PUBLIC SUMMARY DOCUMENT
Product: MIGLUSTAT, capsule, 100 mg, Zavesca®
Sponsor: Actelion Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission requested inclusion in the Life Savings Drugs Program (LSDP) for patients with Niemann-Pick Type C (NP-C) disease.

Through the LSDP, the Australian Government provides subsidised access, for eligible patients, to expensive and potentially life saving drugs for very rare life-threatening conditions. Before a drug is made available on the LSDP, it must generally be accepted by the Pharmaceutical Benefits Advisory Committee as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness.

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

Miglustat was TGA registered on 3 February 2010 for the treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick Type C disease.

4. Listing Requested and PBAC's View

Inclusion on the LSDP for treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick disease Type C.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Niemann-Pick Type C disease is a very rare inherited disorder that is progressive, debilitating, degenerative and ultimately fatal, affecting the liver, lungs, bone marrow and brain. The neurological manifestations are caused by the accumulation of lipids primarily in the brain.

Treatment for Niemann-Pick Type C disease is currently palliative only and depends on the needs of the individual, the symptoms and the clinical manifestations. It is proposed that miglustat will provide a pharmacologic intervention that may interrupt disease progression.

6. Comparator

The submission nominated standard medical management (standard care) comprising of palliative care as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented the following studies in support of the comparative effectiveness of miglustat in patients with NP-C:

- One open-label randomised trial comparing miglustat with standard care in combined adult and juvenile NP-C patients (referred to as the juvenile/adult patient population) over a 12 month period (Study 007a), with a 12 month single arm extension study (Study 007a (ext));
- One single arm study in paediatric NP-C patients over 12 month period (Study 007p), with a 12 month extension study (Study 007p (ext));
- Two surveys, one regarding NP-C patients receiving standard care (Stage II survey), and one concerning NP-C patients initially receiving standard care and subsequently treated with miglustat (Stage I survey).
- Two case-series and 19 case reports.

The trials published at the time of submission are shown in the table below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Study 007a Patterson MC et al 2007	Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study.	Lancet Neurology 2007; 6(9):765-772.
Studies presented in the submission		
Miglustat		
Study 007p		
Patterson MC et al 2007	Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study.	Lancet Neurology 2007; 6(9):765-772.
Study 007a (ext) Wraith JE et al 2009	Miglustat in adult and juvenile patients with Niemann-Pick disease type C: Long-term data from a clinical trial.	Molecular Genetics and Metabolism, epub 30 December 2009.
Study 007p (ext) Patterson MC et al 2010	Long-term miglustat therapy in children with Niemann-pick disease Type C.	Journal of Child Neurology 2010; 25:300-305.
Stage I survey Pineda M et al 2009	Miglustat in patients with Niemann-Pick disease Type C (NP-C): a multicenter observational retrospective cohort study.	Molecular Genetics and Metabolism 2009; 98:243-249.
Pineda M et al 2009	Clinical experience with miglustat therapy in pediatric patients with Niemann-Pick disease type C: a case series.	Molecular Genetics and Metabolism, 2010; 99(4):358-66
Fecarotta et al 2009	Efficacy of miglustat on the neurological involvement in Italian patients with Niemann-Pick disease type C.	Molecular Genetics and Metabolism 2009; 98:70 (Abstract).
Main comparator – standard care		
Stage II survey Wraith JE et al 2009	Natural history of Niemann-Pick disease type C in a multicentre observational retrospective cohort study.	Molecular Genetics and Metabolism 2009; 98:250-254.

8. Results of Trials

Study 007a and Study 007a (ext)

The results for the primary endpoint, horizontal saccade eye movement α (HSEM-α), are presented in the following table. HSEM-α is a metric, estimated as the slope of the linear regression line of peak duration (amplitude/peak velocity, ms) vs. amplitude (degree) of horizontal saccadic eye movement. The submission claimed that this endpoint reflects brainstem involvement in patients with NP-C.

Analysis of changes in HSEM-α from baseline in adults and juveniles in the randomised trial and its extension study

Study	Time point	Adjusted mean change from baseline (ms/deg)[a] (no of patients)		Estimated treatment difference (ms/deg)[a]	95% CI (ms/deg)[a]	p-value
Study 007a		**12-month miglustat (N=20)**	**12-month standard care (N=9)**			
	Month 12	-0.329 (n=17)	-0.055 (n=8)	-0.274	(-0.959, 0.411)	0.414
	Last value	-0.376 (n=18)	-0.050 (n=8)	-0.326	(-1.000, 0.458)	0.327
Study 007a (ext)		**24-month miglustat (N=17)**	**12-month standard care, followed by 12-month miglustat (N=8)**			
	Month 24	0.155 (n=15)	1.150 (n=4)	-0.994	(-2.796, 0.808)	0.258
	Last value	0.166 (n=15)	0.761 (n=6)	-0.594	(-2.078, 0.889)	0.410

CI = confidence interval
[a] ms/deg = amplitude/peak velocity (ms) per amplitude (degree)

The analysis of HSEM-α using an analysis of covariance (ANCOVA) model, which involved terms for baseline, age and treatment group, indicated that HSEM-α was improved in both of the treatment groups. Although the decrease in the miglustat group was greater than that in the standard care group (adjusted mean change = -0.329ms/deg vs. -0.055ms/deg), the difference did not approach statistical significance (p = 0.414). Results from the extension study showed that HSEM-α deteriorated after 24 months of miglustat treatment. Although the patients in the 24-month miglustat group had less worsening of HSEM-α than those who received miglustat treatment for 12 months (adjusted mean change = 0.155ms/deg vs. 1.150ms/deg), the difference was not statistically significant (p = 0.258).

