**PUBLIC SUMMARY DOCUMENT**
**Product:** IDURSULFASE-rhu, concentrate for intravenous solution for infusion, 6 mg/3 mL, Elaprase®
**Sponsor:** Genzyme Australasia Pty Ltd
**Date of PBAC Consideration:** November 2007

## 1. Purpose of Application

The submission sought listing on the PBS as an Authority required (Highly Specialised Drug) Section 100 listing for the treatment of Hunter syndrome (MPS II). The submission was also prepared to have the drug considered for the Life Saving Drugs Program (LSDP).

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

## 2. Background

This drug had not previously been considered by the PBAC.

## 3. Registration Status:

Idursulfase (Elaprase) has received approval for registration for the long term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

## 4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug)
Private hospital authority required
Treatment of patients with Hunter syndrome (MPS II) where the diagnosis has been confirmed by documented deficiency of iduronate sulphatase enzyme activity, where a patient will benefit from treatment by improvements in various symptoms and reduction in complications.

The prescription should allow for sufficient vials for the patients to obtain 0.5 mg/kg (i.e. one treatment). Up to three repeats may be authorised per authority.

*See Recommendation and Reasons for PBAC's view*.

## 5. Clinical Place for the Proposed Therapy

Idursulfase provides an exogenous enzyme for uptake into cellular lysosomes. Treatment with idursulfase may be effective in reducing tissue GAG stores in patients with Hunter syndrome.

## 6. Comparator

The submission nominated placebo as the comparator. The PBAC considered this appropriate.

## 7. Clinical Trials

The submission presented the results of a pivotal single randomised trial comparing idursulfase 0.5 mg/kg weekly infusions, with idursulfase 0.5 mg/kg every other week (EOW) infusions and placebo in patients with MPS II over 53 weeks (Muenzer et al. 2006, TKT024). Idursulfase 0.5mg/kg weekly is the recommended dosing regimen in the

Australian Product Information and is the regimen for which PBS listing is sought. Therefore, the 0.5mg/kg EOW dose regimen is not considered further.

The study has been published as follows:

| Trial/First author | Protocol title | Publication citation |
|---|---|---|
| Muenzer J, Wraith JE, Beck M et al. (Published paper of trial TKT024) | A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome).<br>* Erratum for this publication: Muenzer J (2006) Erratum: A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome) Genetics in Medicine 8:599. | Genetics in Medicine (2006) 8(8):465-473. [comment: vol 8 August] |

## 8. Results of Trials

The results of the key trial are summarised in the table below.

**Summary of results for the primary outcomes in the key trial: *weekly dosing versus placebo***

| Outcome | Idursulfase 0.5 mg/kg Weekly N=32 | | | Placebo N=32 | | | Mean Difference (SE) 95% CI p-value |
|---|---|---|---|---|---|---|---|
| | Baseline (SE) (SD) | Week 53 (SE) (SD) | Adj[a] Change (SE) | Baseline (SE) (SD) | Week 53 (SE) (SD) | Adj[a] Change (SE) | |
| Two-component composite score (**ranked**)[b] | 65.22 (SE 5.67) | 73.72 (5.52) (31.21) | 69.81 (7.03) | 64.78 (SE 4.55) | 56.28 (4.14) (23.45) | 50.86 (8.07) | **18.96** (6.47) **5.99, 31.93** p = 0.0049 |
| Absolute volume FVC (L), mean | 1.19 (0.10) (0.57) | 1.41 (0.14) (0.78) | 0.18 (0.04) | 1.09 (0.09) (0.52) | 1.15 (0.09) (0.50) | -0.01 (0.04) | **0.19** (0.06) **0.08, 0.30** p = 0.0011 |
| % predicted FVC, mean | 55.30 (2.80) (15.85) | 58.74 (3.42) (19.34) | 1.29 (1.73) | 55.57 (2.18) (12.35) | 56.32 (2.78) (15.70) | -2.99 (1.85) | 4.28 (2.27) -0.27, 8.83 p = 0.0650 |
| 6MWT (m), mean | 391.63 (19.10) (108.04) | 435.91 (24.32) (137.59) | 36.95 (10.89) | 392.47 (18.72) (105.87) | 399.75 (18.72) (105.90) | 1.86 (11.84) | **35.09** (13.69) **7.66, 62.52** p = 0.0131 |

