PUBLIC SUMMARY DOCUMENT
Product: Miglustat, capsule 100 mg, Zavesca®
Sponsor: Actelion Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought an Authority required listing for patients who qualify for treatment for Type 1 Gaucher disease with Enzyme Replacement Therapy (ERT) under the Life Saving Drugs Program (LSDP) who cannot be or have not been treated successfully with ERT according to the treatment physician.

2. Background

This was the first time miglustat capsules had been considered by the PBAC.

3. Registration Status

Miglustat was registered by the TGA on 23 October 2007 for the oral treatment of patients with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

4. Listing Requested and PBAC's View

Authority required

Patients who qualify for treatment with Enzyme Replacement Therapy (ERT) under the Life Saving Drugs Program (LSDP) who cannot be or have not been treated successfully with ERT according to the treating physician.

For the PBAC's view of the restriction, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

The submission intended that miglustat be used in patients with moderate GD1 (Type 1 Gaucher's disease). Miglustat will provide a treatment option for patients who are unable to be treated with enzyme replacement therapy (ERT) due to unacceptable toxicity, and will be a second-line therapy in patients with manifestations of GD that are refractory to ERT.

6. Comparator

The submission nominated two comparators: imiglucerase and standard therapy. Standard therapy is the appropriate comparator in patients who cannot take ERT at any dose or rate of administration (e.g. due to poor venous access, severe needle phobia or hypersensitivity). In patients who have not been successfully treated with ERT, the appropriate comparator would be ERT assuming that without the availability of miglustat patients would continue to take ERT as they have demonstrated a response in some aspects of their disease (organ volume or haematological parameters), but have persistent bone disease.

The PBAC noted that there was no evidence comparing the benefit of miglustat versus ongoing ERT in patients not responsive to ERT. Thus, the group who 'have not been successfully treated with ERT' should not be included in the listing and ERT should not be a comparator in this submission.

The PBAC agreed that standard therapy is the appropriate comparator for miglustat in patients with Type 1 Gaucher Disease who cannot be or have not been successfully treated

with ERT. It is not a replacement for ERT and therefore imiglucerase is not an appropriate comparator.

7. Clinical Trials

The submission presented:

- two non-randomised trials examining the efficacy and safety of miglustat in patients with GD1 who are unable or unwilling to be treated with ERT (OGT 918-001 and OGT 918-005, hereafter referred to as trials 001 and 005).
- one supporting non-randomised study of the efficacy of miglustat in patients who are treatment-naïve and patients previously treated with ERT (Giraldo et al, 2006).
- one supporting open-label randomised study comparing miglustat monotherapy, ERT monotherapy, and ERT and miglustat combination therapy in patients with GD who have been on ERT for at least 2 years, and at a stable ERT dose for at least 6 months (OGT 918-004, hereafter referred to as trial 004).
- a published pooled analysis of the bone effects of miglustat treatment (combining results from studies 001, 004 and 005).

Trials and associated reports presented in the submission

Trial ID	Protocol/internal study report title	Publication citation
Non-randomised, non-comparative open-label trials and extension periods		
OGT 918-001	A phase I/II study of open-label OGT 918 in adult patients with Gaucher Disease (2001).	Cox et al. Novel oral treatment of Gaucher's disease with *N*-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. *Lancet* 2000; 355: 1481-85.
OGT 918-001X (24 month)	A phase I/II study of open-label OGT 918 in adult patients with Gaucher Disease (extended treatment period) (2001).	
OGT 918-001X (36 month)		Elstein et al. Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT-918) in type I Gaucher disease. *J. Inherit. Metab Dis* 2004; 27: 757-766.
OGT 918-005	A Phase II monotherapy study of open-label OGT 918 in adult patients with Gaucher Disease (2004).	Pastores GM et al. An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment. *Clin Ther.* 2005;27:1215-1227.
Giraldo et al (2006).		Giraldo et al. Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica* 2006;91:703-706.
Randomised, open-label, parallel group trial		
OGT 918-004	A phase II, randomised study of open-label OGT 918 and Cerezyme given as monotherapy or combination therapy in adult patients with type 1 Gaucher disease (2001).	Elstein et al. Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood* 2007;110:2296-2301.

