Drugs 2003; 63 (22): 2427-2434
0012-6667/03/0022-2427/$33.00/0

Miglustat

Paul L. McCormack and *Karen L. Goa*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Miglustat is an orally administered ceramide glucosyltransferase inhibitor which prevents the lysosomal accumulation of glucocerebroside that occurs in patients with Gaucher's disease.

▲ In noncomparative trials in patients with type 1 Gaucher's disease, miglustat (50 or 100mg three times daily) for 6–12 months significantly reduced baseline liver and spleen volumes. At both 6 and 12 months, the reductions in organ volumes were greater with the higher dosage.

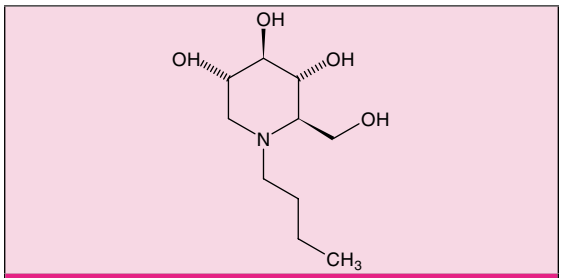
▲ Miglustat 50 or 100mg three times daily for 6–12 months had no significant effect on haemoglobin concentrations. Baseline platelet counts were not significantly improved by either dosage at 6 months, although the higher dosage significantly increased platelet counts at 12 months.

▲ In an open extension phase, patients continued to show further reductions in organ volume as well as significant improvements in haematological parameters at 24 and 36 months.

▲ In a 6-month randomised study in patients with type 1 Gaucher's disease who had previously received long-term enzyme replacement therapy (ERT), liver volume reduction was greater with miglustat plus ERT than with ERT alone.

▲ Diarrhoea and weight loss were the most frequent adverse events associated with miglustat therapy. Fine tremor has been reported in approximately 30% of miglustat-treated patients.

Features and properties of miglustat (OGT 918; Zavesca®)	
Indication	
Mild-to-moderate type 1 Gaucher's disease	
Mechanism of action	
Inhibition of ceramide glucosyltransferase (glucosylceramide synthase)	
Dosage and administration	
Recommended starting dosage	100mg
Route of administration	Oral
Frequency of administration	Three times daily
Pharmacokinetic profile (100mg single dose, unless stated otherwise)	
Peak plasma concentration (C_{max})	0.86 μg/mL
Time to C_{max}	2.5 hours
Elimination half-life	6–7 hours
Steady state C_{max} (100mg three times daily)	1.5 μg/mL
Time to steady state C_{max} (100mg three times daily)	4–6 weeks
Volume of distribution	83L
Adverse events	
Most frequent	Diarrhoea (>80%), and other gastrointestinal events
Common	Weight loss (≈60%), tremor (≈30%), headache, flu-like symptoms



Miglustat

Gaucher's disease is a rare glycosphingolipid lysosomal storage disorder resulting from a deficiency of the lysosomal enzyme β-glucocerebrosidase (also referred to as acid β-glucosidase or β-glucosylceramidase). The enzyme deficiency leads to the intracellular accumulation of the substrate, glucocerebroside (also known as glucosylceramide), the parent compound of many glycosphingolipids. Glucocerebroside accumulates primarily in macrophages, as a result of phagocytosis rather than by *in situ* production within these cells. The disease results from autosomal recessive inheritance of mutations in the gene coding for β-glucocerebrosidase that is located in the q21 region of chromosome 1.[1-5]

Gaucher's disease is classified according to the presence or absence and severity of neurological involvement. Type 1 is the most common subtype and does not involve the central nervous system (CNS), unlike types 2 (acute, infantile form) and 3 (chronic, late-onset form) which are characteristically neuronopathic. The clinical manifestations within each classification type are highly variable and correlate, although not absolutely, with the nature of the mutations in the glucocerebrosidase gene.[3,4] In type 1 Gaucher's disease, lipid-engorged macrophages infiltrate the viscera, especially the liver and spleen, and the bone marrow. The clinical manifestations commonly include hepatosplenomegaly, anaemia, thrombocytopenia, and bone lesions in patients with severe disease.[1-5]