Evaluation of the HSEM-α assessment results was difficult due to the small sample size in the study, the unmatched baseline patient characteristics between the two treatment groups, and the lack of patient and investigator blinding.

The SF-36 Quality of Life Questionnaire, in patients older than 13 years in Study 007a, did not indicate any statistically significant difference in changes from baseline to the last assessment of quality of life between the miglustat group and the standard care group. Additionally, the results of the quality of life assessment are prone to information and observer bias due to the lack of patient and investigator blinding.

Study 007p and Study 007p(ext)

The following table presents an analysis of changes in HSEM-α in the paediatric sub-study of Study 007 and its extension study (all patients received miglustat treatment).

Study	Time point	n	Baseline (ms/deg)[a] (SD)	Actual value (ms/deg)[a] (SD)	Change from baseline (ms/deg)[a] (SD)	95% CI (ms/deg)

Study 007p	Baseline	10		2.201 (1.217)		
	Month 12	9	2.181 (1.289)	1.692 (1.077)	-0.489 (0.139)	(-0.810, -0.167)
	Last value	10	2.201 (1.217)	1.736 (1.025)	-0.465 (0.127)	NR
Study 007p (ext)	Month 24	9	2.181 (1.289)	2.106 (1.213)	-0.075 (1.235)	(-1.024, 0.874)
	Last value	10	2.201 (1.217)	2.109 (1.144)	-0.093 (1.165)	(-0.926, 0.741)

CI = confidence interval; NR = not reported; SD = standard deviation
[a] ms/deg = amplitude/peak velocity (ms) per amplitude (degree)

A statistically significant improvement in HSEM-α from baseline to month 12 was reported in Study 007p, with a decrease of 0.489ms/deg (95% CI = (-0.810ms/deg, -0.167ms/deg)) in paediatric patients with NP-C. However, this beneficial effect of miglustat could not be demonstrated after 24 months' treatment.

In Study 007a, adverse events (AEs) considered to be treatment related were reported for all 20 patients in the miglustat treatment group. Three cases of severe diarrhoea and one case of severe weight loss were considered treatment-related. Two patients experienced an AE that led to withdrawal of miglustat. The most common individual AEs in the miglustat treatment group were diarrhoea (85%), flatulence (70%), weight decrease (65%) and abdominal pain (50%). Neurological system disorders, such as tremor and gait spasticity, were also common. In the paediatric sub-study, adverse events that were considered to be treatment related were reported in 8 of the 12 patients. One patient withdrew from the study due to lethargy, memory impairment and depression. The most common adverse events in paediatric patients were diarrhoea and fatigue.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission presented Stage I and Stage II surveys to support the claim that treatment with miglustat improves composite disability score, which the submission presented as an appropriate surrogate for survival in NP-C patients.

The submission claimed that the data from the surveys consistently indicated that stabilisation of the disease and, in some cases, improvement, can be achieved with miglustat treatment in the majority of NP-C patients with progressive neurological disease.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a trial-based cost-utility analysis, based on the outcomes of the direct randomised trial, Study 007a, for juvenile and adult NP-C patients. The time horizon was 12 months. An economic analysis for paediatric patients was not included.

The incremental cost per quality adjusted life-year was greater than $10 million.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The drug cost per patient per year was estimated by the submission, for juvenile and adult patients, assuming a daily dose of 600 mg miglustat and for paediatric patients, assuming an average daily dose of 400 mg miglustat.

The requested cost per pack of miglustat was consistent with the cost in the current LSDP listing, however the recommended dose for treating NP-C is double that for the treatment of Gaucher. Therefore, the drug cost per patient per year for miglustat for the treatment of NP-C is double the cost per patient per year for treating Gaucher disease.

The net financial cost/year to the PBS was estimated by the submission to be less than $10 million in Year 5. The estimate was uncertain, as there was a substantial degree of uncertainty in the prevalence of NP-C disease in Australia. As variations in the number of eligible patients are likely to have considerable impact on the financial implications, any estimate of the net cost to the PBS was equally uncertain.

12. Recommendation and Reasons

The PBAC considered that placebo plus standard medical management (standard care) was the appropriate comparator for miglustat in the treatment of Niemann-Pick Type C (NP-C) disease, rather than standard care alone as nominated in the submission. The PBAC noted the submission stated that miglustat would be used in addition, rather than replacing, standard care.

The PBAC noted the requested restriction for miglustat was consistent with the TGA approved indication.

The PBAC noted that the difference in the change of horizontal saccade eye movement α (HSEM-α) from baseline, the primary endpoint of Study 007a and Study 007a (ext), was not significantly different between the miglustat group and the standard care group. The PBAC also noted that the analysis of changes in quality of life scores from baseline on various SF-36 domains in Study 007a did not indicate any statistically significant difference between the miglustat group and the standard care group.

The PBAC noted there was some suggestion of a small improvement in HSEM-α from baseline in paediatric patients with NP-C who were treated with miglustat for 12 months (mean change = -0.489ms/deg (95% CI, -0.810ms/deg, -0.167ms/deg)) in the single arm study 007p, however no statistically significant difference was reported after 24 months in 007p (ext).

The PBAC hence considered that the clinical efficacy of miglustat in the treatment of NP-C was uncertain. The PBAC considered that the relationship between HSEM-α as a primary endpoint for the assessment of miglustat in the treatment of NP-C and survival was uncertain, and considered that the submission did not provide sufficient evidence to indicate a direct relationship between trial outcomes (HSEM-α) and survival.

The PBAC noted the submission also presented two surveys, one regarding NP-C patients receiving standard care (Stage II survey), and one concerning NP-C patients initially receiving standard care and subsequently treated with miglustat (Stage I survey). The PBAC noted that the composite disability score was a surrogate outcome derived retrospectively from a non-blinded assessment of subjective data, using a non-validated disability scale and that the data were based on a small number of patients with large variability in intra- and inter-individual rates of progression. The PBAC also noted that the utility of the results was further limited by the potential for bias and large degree of uncertainty in the estimates. The

PBAC did not consider that the survey results provided sufficient evidence to support the submission's claim of an increased survival in NP-C patients treated with miglustat. The PBAC also considered the use of the composite disability score as a surrogate for survival was uncertain.

The PBAC considered there is limited information on the long-term safety of miglustat treatment, especially at the relatively high dose recommended for NP-C disease; however, the evidence presented indicated that miglustat is not as safe as standard care alone.

The PBAC considered there were a number of translation issues, including the extrapolation of the survey results. The PBAC noted that the submission assumed that the rate of progression in the composite disability score, for both patients receiving standard care and patients receiving miglustat, would remain constant over time, up to 10 years after diagnosis. The PBAC considered this assumption is not justified as the evidence suggested that there can be variation in the rate of disease progression over the course of the disease. The PBAC also noted that the outcome used in the extrapolation (composite disability score) is not the outcome used in the economic evaluation.

The submission presented a trial-based cost-utility analysis, based on the outcomes of the direct randomised trial, Study 007a, for juvenile and adult NP-C patients. An economic analysis for paediatric patients was not included. The PBAC considered that the time horizon of 12 months was not realistic and noted that only the cost of treatment and the costs associated with treating the most common adverse event, as determined from the trial, were included. The health outcome used in the evaluation was quality adjusted life-years, derived from quality of life data recorded during the trial. The PBAC noted the cost per adult or juvenile patient per year, and that the incremental cost per quality adjusted life-year was greater than $10 million.

The PBAC hence rejected the application to list miglustat on the PBS for the treatment of NP-C disease on the basis of uncertain clinical efficacy and a very high and uncertain cost effectiveness ratio.

The PBAC considered that miglustat for the treatment of NP-C disease meets criterion one of the Life Saving Drug Program (LSDP), as miglustat is TGA registered for the treatment of progressive neurological manifestations in adult and paediatric patients with NP-C disease. The PBAC however noted that in making the recommendation for registration the TGA, the ADEC noted the limited evidence of efficacy. The PBAC also considered that criteria two, three, six, seven and eight of the LSDP are met.

The PBAC did not consider that there was acceptable evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use miglustat in NP-C disease and hence considered that criterion four of the LSDP was not met. The PBAC considered that there was uncertainty in the relationship between the surrogate measure of HESM-α and survival and the use of the composite disability score derived from the survey results as a surrogate for survival, and considered that no evidence was presented to conclude that the lifespan of NP-C patients is substantially extended by receiving treatment with miglustat.

The PBAC considered that as there is considerable uncertainty regarding the clinical efficacy of miglustat in the treatment of NP-C disease, it is uncertain whether miglustat meets criterion five of the LSDP.

The PBAC hence recommended that miglustat for the treatment of Niemann-Pick Type C disease does not meet the criteria for the LSDP, and hence is not suitable for consideration of inclusion in the LSDP.

The PBAC welcomed and noted the consumer comments provided in relation to the miglustat submission.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

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, Actelion Pharmaceuticals, acknowledges the recommendations of the PBAC. Actelion recognises the significant challenges faced in the clinical study of such rare diseases, but remains committed to working cooperatively with the PBAC in seeking a favorable outcome in the future.