OGT 918-004 X (+6 month)*	A Phase II randomised study of open-label OGT 918 and Cerezyme given as monotherapy or combination therapy in adult patients with type 1 Gaucher disease (extended treatment period) (2001).	
OGT 918-004X (+12 month)*	A Phase II randomised study of open-label OGT 918 and Cerezyme given as monotherapy or combination therapy in adult patients with type 1 Gaucher disease (final analysis) (2004).	
OGT 918-004 (patient level analysis)	Clinical Study OGT 918-004 individual patient-level analysis if outcomes of miglustat monotherapy (2005).	
Pooled analysis of bone effects		
OGT 918-001,-004, -005.		Pastores GM et al. Effect of miglustat on bone disease in adults with Type 1 Gaucher disease: A pooled analysis of three multinational, open-label studies. *Clin Ther*. 2007;29:1645-1654

*Extension periods of OGT-004 were non-comparative. All patients chose to have miglustat monotherapy.

8. Results of Trials

A clinically significant response is a ≥10% reduction in organ volume. Therefore, the mean change in the primary outcome (liver volume) was only clinically significant at 12 and 24 months in trial 001, and was not clinically significant at any time point in trial 005.

The results are summarised in the table below.

	6 months	12 months	24 months
Trial 001			**(Extension phase)**
N	22	21	12
Mean liver volume baseline (L)	2.4	2.4	2.5
% Change	-7.0	-12.1	-14.5
[95% CI]	[-10.5, -3.4]	[-16.4, -7.9]	[-19.3, -9.7]
N	19	18	10
Mean spleen volume baseline (L)	1.7	1.7	1.7
% Change	-15.1	-19.0	-26.4
[95% CI]	[-18.4, -11.8]	[-23.7, -14.25]	[-30.4, -22.4]
Trial 005			**(Extension phase)**
N	8	7	7
Mean liver volume baseline (L)	2.3	2.3	2.3
% Change	-8.4	-9.4	-5.6
[95% CI]	[-16.1, -0.7]	[-19.5, 0.6]	[-12.1,1.0]
N	8	7	7
Mean spleen volume baseline (L)	1.1	1.1	1.1
% Change	-19.0	-14.4	-15.4
[95% CI]	[-30.4, -7.6]	[-31.9, 3.1]	[-34.4,3.5]

The results for haematological parameters were presented in the submission but were not considered to be the best indicators of efficacy as splenectomised patients often have higher Hb and platelet counts than patients with an intact spleen.

Patient-relevant endpoints (e.g. reduction in symptoms, improved lifespan) were not collected as part of the outcome measures, although 'neuropsychological assessments' were included in some studies, but not reported in the submission. The submission did not adequately justify the clinical importance of study outcomes.

Effects on bone disease were provided in a published pooled analysis of three trials (001, 004 and 005), two of which are non-comparative. Fifty-seven percent of the 72 subjects had received previous ERT. During a 2-year period of miglustat therapy, bone pain was reported by fewer patients at 2 years than at baseline, with the results being similar in treatment-naïve patients and those who had previously had ERT. The PBAC noted the relevance of these data are very uncertain, given a dichotomous subjective variable (presence or absence of bone pain) has been measured in an open study design. It was not possible to draw specific conclusions about the impact of miglustat on bone disease in patients unable to have ERT.

The PBAC commented that the safety data were poorly presented in terms of a breakdown of specific adverse effects in each trial.

The trial data and the published reviews suggested that the majority of patients taking miglustat got diarrhoea. In the pooled clinical trial data, diarrhoea occurred in 88% of patients, and this declined to 30% by 24 months of follow-up. The submission did not indicate how many subjects withdrew from each trial because of diarrhoea or other adverse effects, although post-marketing data suggested that 23% of patients discontinued treatment, mainly due to GI symptoms and most within the first 6 months.

Long-term safety data were limited, because only 20 subjects were exposed to miglustat for more than 24 months in the trials. However, there is experience from post-marketing surveillance to suggest that neurological adverse effects were also common (23% overall; 17% tremor, 9% neuropathy, 12% memory problems, 13% cognitive abnormalities). These observations were difficult to interpret in the absence of a comparator group.

9. Clinical Claim

The submission claimed that miglustat is more effective than standard therapy. The submission claimed that miglustat is as effective as ERT in maintaining liver and spleen volumes in patients previously treated with ERT. The submission claimed that miglustat is effective in improving bone mineral density (BMD) and reducing bone pain in patients previously treated with ERT.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission did not present an economic evaluation. The sponsor stated that it was unlikely to meet conventional cost-effectiveness criteria even under the most optimistic of assumptions.

The Committee agreed that it was appropriate for the submission not to present a modelled economic evaluation and considered that the results of any economic evaluation would have indicated that treatment with miglustat is associated with an unacceptably high incremental cost effectiveness ratio.