There are estimated to be about 20 000 patients with Gaucher's disease worldwide (predominantly type 1). The disease is panethnic, but is highly prevalent in Ashkenazi Jews with a frequency of approximately 1 in 850, compared with a prevalence of about 1 in 40 000 in non-Jewish populations.[1,2,5]

The current treatment of choice for type 1 Gaucher's disease is enzyme replacement therapy (ERT) with macrophage-targeted β-glucocerebrosidase. Originally, the enzyme (alglucerase) was isolated from human placentae prior to modification to expose terminal mannose residues required for targeting to macrophages, but recombinant enzyme (imiglucerase) has now replaced the placenta-derived form. ERT reduces organomegaly and improves haematological and biochemical indices. It also decreases bone pain, prevents new bone crises, and improves bone mineralisation, at a slower rate.[2,6] However, treatment is lifelong, requires repeated intravenous infusions and is extremely expensive.[5] Prior to the advent of ERT, the only curative therapy was allogeneic bone marrow transplantation. Therapeutic interventions included fracture treatment, joint replacement and splenectomy.[7-9]

Miglustat (Zavesca®[1]; previously named Vevesca) is an orally active agent that offers a new approach to the therapy of Gaucher's disease by inhibiting the formation of substrate for the deficient enzyme (figure 1). All patients with type 1 Gaucher's disease have some level of residual β-glucocerebrosidase activity. The aim of substrate reduction therapy is to lower the production of substrate to a level with which the residual enzyme activity can cope.[10,11] Miglustat reversibly inhibits the enzyme, ceramide glucosyltransferase, that catalyses the formation of glucocerebroside and thereby prevents its accumulation within macrophages.[10,11]

This review focuses on the use of miglustat in adult patients with type 1 Gaucher's disease.

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

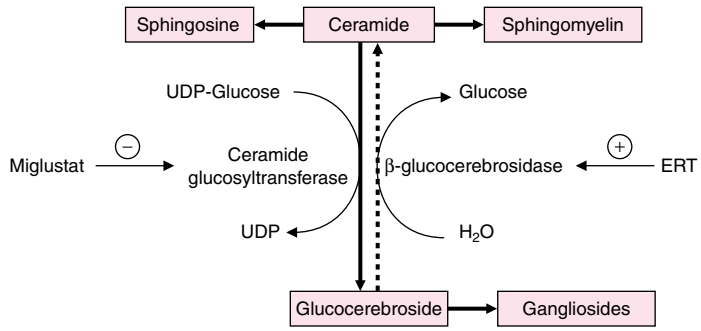


Fig. 1. Biochemical point of action of miglustat. The portion of the metabolic pathway in the biosynthesis of glycosphingolipids that is disrupted in type 1 Gaucher's disease, showing the points of action of miglustat and enzyme replacement therapy (ERT). **UDP** = uridine 5′-diphosphate.

1. Pharmacodynamic Profile

Miglustat is a non-peptidic, water-soluble *N*-butyl derivative of the naturally occurring glucosidase inhibitor deoxynojirimycin. It inhibits ceramide glucosyltransferase (glucosylceramide synthase; *N*-acylsphingosine glucosyltransferase) which catalyses the transfer of glucose to ceramide to form glucocerebroside, the first step in glycosphingolipid biosynthesis.[10,11]