Bolded typography indicates statistically significant differences between treatment groups.
Abbreviations: FVC = forced vital capacity, 6MWT = six-minute walk test, SE = standard error, SD = standard deviation, BL = baseline, wk = week, CI = confidence interval, m = meters, L = liters
[a] Adjusted change = Adjusted least squares means and standards errors from the fitted ANCOVA model with corresponding 95% confidence intervals of the treatment difference.
[b] Two-component composite score consists of the sum of the ranked changes from baseline to week 53 for % predicted FVC and 6MWT (distance in meters)

The primary outcome for the pivotal trial TKT024 was a single two-component composite score, combining the ranked changes from baseline to week 53 for percentage predicted forced vital capacity (FVC) measuring respiratory function, and the six-minute walk test (6MWT) measuring physical functional capacity.

Treatment with idursulfase 0.5mg/kg weekly compared to placebo was associated with a statistically significant mean increase from baseline to Week 53 in the primary outcome of the two-component composite score in the intent-to-treat population. Reductions in the

secondary outcomes including the six-minute walk test (6MWT), urinary GAG excretion, and mean liver and spleen sizes also showed statistical significance. The percentage predicted forced vital capacity (%FVC) favoured the idursulfase group, but did not reach statistical significance during the course of the clinical trial nor did the global range of movement score or the left ventricular mass index.

The submission claimed that the 4.28% increase in percent predicted FVC (95% CI -0.27, 8.83; p= 0.0650) and the 35.09 m improvement in the 6MWT (95% CI 7.66, 62.52; p=0.0131) from baseline to Week 53 in the idursulfase treatment group were clinically meaningful changes. These changes were based on the clinical trials of laronidase (Aldurazyme®) in MPS I patients.

The TKT024 clinical trial protocol used the percent predicted FVC as the most appropriate measure, as it adjusts for differences in patient height and age. The submission argued that absolute volume FVC, which reached statistical significance compared to placebo, rather than the percentage predicted FVC, which was not statistically significantly different from placebo, was the most appropriate analyses in terms of FVC.

Idursulfase had an acceptable safety profile in the pivotal study, with most adverse events being mild to moderate in severity, and resolving without sequelae. Only 2 patients experienced serious adverse events (cyanosis and pulmonary embolism) that were considered by the investigators to be possibly or probably related to idursulfase therapy. These two episodes resolved without sequelae and both patients tolerated their subsequent idursulfase infusions.

No patient withdrew from therapy due to treatment related problems. There was no evidence of organ damage due to drug toxicity. Considering the severity of the multi-system problems in patients at baseline, the symptoms reported by patients during the study were generally related to the underlying complications of the disease MPS II.

A Periodic Safety Update Report for idursulfase was presented in the submission for the period of 24 July 2006 to 23 July 2007. Generally, the adverse events presented in this report were consistent with the evidence presented in the pivotal trial TKT024. However, two cases of severe, life threatening late emergent anaphylactic reactions (almost 24 hours following initial infusion reactions to idursulfase) were reported. A proposed amendment to the Company Core Safety Information was presented to incorporate these unexpected reactions. The TGA evaluation report also recommended ongoing, longer-term studies of idursulfase to evaluate efficiency and safety in the longer-term.

*For PBAC's comments on these results, see Recommendation and Reasons.*

## 9. Clinical Claim

The submission claimed that idursulfase is therapeutically superior to placebo and is associated with equivalent toxicity based on the clinical evidence presented.

*For the PBAC's view of this claim, see Recommendation and Reasons.*

## 10. Economic Analysis

A trial-based economic evaluation was presented. The choice of a cost- effectiveness approach was considered valid. The cost-effectiveness analysis was based on two outcomes of absolute volume forced vital capacity (FVC) and the six-minute walk test (6MWT) for idursulfase weekly versus placebo. The resources included were drug costs and infusion costs only.

The submission reported an incremental cost per additional metre walked in a 6MWT, in the range of $15,000 - $45,000. There were doubts over whether this was a meaningful incremental cost-effectiveness ratio (ICER). Expressing the ICER as an incremental cost/day was potentially more informative. Further, the 6MWT was a surrogate measure and it was not clear that expressing the ICER in terms of incremental cost per additional metre walked translated to improved quality of life or to longer term measures of decreased morbidity and increased survival.

*For the PBAC's view of the economic analysis, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The submission estimated that the listing of idursulfase would result in a net cost to the government of less than $10 million in years 1-3 and between $10 - $30 million in Year 4 of listing.

## 12. Recommendation and Reasons

The PBAC noted that there are two forms of mucopolysaccharidosis type II (MPS II, Hunter syndrome): a severe form (type A) and a milder form (type B). The key pivotal clinical trial, (TKT024), excluded patients with severe CNS involvement (which is more likely to occur in type A). The PBAC concluded that it would advise the Government to consider limiting treatment under the LSDP to patients without severe CNS involvement. The PBAC agreed that in the pivotal trial, TKT024, weekly dosing of idursulfase (plus standard medical management), appears to have significant and clinically important advantages in effectiveness over placebo plus standard medical management for the primary outcome comprising the ranked changes from baseline to week 53 for percentage predicted forced vital capacity (FVC) and 6MWT. Although the percentage predicted forced vital capacity (%FVC) favoured the idursulfase group, it did not reach statistical significance. However, the PBAC noted that in its earlier consideration of laronidase for mucopolysaccharidosis type I (MPS I), it had accepted that it was appropriate to consider improvement in percentage FVC based on the patient's height at baseline (i.e. the absolute percentage FVC result) and that when this comparison is done for idursulfase, the results are statistically significant and of likely clinical relevance.

The PBAC further accepted that the longer term effectiveness and toxicity of idursulfase and the impact of treatment on disease progression and mortality rates are unknown. However the Committee considered it sufficiently likely that treatment with idursulfase would be associated with improved survival in MPS II.

The Committee noted that, at the price requested, the annual cost per patient treated with idursulfase was higher than that for patients treated with laronidase for MPS I. After it considered the evidence presented in the submission and the expert advice provided at the hearing that MPS I and MPS II are clinically very similar, the PBAC recommended that the price of idursulfase for MPS II be comparable to the price of laronidase for MPS I..

The Committee agreed that it was appropriate for the submission not to present a modelled economic evaluation but considered that the results of the preliminary economic evaluation indicated that treatment with idursulfase was associated with an unacceptably high incremental cost effectiveness ratio. This conclusion remains valid even if the price of idursulfase is reduced in line with that of laronidase.

The PBAC therefore rejected the application to list idursulfase on the PBS on the basis of unacceptably high cost-effectiveness. However the Committee indicated that the use of idursulfase for the treatment of MPS II meets the criteria for the Life Saving Drugs Program (LSDP). Given that idursulfase produced a clinical benefit in terms of the 6 MWT and absolute FVC values and that it was plausible that the treatment will be associated with a survival benefit, several of the LSDP criterion were considered to have been met. The PBAC therefore recommended that Government considers including idursulfase on the LSDP.

**13. Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**14. Sponsor's Comment:** Genzyme Australasia is looking forward to working with the Life Savings Drug Program to ensure Elaprase (idursulfase) becomes available through government funding to improve the quality of life and survival benefit of Hunter syndrome patients.