11. Estimated PBS Usage and Financial Implications

The submission estimated the cost per year to the PBS to be less than $10 million in each of the first 5 years. The submission's estimate was considered uncertain due to uncertainty in the estimated number of patients.

The submission estimated financial savings per year to the government of less than $10 million in each year generated by a reduction of use of ERT in patients who are unsuccessfully treated with this drug. This estimate was based on the assumption that patients refractory to ERT would continue to be treated with ERT in the absence of miglustat.

12. Recommendation and Reasons

The PBAC agreed that standard therapy is the appropriate comparator for miglustat in patients with Type 1 Gaucher Disease who cannot be or have not been successfully treated with Enzyme Replacement Therapy (ERT). It is not a replacement for ERT and therefore imiglucerase is not an appropriate comparator. The PBAC also noted a recent article in *Blood*[1] stating that combining miglustat with ERT (imiglucerase), did not show additional benefit.

The PBAC was concerned about the wording used in the requested restriction. The requested listing is slightly different to the TGA registered indication, which is for oral treatment of patients with mild to moderate Type I Gaucher disease for whom ERT is not a therapeutic option. For patients in whom ERT is not a therapeutic option, miglustat would be used as a first line treatment. However, it may be less efficacious than ERT and therefore the restriction should be carefully worded to avoid miglustat being used as an alternative to ERT. This is of particular concern given miglustat is an oral agent, whereas imiglucerase is an IV infusion. Patients who "cannot" be successfully treated with ERT must be well defined by any guidance provided by the Gaucher Disease Advisory Committee (GDAC) and treatment with miglustat should be limited to those patients who have:

- poor venous access;
- severe needle phobia; or
- hypersensitivity.

The PBAC acknowledged that the clinical evidence provided was in adult patients over the age of 18, but did not believe it would be necessary to restrict the listing of miglustat to adult patients only.

The PBAC agreed that the poor quality of the evidence provided in support of the listing reflected the difficulty in gathering clinical trial evidence for a rare condition with a small

[1] Deborah Elstein, Altoon Dweck, Drorit Attias, Irith Hadas-Halpern, Shoshana Zevin, Gheona Altarescu, Johannes F. M. G. Aerts, Sonja van Weely, and Ari Zimran, *Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement* Blood, Oct 2007; 110: 2296 - 2301.

patient population. The Committee agreed that miglustat showed a significant and clinically meaningful improvement in liver volume over placebo in Trial 001, which was the larger of the two trials in the relevant patient population. There was also some (weak) evidence in support of improvement in bone pain.

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

The Committee agreed that it was appropriate for the submission not to present a modelled economic evaluation and considered that the results of any economic evaluation would have indicated that treatment with miglustat is associated with an unacceptably high incremental cost effectiveness ratio.

The PBAC therefore rejected the application to list miglustat on the PBS based on an unacceptably high cost-effectiveness ratio. However the Committee indicated that the use of miglustat for the treatment of Gaucher Disease where ERT cannot be used or has failed meets the criteria for the Life Saving Drugs Program (LSDP), given that it produced a clinical benefit in terms of the reduced liver volume (in Trial 001) and that it was plausible that the treatment will be associated with a survival benefit. Therefore, both criterion 2 and criterion 5 for the LSDP were considered to have been met. The PBAC therefore recommended that miglustat is suitable for the Government to consider for inclusion 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

The Sponsor welcomes the PBAC's decision to recommend miglustat for inclusion on the Life Saving Drugs Program (LSDP), with guidance on appropriate patient selection to be provided by the Gaucher Disease Advisory Committee (GDAC). The Sponsor agrees with the Committee's conclusion that miglustat treatment provided a significant and clinically meaningful improvement in liver volume *versus* placebo and the Committee's belief that it is "sufficiently likely that treatment with miglustat would be associated with improved survival in Gaucher Disease". Under these circumstances, the sponsor does not agree with the PBAC that treatment with miglustat in patients who "cannot" be treated successfully with ERT be limited only to patients with poor venous access, severe needle phobia, or hypersensitivity. The TGA approved miglustat "for the oral treatment of patients with mild to moderate Type 1 Gaucher Disease for whom ERT is not a therapeutic option" and the Sponsor believes that decisions as to what constitutes "cannot be treated" involve complex clinical judgements that should be left to the GDAC to define on a case-by-case basis. The Sponsor is prepared to work constructively with the GDAC to define appropriate treatment guidelines to reflect this indication.