- The inhibitory constant (K_i) of miglustat was 7.4 μmol/L using ceramide as the acceptor and human HL-60 cells as the source of glucosyltransferase.[12] In HL-60 cell microsomal preparations, miglustat inhibited ceramide glucosyltransferase with an IC_{50} (concentration producing 50% inhibition of glucose transfer) of 20.4 μmol/L.[13]
- In an *in vitro* model of Gaucher's disease, miglustat 50–500 μmol/L prevented the accumulation of glucocerebroside in murine macrophages as determined by thin layer chromatography.[14] At the highest concentration tested (500 μmol/L), glucocerebroside was almost undetectable. The lack of glycosphingolipid accumulation in lysosomes was confirmed visually by electron microscopy.
- The use of miglustat for substrate deprivation was shown to be a valid approach to the treatment of glycosphingolipid lysosomal storage diseases by its beneficial effects in a symptomatic mouse model of Sandhoff disease, which results in peripheral and CNS accumulation of glycosphingolipids. In this model, treatment with miglustat 4800 mg/kg from 3 weeks of age or 2400 mg/kg from 6 weeks of age significantly reduced glycosphingolipid storage in the brain and liver (by 35–86% for gangliosides G_{M2} or G_{A2} at 112 days; $p < 0.05$–0.001), slowed the onset of symptoms (136 days in treated mice vs 104 days in untreated mice; $p < 0.001$) and extended the life expectancy by approximately 40% (170 vs 125 days; $p < 0.001$).[15]
- Miglustat therapy (100mg three times daily) in patients with type 1 Gaucher's disease (n = 5) [see section 3] reduced G_{M1} ganglioside concentrations in circulating leucocytes by 38.5% ($p = 0.006$ versus baseline) over 12 months.[16] Miglustat did not appear to inhibit N-glycan processing α-glucosidases in these patients, since there was no increase in the plasma concentration of N-linked glycosylated oligosaccharide.

2. Pharmacokinetic Profile

There are limited data available on the pharmacokinetic properties of miglustat at the dosages used in the treatment of type 1 Gaucher's disease. The bulk of the available information derives from a subset of patients (n = 11) enrolled in two noncomparative clinical trials[16,17] and the manufacturer's summary of product characteristics.[18] There are no pharmacokinetic data available in patients with hepatic impairment or in the elderly (>70 years).[18]

- Miglustat is rapidly absorbed after oral administration, with a time to maximum plasma concentration (t_{max}) of 2.5 hours.[16,17] A single 100mg dose produced a maximum plasma concentration (C_{max})

of 0.86 μg/mL.[16] The rate of absorption is decreased when miglustat is administered with food (C_{max} decreased by 36% and t_{max} delayed by 2 hours), although the extent of absorption is not significantly altered (area under the plasma concentration-time curve [AUC] decreased by 14%).[18]

- According to the product information sheet, miglustat does not bind to plasma proteins and has an apparent volume of distribution equal to 83L.[18] The absolute bioavailability has not been determined.
- In clinical trials, steady-state plasma concentrations were attained within 4–6 weeks. The peak and trough steady state concentrations for a miglustat 50mg three times daily dosage regimen were 0.8 and 0.3–0.4 μg/mL, respectively,[17] while those for a 100mg three times daily dosage regimen were 1.5 and 0.8 μg/mL (values estimated from a graph).[16]
- The apparent elimination half-life ($t_{1/2}$) of miglustat is between 6–7 hours.[16,17] According to the manufacturer's product information, the major route of excretion appears to be renal and data from a limited number of patients with Fabry's disease show that the oral clearance decreases with decreasing renal function.[18] The apparent oral clearance is 230 ± 39 mL/min and decreases by approximately 40%, 60% and >70% in patients with mild, moderate and severe renal impairment, respectively.
- Limited data from a small parallel group study suggest that concomitant administration of miglustat and ERT (imiglucerase) may decrease the exposure to miglustat (22% reduction in C_{max} and 14% reduction in AUC),[18] but miglustat has negligible effects on the pharmacokinetics of ERT.
- Although data are limited, there are no indications of alterations in pharmacokinetic parameters with age, gender or body mass.[18]

3. Therapeutic Trials

The results from three studies of miglustat in adults with mild-to-moderate type 1 Gaucher's disease are currently in the public domain (two noncomparative studies[16,17] and one randomised comparative study[19,20]). The two noncomparative studies have been published in full, while details for the comparative study were obtained from a media release and the US prescribing information (package insert). Miglustat has not been studied in patients with severe Gaucher's disease (defined as a haemoglobin concentration < 9 g/dL, a platelet count < 50 × 10^9/L or active bone disease).[18]

In the noncomparative studies, patients who were unable or unwilling to receive ERT, and who had not received ERT in the previous 3 months, were enrolled. The primary efficacy endpoints were reduction in volume of liver and spleen, and elevation of haemoglobin levels and platelet counts. Plasma activity of the enzyme chitotriosidase, which is released from activated macrophages and is elevated in Gaucher's disease, was also monitored as a biochemical marker of disease activity. The primary endpoint in the comparative study, in which patients on long-term ERT therapy were enrolled, was reduction in liver volume, although spleen volume, haemoglobin levels and platelet counts were also monitored.

At the end of all studies, patients who benefited from miglustat therapy (defined by organ volume reduction or improved symptoms) were eligible to continue treatment with miglustat in extended-use phases.

Noncomparative Studies

In the first noncomparative trial, conducted by Cox et al.,[16] 28 adult patients from four centres received miglustat 100mg three times daily for 12 months. Twenty three patients were evaluated at 6 months, while 22 patients were evaluated at 12 months. The study population included seven patients who had undergone previous splenectomy and six patients who had previously received ERT. Miglustat dosage adjustment was permitted throughout the study, based on plasma drug levels (target plasma concentrations ≤2 μg/mL), tolerability, and organ volume response after 6 months. The maximum administered dosage was 200mg three times daily in three patients. Eighteen patients entered the extended-use protocol and continued to receive miglustat for up to 36 months (n = 13).

In the second study, by Heitner et al.,[17] 18 patients from two centres were treated with miglustat 50mg three times daily for 6 months. Seven of these patients had undergone previous splenectomy. The same study design was employed, including dosage adjustment, to allow direct comparison with the other noncomparative trial conducted by Cox et al. The lower initial dose of 50mg was assessed to determine the lowest effective dose, since it had been suggested that potential bone marrow toxicity might explain the lower than expected haematological response with the higher 100mg dose used in the Cox et al. study. At the end of the study period, 16 patients continued to receive miglustat in a 6-month extension phase with dosages up to 100mg three times daily, although most patients (n = 12) received 100mg twice daily.

Liver and Spleen Volumes

- In both studies, there were significant mean reductions from baseline in liver and spleen volume at 6 and 12 months (figure 2). The percentage reduction in liver volume at 6 months was slightly greater with the higher 100mg dosage regimen used in the study by Cox et al.[16] Additional liver volume reduction was observed at 12 months with the 100mg dose,[16] but not with the 50mg initial dose used in the Heitner et al. study.[17] Spleen volume reductions from baseline were 3-fold higher with the 100mg dose[16] than with the 50mg dose[17] at 6 months. With both dosage regimens, spleen volumes were further reduced at 12 months.[16,17]
- In the extension phase of the study by Cox et al.,[16] the mean reductions from baseline at 24 (n = 14) and 36 months (n = 13) for liver volume were 14.5% and 17.5%, respectively, while the reductions in spleen volume were 26.4% and 29.6%, respectively.[21,22]

Haemoglobin and Platelets

- There were no statistically significant changes from baseline in mean haemoglobin concentrations at 6 or 12 months in either study (−1.3 g/dL[17] or value not reported[16] at 6 months; +0.26[16] or +1.2[17] g/dL at 12 months). In patients from the Cox et al. study[16] who continued to receive miglustat during the extended-use phase, mean haemoglobin concentrations at 24 (n = 14) and 36 months (n = 13) increased from baseline by 0.91 ($p < 0.05$) and 0.95 g/dL, respectively.[21-23]

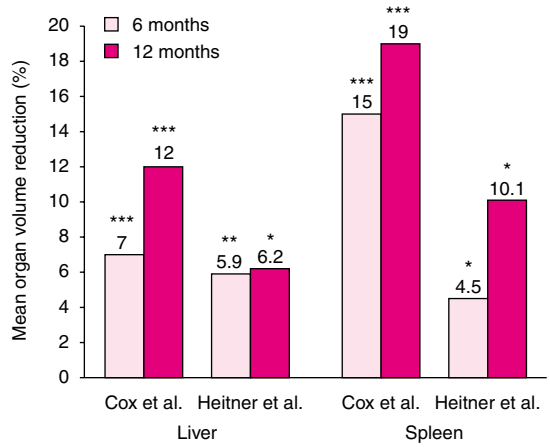


Fig. 2. Efficacy of miglustat on organomegaly in type 1 Gaucher's disease. Mean percentage reduction from baseline in liver and spleen volume in patients with mild-to-moderate type 1 Gaucher's disease after treatment with miglustat for 6 or 12 months in the studies by Cox et al.[16] (100mg three times daily initial dosage) and Heitner et al.[17] (50mg three times daily initial dosage). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs baseline.

- Mean platelet counts at 6 months were also not significantly different from baseline in either study ($+2.0 \times 10^9$/L[17] or value not reported[16]). At 12 months, increases in platelet counts were statistically significant versus baseline in the higher dose study (8.3×10^9/L, $p = 0.014$),[16] but not in the lower dose study (14.7×10^9/L).[17] During extended therapy, patients from the Cox et al. study[16] displayed mean increases in platelet counts of 13.6×10^9/L ($p < 0.05$) at 24 months (n = 14) and 22.2×10^9/L at 36 months (n =13).[21-23]

Plasma Chitotriosidase

- Plasma chitotriosidase activity declined slowly throughout treatment in both studies, indicating a progressive reduction in disease activity. The reduction from baseline in the Cox et al. study was 16.4% ($p < 0.001$) at 12 months,[16] while in the Heitner et al. study, the reductions were 6.6% at 6 months ($p = 0.039$) and 15.3% at 12 months ($p < 0.001$).[17]

Quality of Life

• In the study by Heitner et al.,[17] patient quality of life was assessed at day 1, 3 months and 6 months using the SF-36 quality of life questionnaire. This questionnaire assesses quality of life in eight dimensions including physical function, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social function, role limitations due to emotional problems and mental health. At 6 months, patients receiving miglustat reported improvements in physical functioning ($p = 0.052$) and statistically significant improvements in energy levels ($p = 0.004$). For the remaining parameters assessed, subjects either reported improvements of at least 5% (social functioning, role limitations due to physical problems) or little change.[24]

Comparative Study

In the only comparative study to date,[19,20] 36 patients who had been receiving intravenous ERT for at least 2 years were randomly assigned (nonblind) to either switch to miglustat 100mg three times daily (n = 12) for 6 months, to receive miglustat 100mg three times daily in addition to ERT (n = 12) or to continue on ERT monotherapy (n = 12). After 6 months of randomised therapy, all patients were eligible to receive miglustat monotherapy in an extended-use phase.

• At 6 months, there were small decreases from baseline in mean liver (3–5%) and spleen volumes (5–9%) in patients receiving miglustat, either alone or in combination. The changes in mean absolute liver and spleen volumes were not significantly different between the three treatment groups. Mean haemoglobin concentrations were reduced slightly from baseline in all three groups (0.5–2.4%), with no significant differences between groups. However, mean platelet counts were significantly (p value not stated) reduced from baseline in the miglustat monotherapy group (−9.6%), compared with increases in the ERT (10.1%) and combination therapy groups (3.2%). Additionally, reductions in chitotriosidase activity were significantly (p value not stated) greater in the ERT and combined therapy groups, than in the miglustat monotherapy group.[19,20]

• Analysis of a quality of life questionnaire (SF-36 with additional validated treatment-specific questions) demonstrated that patients receiving miglustat monotherapy reported significantly greater treatment convenience than those receiving ERT ($p = 0.028$) and nonsignificant ($p = 0.053$) improvement in overall treatment satisfaction compared with those receiving ERT. None of the patients receiving miglustat monotherapy reported less satisfaction with treatment at 6 months relative to baseline.[19]

• Of the 29 patients who entered the extended-use phase, 22 were still receiving miglustat monotherapy at 18 months, and none had reverted to ERT. Reasons for withdrawal were related to miglustat tolerability rather than lack of efficacy (no further details provided).[19] At 12 months, there were no significant changes from baseline in liver or spleen volume, or haemoglobin concentrations in any of the three treatment group (as originally randomised).[20] There were non-significant reductions from baseline in mean platelet counts in all three treatment groups. However, the reductions in platelet counts between 6 and 12 months (the extension period) were significant in the ERT and combination therapy groups (no data provided).[20]

4. Tolerability

• Diarrhoea is the most common adverse effect of miglustat therapy, occurring in >80% of patients. In the three clinical trials discussed in section 3, diarrhoea occurred in 79%,[16] 94%[17] and 100%[19] of patients. However, it was usually of mild-to-moderate severity, was often self-limiting and responded well to treatment with loperamide or codeine phosphate. Dosage increases resulted in transient recurrence of diarrhoea in two of three patients in one study.[16] Diarrhoea has been the reason for discontinuation of therapy in only approximately 5% of patients in these clinical trials. Other gastrointestinal events occurring at much lower frequency include flatulence, abdominal pain, nausea, constipation and dyspepsia.[16-18,23]

• Weight loss (defined as ≥5% of baseline values)[17] has been observed in approximately 60% of miglustat recipients, but is generally transient with most patients stabilising or returning to baseline bodyweight after 12 months.[17,18]

• Fine tremor of the hands or exacerbation of existing tremor has been reported in approximately 30% of miglustat recipients.[17,18] The incidence of fine tremor in the study by Heitner et al. was 39%, but it did not result in any treatment withdrawals.[17] One patient in the miglustat monotherapy treatment arm withdrew from the comparative trial partly as a result of developing transient tremor.[19] Tremor was not noted as a significant adverse event in the study by Cox et al.[16] in which patients received higher doses of miglustat than in the Heitner et al. study.[17]

• Other common adverse events reported only in the Heitner et al. study[17] were headache (50% of patients) and flu-like symptoms (33%).

• Two patients in the extension phase of the Cox et al. study[16] developed peripheral neuropathy. Two patients in the Heitner et al. study[17] developed neurological symptoms or abnormal electrodiagnostic findings after the 12-month assessment. In one of these patients, the neuropathy was believed to be secondary to concurrent vitamin B_{12} deficiency for which the patient was non-compliant with medication.

• Isolated cases of cognitive dysfunction have been observed, but their relationship to miglustat therapy is not certain. The one publicised case[25] involved an elderly patient who developed cognitive dysfunction early in 2002, several months after stopping miglustat therapy. The patient was originally enrolled in 1998 in the Cox et al. study[16] and had continued to receive miglustat in the extended treatment phase until October 2001. Although a relationship to drug therapy appeared unlikely, all treatment was withdrawn at the study site in Israel as a precautionary measure. Following a review of the clinical data, miglustat treatment was reinstated or continued uninterrupted at all clinical study sites.[26]

• Studies in animals have indicated that miglustat may adversely affect spermatogenesis and male fertility, although the effects are reversible.[27] Miglustat affects embryo/foetal survival in animals.[18]

5. Dosage and Administration

The recommended starting dose of miglustat in type 1 Gaucher's disease is 100mg orally three times daily, with or without food, in adult patients under the direction of physicians experienced in the treatment of Gaucher's disease. Diarrhoea or tremor may necessitate dosage reduction to 100mg once or twice daily in some patients.[18,20]

6. Miglustat: Current Status

Miglustat has been approved in the EU, Israel and the US for the treatment of adult patients with mild-to-moderate type 1 Gaucher's disease for whom ERT is unsuitable.

In clinical trials, miglustat significantly reduced organomegaly associated with mild-to-moderate type 1 Gaucher's disease, but had only a limited effect on the haematological signs of the disease. Switching patients from ERT to miglustat monotherapy was associated with decreases in platelet counts. Diarrhoea was the most frequent adverse effect, with weight loss and tremor also being common. However, the adverse effects only infrequently resulted in treatment withdrawal.

References

1. Mistry PK. Gaucher's disease: a model for modern management of a genetic disease. J Hepatol 1999; 30 Suppl. 1: 1-5
2. Niederau C, Häussinger D. Gaucher's disease: a review for the internist and hepatologist. Hepatogastroenterology 2000 Jul; 47 (34): 984-97
3. Beutler E. Gaucher's disease. N Engl J Med 1991 Nov 7; 325: 1354-60
4. Beutler E. Modern diagnosis and treatment of Gaucher's disease. Am J Dis Child 1993 Nov; 147: 1175-83
5. Elstein D, Abrahamov A, Hadas-Halpern I, et al. Gaucher's disease. Lancet 2001 Jul 28; 358: 324-7
6. Poll LW, Maas M, Terk MR, et al. Response of Gaucher bone disease to enzyme replacement therapy. Br J Radiol 2002; 75 Suppl. 1: A25-36
7. Chakrapani A, Wraith JE. Principles of management of the more common metabolic disorders. Curr Paediatr 2002; 12 (2): 117-24
8. Wraith JE. Advances in the treatment of lysosomal storage disease. Dev Med Child Neurol 2001; 43 (9): 639-46

9. Teckman J, Perlmutter DH. Conceptual advances in the pathogenesis and treatment of childhood metabolic liver disease. Gastroenterology 1995 Apr; 108: 1263-79
10. Lachmann RH, Platt FM. Substrate reduction therapy for glycosphingolipid storage disorders. Expert Opin Invest Drugs 2001; 10 (3): 455-66
11. Pastores GM, Barnett NL. Substrate reduction therapy: miglustat as a remedy for symptomatic patients with Gaucher disease type 1. Expert Opin Investig Drugs 2003 Feb; 12 (2): 273-81
12. Butters TD, van den Broek LAGM, Fleet GWJ. Molecular requirements of imino sugars for the selective control of N-linked glycosylation and glycosphingolipid biosynthesis. Tetrahedron Asymmetry 2000; 11: 113-24
13. Platt FM, Neises GR, Karlsson GB, et al. N-Butyldeoxygalactonojirimycin inhibits glycolipid biosynthesis but does not affect N-linked oligosaccharide processing. J Biol Chem 1994 Oct 28; 269 (43): 27108-14
14. Platt FM, Neises GR, Dwek RA, et al. N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. J Biol Chem 1994 Mar 18; 269 (11): 8362-5
15. Jeyakumar M, Butters TD, Cortina-Borja M, et al. Delayed symptom onset and increased life expectancy in Sandhoff disease mice treated with N-butyldeoxynojirimycin. Proc Natl Acad Sci U S A 1999 May 25; 96 (11): 6388-93
16. Cox T, Lachmann R, Hollak C, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 2000 Apr 29; 355 (9214): 1481-5
17. Heitner R, Elstein D, Aerts J, et al. Low-dose N-butyldeoxynojirimycin (OGT 918) for type I Gaucher disease. Blood Cells Mol Dis 2002 Mar; 28 (2): 127-33
18. Oxford GlycoSciences. Zavesca™ 100mg hard capsules (miglustat): summary of product characteristics [online]. Available from URL: http://www.ogs.com [Accessed 2003 Feb 3]
19. Oxford GlycoSciences Plc. Oxford GlycoSciences Plc switch/combination study 004 results on Vevesca (OGT 918) presented at EWGGD [media release]. 2002 May 2
20. Actelion Ltd. Zavesca® Package Insert (US prescribing information) [online]. Available from URL: http://www.actelion.com/Apps/WebObjects/Actelion [Accessed 2003 Sep 2]
21. Oxford GlycoSciences Plc. Latest clinical results on OGT 918 for Gaucher Disease in long-term follow up and dose comparison studies presented at ESGLD meeting [media release]. 2001 Sep 24
22. EMEA. Committee for Proprietary Medicinal Products Summary of Opinion for Zavesca [online]. Available from URL: http://www.emea.eu.int [Accessed 2003 Feb 3]
23. Zimran A, Hollak C, Aerts J, et al. Efficacy and tolerability of N-butyldeoxynojirimycin (OCT 918) in adult patients with type 1 Gaucher disease: long-term follow-up. Blood 2001 Nov 16; 98 Pt 2: 26
24. Data on file, Oxford Glycosciences, 2003
25. Oxford GlycoSciences Plc. OGS temporarily halts Vevesca (OGT 918) treatment in Israel as a precaution pending investigation of an unexplained adverse event [media release]. 2002 Apr 24
26. Oxford GlycoSciences Plc. OGS announces decision by Ethics Committee in Israel to end temporary suspension of Vevesca (OGT 918) trials [media release]. 2002 Jul 24
27. van der Spoel AC, Jeyakumar M, Butters TD, et al. Reversible infertility in male mice after oral administration of alkylated imino sugars: a nonhormonal approach to male contraception. Proc Natl Acad Sci U S A 2002 Dec 24; 99 (26): 17173-8

Correspondence: *Paul L. McCormack*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz