particularly if they have two consecutive increases to >6 mg/dL), serum uric acid levels should be monitored prior to infusions, and discontinuation of treatment should be considered if levels are >6 mg/dL. Exacerbation of pre-existing congestive heart failure has been experienced by some patients receiving pegloticase; caution and close monitoring is, therefore, advised in patients with congestive heart failure.

Acknowledgements and Disclosures

The manuscript was reviewed by: ***H.S.B. Baraf***, Center for Rheumatology and Bone Research, Arthritis and Rheumatism Associates, Wheaton (MD), USA; ***S. Chohan***, University of Chicago Medical Center, Chicago (IL), USA; ***J.G. Gums***, Department of Pharmacotherapy and Translational Research, University of Florida, Gainsville (FL), USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit.

References

1. Richette P, Bardin T. Gout. Lancet 2010 Jan 23; 375 (9711): 318-28
2. Schlesinger N. Difficult-to-treat gouty arthritis: a disease warranting better management. Drugs 2011; 71 (11): 1413-9
3. Sherman MR, Saifer MG, Perez-Ruiz F. PEG-uricase in the management of treatment-resistant gout and hyperuricemia. Adv Drug Deliv Rev 2008 Jan 3; 60 (1): 59-68
4. Fels E, Sundy JS. Refractory gout: what is it and what to do about it? Curr Opin Rheumatol 2008; 20 (2): 198-202
5. Edwards NL. Treatment-failure gout: a moving target. Arthritis Rheum 2008 Sep; 58 (9): 2587-90
6. Li-Yu J, Clayburne G, Sieck M, et al. Treatment of chronic gout: can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 2001; 28: 577-80
7. KRYSTEXXA™ (pegloticase) injection for intravenous injection: US prescribing information. East Brunswick (NJ): Savient Pharmaceuticals, Inc., 2010 Sep
8. Sundy JS, Ganson NJ, Kelly SJ, et al. Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. Arthritis Rheum 2007 Mar; 56 (3): 1021-8
9. Sundy JS, Becker MA, Baraf HS, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. Arthritis Rheum 2008 Sep; 58 (9): 2882-91
10. Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011 Aug 17; 306 (7): 711-20
11. Application number 1252930: clinical pharmacology and biopharmaceutics review(s). Silver Spring (MD): FDA Center for Drug Evaluation and Research, 2009 Feb 5
12. Kelly SJ, Delnomdedieu M, Oliverio MI, et al. Diabetes insipidus in uricase-deficient mice: a model for evaluating therapy with poly(ethylene glycol)-modified uricase. J Am Soc Nephrol 2001 May; 12 (5): 1001-9
13. Baraf HS, Matsumoto AK, Maroli AN, et al. Resolution of gouty tophi after twelve weeks of pegloticase treatment. Arthritis Rheum 2008 Nov; 58 (11): 3632-4
14. Armstrong JK, Hempel G, Koling S, et al. Antibody against poly(ethylene glycol) adversely affects PEG-asparaginase therapy in acute lymphoblastic leukemia patients. Cancer 2007 Jul 1; 110 (1): 103-11
15. Elitek® (rasburicase) powder for solution, for intravenous infusion: US prescribing information. Bridgewater (NJ): sanofi-aventis U.S. LLC, 2010 Feb
16. Singh JA, Yang S, Strand V, et al. Validation of pain and patient global scales in chronic gout: data from two randomised controlled trials. Ann Rheum Dis 2011 Jul; 70 (7): 1277-81
17. Lubeck D. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics 2004; 22 Suppl. 1: 27-38
18. Wells G, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993; 20 (3): 557-60
19. Sundy JS, Baraf HSB, Gutierrez-Urena SR, et al. Chronic use of pegloticase: safety and efficacy update [abstract no. 1113]. Arthritis Rheum 2009 Oct; 60 (10 Suppl.). Plus poster presented at the American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting; 2009 Oct 16-21; Philadelphia (PA)
20. Hamburger SA, Lipsky P, Khanna D, et al. Safety and efficacy of long-term pegloticase (KRYSTEXXA™)

treatment in adult patients with chronic gout refractory to conventional therapy [abstract no. OP0113]. 12th Annual Congress of the European League Against Rheumatism; 2011 May 25-28; London

21. Antiplatelet Trialists' Collaboration. Collaboration overview of randomized trials of antiplatelet therapy. BMJ 1994; 308 (6921): 81-106
22. Somberg JC, Cvetanovic I, Rosario-Jansen T, et al. Peglotocase does not cause QT interval prolongation [abstract no. 94]. J Investig Med 2011 Apr; 59 (4): 720
23. Sampson HA, Munoz-Furlong A, Campbell RI, et al. Second symposium on the definition and management of anaphylaxis. Ann Emerg Med 2006; 47 (6): 373-80

Correspondence: *Katherine A. Lyseng-Williamson*, Adis, a Wolters Kluwer Business, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz