**PUBLIC SUMMARY DOCUMENT**
**Product:** Miglustat, capsule, 100 mg, Zavesca®
**Sponsor:** Actelion Pharmaceuticals Australia Pty Ltd
**Date of PBAC Consideration:** November 2011

## 1. Purpose of Application

The re-submission requested inclusion in the Life Saving Drugs Program (LSDP) for the treatment of progressive neurological manifestations in adults and paediatric 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 (PBAC) as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness.

Subsidised access through the LSDP is granted in accordance with specified eligibility criteria and subject to certain conditions:

Life Saving Drugs Program Criteria and Conditions (PDF 17 KB)

## 2. Background

At the July 2010 meeting, the PBAC rejected an application to include 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 did not meet the criteria for the LSDP, and hence was not suitable for consideration of inclusion in the LSDP.

*See July 2010 Public Summary Document for full details.*

## 3. Registration Status

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

## 4. Listing Requested and PBAC's View

Authority required
Treatment of progressive neurological manifestations in adults and paediatric patients with Niemann-Pick disease Type C disease.

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

NP-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 NP-C disease is currently palliative only and depends on the needs of the individual, the symptoms and the clinical manifestations.

The submission proposed that miglustat will provide a pharmacologic intervention that may interrupt disease progression.

## 6. Comparator

The submission nominated standard medical management comprising of palliative care.

At the July 2010 meeting, the PBAC considered that placebo plus standard medical management (standard care) was the appropriate comparator, noting that miglustat would be used in addition to, rather than replacing, standard care.

## 7. Clinical Trials

The previously submitted trials were:

- Randomised controlled trial OGT918-007a and its extension study (OGT918-007a(ext));
- Paediatric sub-study of the above trial (OGT918-007p) and its extension study (OGT918-007p(ext));
- Stage I survey; and
- Two case-series and 19 case reports.

The new data presented in the submission were from:

- Three videofluoroscopy swallowing studies (VFSSs) of up to six patients (Australian, Italian and Taiwanese); and
- Other patient case series data: UK data, Spanish and Portuguese data, and Italian data;
- Survival analysis of patients treated with miglustat compared with an untreated cohort compiled from several patient sources.

Details of the studies published at the time of submission are shown in the table below:

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **RCT data** | | |
| Trial OGT 918-007a | | |
| Patterson MC et al 2007 | Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. | Lancet Neurology 2007; 6(9): 765-772. |
| **RCT extension data** | | |
| Study OGT 918-007p | | |
| 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 OGT 918-007a (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 OGT 918-007p (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. |
| **Videofluoroscopy data** | | |

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|---|---|---|
| Italian case studies<br>Feracotta S et al 2011<br>Brushini D et al 2008 | The videofluoroscopic swallowing study shows a sustained improvement of dysphagia in children with Niemann-Pick disease type C after therapy with miglustat.<br>Efficacy of Miglustat on Dysphagia in Four Niemann Pick Patients. | American Journal of Medical Genetics, Part A 2011; 155: 540-547.<br><br>Journal of Inherited Metabolic Disease 2008; 31 (Sup 1):123. |
| Taiwanese case studies<br>Chien YH et al 2007 | Treatment of Niemann-Pick disease type C in two children with miglustat: Initial responses and maintenance of effects over 1 year. | JIMD Short Reports #063 (2007) DOI 10.1007/S 10545-007-0630-Y. |
| **Other patient data** | | |
| UK data<br>Jacklin E et al 2010 | Review of 11 patients with NPC1 treated with miglustat. | Molecular Genetics and Metabolism. 2010; 99: S22. |
| Spanish and Portuguese data<br>Pineda M et al 2010 | Clinical experience with miglustat therapy in paediatric patients with Niemann–Pick disease type C: A case series. | Molecular Metabolism. 2010; 99: 358-366. |
| Italian data<br>Fecarotta S 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). |
| Pineda M et al 2009<br><br>Sedel F 2010 | Miglustat in patients with Niemann-Pick disease Type C (NP-C): a multicenter observational retrospective cohort study.<br>Changing the disease course: Disease modifying treatment for Niemann-Pick type C. | Molecular Genetics and Metabolism 2009; 98 (3):243-249.<br>European Neuropsycho-pharmacology. 2010; 20(Sup 3): S639. |

NP-C = Niemann-Pick disease Type C; RCT = randomised controlled trial

## 8. Results of Trials

The instruments used in the three videofluoroscopy case studies included the Dysphagia Severity Scale, Han Functional Dysphagia Scale, Penetration/Aspiration Scale, and Melbourne Health VFSS Rating Scale.

Overall, the results from the VFSSs showed a high degree of variation across subjects.

The re-submission did not provide information regarding whether the swallowed material used in the assessment of swallowing function was consistent across studies or across patients. Due to a lack of pre-treatment assessment for most of the patients (and/or a control group), it could not be determined whether the observed changes in swallowing function during the treatment period were due to natural disease progression or resulted from the use of miglustat. Given that the rate of progression of neurological symptoms in NP-C, including swallowing function, can vary over the course of the disease, and there may also be temporary periods of spontaneous improvement, the lack of baseline data and/or a control group severely hindered interpretation of the swallowing study results.

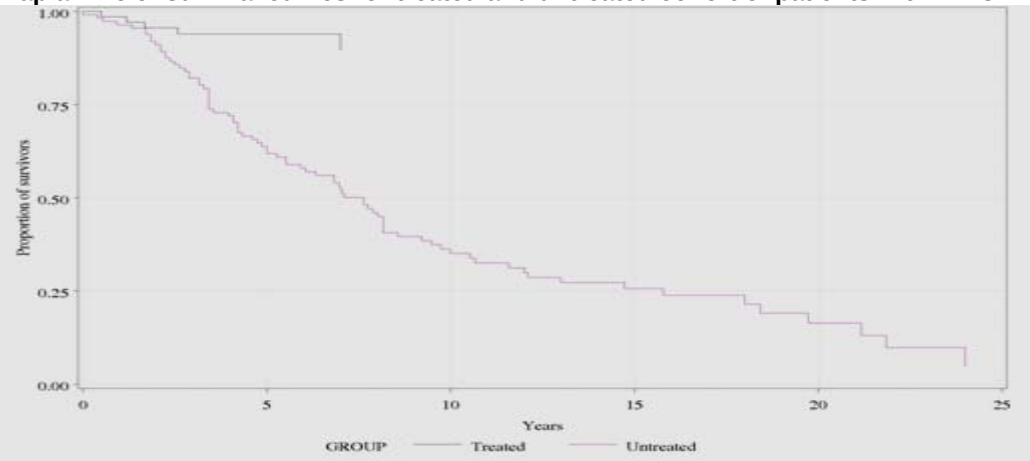
Additional patient data:

The data are based on a small number of patients, with large intra- and inter-individual variability in rates of disease progression. The utility of the results was further limited by the potential for observer bias.

Longitudinal analysis of survival data:
A significantly lower risk of mortality was reported in the miglustat cohort than in the untreated cohort (hazard ratio: 0.16 [0.063, 0.391]), based on 10 years of patient data after the onset of neurological symptoms for both groups.

The Kaplan-Meier survival curves for the treated and untreated cohort of patients with NP-C are shown below:

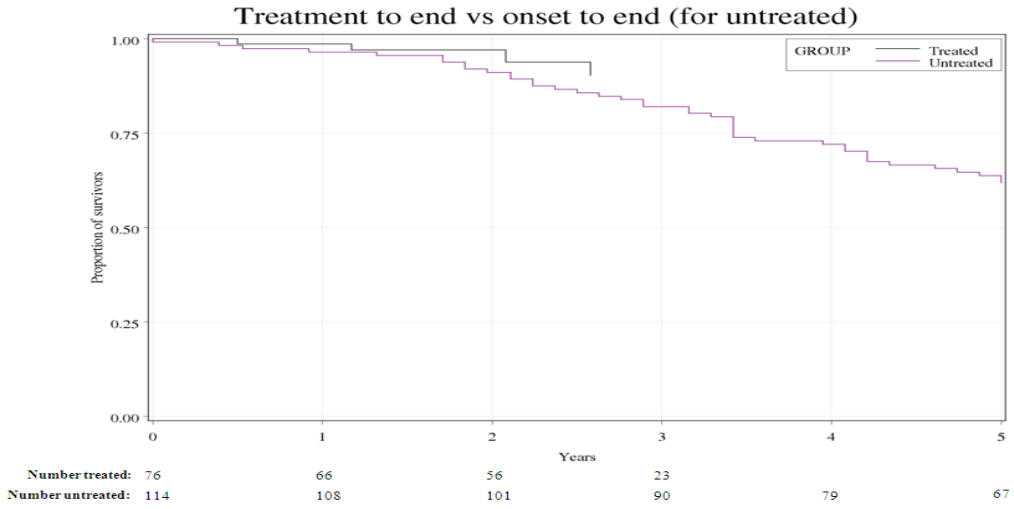
**Kaplan-Meier survival curves for treated and untreated cohort of patients with NP-C**




The survival curves of the two cohorts diverge within the first 3 years after the onset of neurological involvement.

The Pre-Sub-Committee Response (PSCR) stated that the data used in the survival analysis are real world data of patients and that these patients are reflective of the likely patient population to receive miglustat if funded on the LSDP.

The survival curves, time from miglustat treatment initiation compared with time from symptom onset in the control arm, are shown in the figure below:



*For PBAC's view of these results, see Recommendation and Reasons.*

No new toxicity data from clinical studies were presented in the re-submission.

## 9. Clinical Claim

The re-submission described miglustat as superior to placebo in terms of effectiveness in patients with NP-C.

Based on the data presented in the resubmission, the PBAC did not accept the clinical claim that miglustat is superior to placebo in terms of effectiveness. The PBAC also reaffirmed its previous conclusion from July 2010 that miglustat is not as safe as placebo.

## 10. Economic Analysis

An updated modelled economic evaluation was not presented.

At the July 2010 PBAC meeting, the PBAC accepted that miglustat is unlikely to be cost-effective.

## 11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year to be less than 10,000 in the first 5 years.

The net financial cost to the PBS was estimated by the submission to be less than $10 million in Year 5.

The estimates were uncertain as the prevalence and incidence of NP-C disease in the Australian population is uncertain, and therefore so are the number of patients likely to be treated.

## 12. Recommendation and Reasons

The PBAC noted that NP-C disease is highly heterogeneous in nature and characterised by a widely varying life expectancy and wide variability in age of onset and clinical presentations. The PBAC acknowledged the scarceness of clinical data for the use of miglustat in the treatment of patients with NP-C disease given the rarity of NP-C disease.

However, based on the data presented in the resubmission, the PBAC did not accept the clinical claim that miglustat is superior to placebo in terms of effectiveness. The PBAC also reaffirmed its previous conclusion that miglustat is not as safe as placebo.

The PBAC noted the new clinical data presented in the re-submission, which comprised three videofluoroscopy swallowing studies (VFSSs) of up to six NP-C patients (Australian, Italian and Taiwanese), other NP-C patient case series data (UK data, Spanish and Portuguese data, and Italian data), and a survival analysis of NP-C patients treated with miglustat compared with an untreated N-PC cohort sourced from elsewhere.

Regarding the VFSSs, the PBAC considered that the evidence provided was not sufficient to support the validity and reliability of the four scales used in the studies. Additionally, given the lack of blinded outcome assessment there is potential for investigator/assessor bias in the assessment of the subjective outcome of swallowing function.

The PBAC noted that the results of the three VFSSs did not show consistent improvement or stabilisation across treated patients in swallowing function/dysphagia scores and there was no information on a control group of either untreated NP-C patients or consistent results prior to treatment. The PBAC considered it is therefore unknown from these results whether miglustat mitigates disease progression as measured by dysphagia.

Regarding the NP-C patient case series data, the PBAC noted that the composite scales used to measure NP-C disease severity in the UK, Spanish and Portuguese patients have not been validated. The data are based on a small number of patients, with large intra- and inter-individual variability in rates of disease progression. The utility of the results is further limited by the potential for observer bias.

Regarding the longitudinal analysis of survival data presented in the re-submission, the PBAC noted that a significantly lower risk of mortality was reported in the miglustat cohort than in the untreated cohort (hazard ratio: 0.16 [0.063, 0.391]), based on 10 years of patient data after the onset of neurological symptoms for both groups. The survival data on both cohorts were pooled from a variety of patient sources, but there was no explanation of how these patients were selected. The comparability of the two cohorts in terms of potential confounding factors, eg age of neurological symptom onset, was not assessed in the re-submission. The PBAC noted that the survival curves of the two cohorts diverged within the first 3 years after the onset of neurological involvement. However, the observed lower mortality in the treated cohort may have resulted from less severe or slower natural disease progression of NP-C in the treated patients rather than miglustat therapy.

The PBAC noted that the Pre Sub-Committee Response re-created survival curves looking at time from symptom onset in the control group compared with time from treatment initiation in the miglustat group. It states that the divergence of the survival curves from the time of treatment initiation is again significant (test p=0.0192). The PBAC considered that the interpretation of the survival data remains unclear; given that patient baseline characteristics were unmatched and that, due to more extensive right-censoring in the miglustat cohort, the most reliable data were at the top of the curves, before they diverge. Although the applicant has emphasised the representativeness of patients in the miglustat cohort to patients taking miglustat "in the real world", the PBAC's concern is the comparability of the two cohorts in terms of all aspects that might influence survival of NP-C patients, so that the reported statistically significant difference between the survival of the two cohorts can be confidently attributed to miglustat or not. This concern is not addressed either by assessing the effect of age on survival across all treated and untreated patients, or by restricting the survival analyses to patients who have been included in published data.

The PBAC noted the articles in the re-submission reporting on dysphagia and aspiration pneumonia in patients with neurodegenerative disorders or stroke. A total of 12 cohort studies were identified. A low to moderate degree of heterogeneity in study results was observed across the studies ($I^2$: 23%, $Chi^2$ p-value: 0.21). The overall estimate of the odds ratio (OR) of aspiration pneumonia in patients with dysphagia is 14.12 (95% CI: [13.95, 14.38]). The PBAC considered that, although dysphagia may increase the risk of aspiration pneumonia in patients with stroke and neurodegenerative disorders, the applicability to NP-C patients is less clearly established.

The PBAC noted the literature search used to identify studies providing data on aspiration pneumonia (or pneumonia) and mortality. The results of a meta-analysis of the identified six cohort studies which examined the relationship between aspiration pneumonia and mortality, using a Mantel-Haenszel fixed-effects model indicated an increased risk of mortality was observed in patients experiencing aspiration pneumonia, with pooled OR of 3.23 (95%: [2.46, 4.25]), which is not as strong a signal as the OR of aspiration pneumonia in patients with dysphagia. Results showed a high degree of consistency across studies ($I^2$: 0%, $Chi^2$ p-value: 0.64). However, none of the six identified studies were in patients with NP-C (3 in stroke patients, 1 in patients with epilepsy, 1 in patients with Parkinson's disease, and 1 in a population with a variety of neurodegenerative disorders). Therefore, the PBAC again considered that the applicability of these results to NP-C patients is uncertain.

The PBAC noted that no evidence was presented to allow an assessment of the benefits of early intervention with miglustat for pediatric patients and how this may alter disease progression and life expectancy, given that the presentation of NP-C disease is different in children compared to adults.

The PBAC therefore rejected the re submission for the inclusion of miglustat in the Life Saving Drugs Program (LSDP) for the treatment of progressive neurological manifestations in adults and paediatric patients with Niemann-Pick type C (NP-C) disease on the basis that the clinical evidence presented failed to show that miglustat meets eligibility criterion 4 and 5 of the LSDP.

In relation to the new clinical evidence in the re-submission to address criterion 5 of the LSDP, the PBAC did not accept that the several sets of case series presenting dysphagia results (including the VFSSs) provided a convincing basis to conclude that miglustat is clinically effective for this outcome. The PBAC also did not accept that the comparison of survival across treated and untreated patients enabled a conclusion of clinical effectiveness because it could not assess the comparability of the two cohorts for other aspects that might influence survival and so could not exclude sources of confounding. For these reasons, together with the extremely high cost per patient per year the PBAC re-affirmed its previous decisions not to recommend listing on the PBS and not to accept that miglustat meets eligibility criterion 4 of the LSDP.

In relation to the new clinical evidence in the re-submission to address criterion 4 of the LSDP, the PBAC did not accept the comparison of survival for the reasons already identified in relation to criterion 5. The PBAC also did not accept that the chain of argument presented in the re-submission (i.e., from a treatment effect of miglustat on dysphagia to a treatment effect of miglustat on extending a patient's lifespan via a reduction in aspiration pneumonia) was sufficiently established. Based on data in other diseases, the association between dysphagia and aspiration pneumonia is more strongly established than between aspiration pneumonia and death. However, the applicability of these associations to NP-C patients is uncertain. More importantly, a clear treatment effect of miglustat on dysphagia, the first link in this chain of argument, was not accepted for the reasons already identified in relation to criterion 5. Overall, the PBAC re-affirmed its previous decision not to accept that miglustat meets eligibility criterion 4 of the LSDP.

The PBAC expressed the view that, although the new clinical evidence provided for its consideration was not sufficient to change its previous conclusions, comparing survival

curves across treated and untreated cohorts which are otherwise similar in terms of characteristics with known prognostic value would be informative. Identifying patients who would be most likely to gain an extension in their lifespan from treatment may also be informative.

The PBAC also noted that, relevant to criterion B2 for the LSDP, the cost per patient for treating NP-C disease is double that for treating Gaucher disease under the LSDP based on the relevant recommended doses being double in NP-C disease compared with Gaucher disease and an identical cost per pack.

The PBAC also acknowledged and noted the consumer comments on this item.

***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

Actelion acknowledges the difficulties in meeting the LSDP criteria in a very rare condition such as Niemann-Pick Disease Type C. Actelion remains committed to working with the PBAC and LSDP to ensure that patients with Niemann-Pick Disease Type C have funded access to treatment.