Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Miglustat

Proprietary Product Name: Zavesca

Sponsor: Pharmaceuticals Australia Pty Ltd

March 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision	3 February 2010
Active ingredient(s):	Miglustat
Product Name(s):	Zavesca
Sponsor's Name and Address	Actelion Pharmaceuticals Australia Pty Ltd PO Box 372 Frenchs Forest NSW 1640
Dose form(s):	Capsule
Strength(s):	100 mg
Container(s):	Blister carton
Pack size(s):	90 capsules
Approved Therapeutic use:	Treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick disease Type C
Route(s) of administration:	Oral
Dosage:	The recommended dose for the treatment of adult and adolescent patients with Niemann-Pick type C disease is 200 mg three times a day. Dosing in patients under the age of 12 should be adjusted on the basis of body surface area.

Product Background

The Australian Mucopolysaccharidoses Society (MPS) website gives the prevalence of Nieman-Pick disease type C (NPC) in Australia as approximately 1 in 211,000 live births. It can present at any time from intrauterine life to adulthood (late infantile and adolescent are the most common at 60% of cases). Manifestations may be primarily hepatic, neurological, or psychiatric. Cognitive impairment occurs in as many as 80% of NPC patients, and about one-third have seizures. About 20% of children with NPC disease have gelastic cataplexy, a sudden loss of muscle tone, with or without narcolepsy.

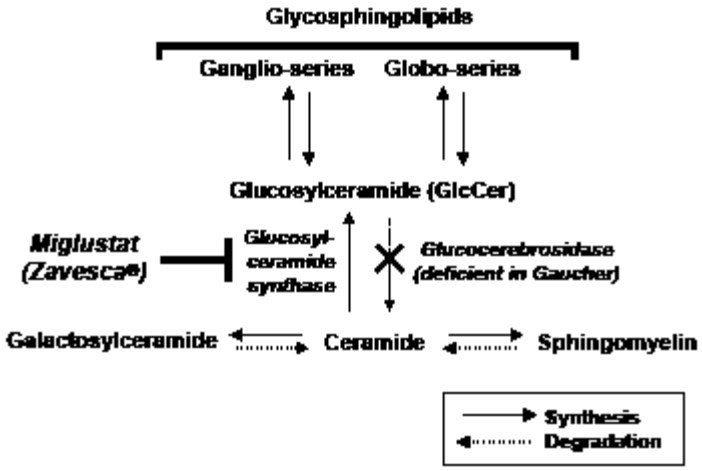
NPC is an autosomal recessive lipidosis with an error in intracellular transport of exogenous LDL-derived cholesterol that is associated with lysosomal accumulation of non-esterified cholesterol.[1]

Miglustat competitively inhibits the activity of the enzyme glucosylceramide synthase (GCS) which catalyses the transfer of glucose from a UDP-glucose donor to a ceramide acceptor.

[1] In liver and spleen, non-esterified cholesterol, sphingomyelin, and a specific phospholipid – bis(monoacylglycero)phosphate – are the predominant compounds. However, GSLs (glucosylceramide, lactosylceramide, GM2 and GM3 gangliosides) are also increased over control values. In the brain, where the pattern of lipid storage is different (and mainly confined to neurons), the most striking alterations are in the elevated concentrations of these GSLs.

This inhibition reduces the amount of glucosylceramide (the first and committed step in glycosphingolipid biosynthesis).

The biosynthetic pathways of glycosphingolipids (G_{M2} and G_{M3} gangliosides, and glucosyl- and lactosylceramide are shown below.



Miglustat (Zavesca, 100 mg capsule) is registered for the treatment of Type 1 Gaucher disease in adult patients. In the current submission, Actelion Pharmaceuticals Australia Pty Ltd seeks an extension of indications to include treatment of Niemann-Pick disease type C (NPC disease) for adult and paediatric (age not specified) patients, at a proposed dose of 200 mg three times daily (tds), compared with 100 mg tds for the treatment of Gaucher disease. The medicine is currently designated in Australia as an Orphan Drug for the progressive neurological manifestations in adult and paediatric patients with NPC. Orphan drug designation for NPC disease type C was granted on 8 July 2008 by the TGA.

Miglustat (Zavesca) is currently indicated for oral treatment of patients with mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option. The clinical evaluator stated that the currently approved indication was initially rejected for registration on the grounds of inconclusive efficacy evidence, but was subject to a Section 60 appeal**.** The latter was partly upheld by approving registration "for mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option", but not for registration for "oral maintenance therapy of patients with Type 1 Gaucher disease stabilised on enzyme replacement therapy".

Regulatory Status at the Time of Submission

Miglustat was registered (23 Oct 2007) for adults with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

A submission for the Niemann-Pick disease Type C (NPC) indication was made in the European Union (EU) in November 2006 and subsequently withdrawn pending further collection of data. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency felt that the evidence provided was incomplete as the natural history of the disease at patient's level was not sufficiently understood to rule out a bias in the interpretation of the data submitted. Actelion indicated their intention to resubmit with the results from an ongoing retrospective survey of the NPC patients treated with miglustat when completed. The same application as the current Australian submission was submitted to the EU on 12 September 2008. It was approved on 18 December 2008 for the treatment of

progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.

The NPC indication has been approved in Brazil and Taiwan.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Introduction

Miglustat (Zavesca) has been registered on the ARTG (No. 122957), indicated for the treatment of Type 1 Gaucher disease in adult patients. In the current application, an extension of indication was proposed for the treatment of patients with NPC disease. The daily dose proposed for the treatment of NPC disease was also increased to 200 mg three times a day (tds) for adults and adolescents, compared to the dose (100 mg tds for adult patients) registered on the ARTG for the treatment of Gaucher disease. Furthermore, Zavesca was registered for adult patients only for Gaucher disease, while in the current application, the product is proposed to be used in paediatric (age not specified) and adult patients with NPC disease. For children under the age of 12, doses are adjusted on the basis of body surface area (BSA) (the lowest dose: 100 mg/day for ≤ 0.47 m^2).

No nonclinical studies were conducted for the current application. The sponsor has provided 11 published papers and 4 study reports/summaries submitted for the original application. The literature papers included pharmacodynamics and pharmacokinetics of miglustat in relation to NPC disease. No new nonclinical safety data was provided. However, the nonclinical safety of miglustat was evaluated in the original application and there are no modifications in the quality or formulation of the product. Therefore, no changes in the product-related safety are expected for the current application. The data provided was sufficient to evaluate nonclinical aspects of miglustat for treatment of NPC disease.

Pharmacology

Pharmacodynamics

The NPC disease is a lipid storage disease caused by mutations in the NPC1 and NPC2 genes (Mellon *et al.*, 2008*)* and most human cases are caused by defects in NPC1 (Kolter *et al.*, 1998). NPC1 protein possesses a sterol-sensing domain (Liu *et al.*, 2009) and has been localized to vesicles that are believed to facilitate the recycling of unesterified cholesterol from late endosomes/lysosomes to the endoplasmic reticulum and Golgi (Higgins *et al.*, 1999; Neufeld *et al.*, 1999). Mutations in these genes therefore results in accumulation of cholesterol and glycosphingolipids (GSLs) in the endosomal compartments (Su, 1998). The main pathological feature of NPC is an accumulation of foamy cells in visceral organs and accumulation of GSLs in neurons and glial cells in the nerve system. Although the enlargement of the spleen and/or liver is not usually involved in major complications, the accumulation of lipids in the CNS causes a progressive decrease in many functions, including muscle coordination and cognition. The disease is invariably progressive and eventually fatal.

In vitro, miglustat inhibits activity of glucosylceramide synthase, the enzyme responsible for the first step in the synthesis of most GSLs. The compound inhibited glucosyltransferase-catalysed biosynthesis of glucosylceramide, with IC_{50} of 20 µM in human HL-60 cells (Platt *et al.*, 1994). Miglustat also inhibits activities of α-glucosidases I and II, and other enzymes.

In addition to the above activities, the compound increased the activity (217% compared to untreated cells) of acid β-glucosidase in COS-7 cells (Alfonso *et al.*, 2005). The acid β-glucosidase is a lysosomal enzyme responsible for the breakdown of glucosylceramide to ceramide and glucose, and is defective in Gaucher disease. Computer modelling shows that there are three potential enzyme binding sites for miglustat, one being the substrate binding site of the enzyme. This may indicate that miglustat exerts its chaperoning activity on acid β-glucosidase by acting as an inhibitor for the substrate binding to the active site, resulting in the compound not only acting as a substrate reducer but also as an inhibitor of the acid β-glucosidase degradation.

The effect of miglustat on the inhibition of glucosylceramide synthesis was also investigated *in vitro* for other diseases caused by GSL metabolism disorder. In Fabry disease lymphoblasts, miglustat reduced globotriaosylceramide (a glucosylceramide-based lipid) at IC_{50} of > 10 µM, following treatment of the cells with the compound for 2 days (Abe *et al.*, 2000). In a mouse (Hexb-/-) model of Sandhoff disease (caused by accumulation of GM2 ganglioside, which is one of the GSLs), miglustat corrected the impairment of Ca^{2+} uptake in brain microsomes in an *ex vivo* experiment (Pelled *et al.*, 2003).

In vivo, miglustat treatment of NPC mice (1200 mg/kg/day by diet) and cats (started with 150 mg/kg/day, then reduced to 50 mg/kg/day by gavage) delayed the onset of neurological dysfunction (ataxia and intention tremor), increased average life span (in mice), and reduced ganglioside accumulation and accompanying neuropathological changes (Zervas *et al.*, 2001).

Similarly, Sandhoff mice treated with miglustat (2400 or 4800 mg/kg/day by diet from 6 or 3 weeks of age, respectively) delayed the onset of symptoms (hind-limb paralysis and impaired coordination), reduced lipid storage in the brain and peripheral tissues, and increased life expectancy (about 1.4-fold) (Jeyakumar *et al.*, 1999). The treatment (2400 mg/kg/day) also delayed the onset of the inflammatory process and disease pathogenesis.

Pharmacodynamic Drug Interactions

Information on drug interactions of miglustat in NPC animals was not provided. Instead, a submitted paper (Jeyakumar *et al.* 2004) reported drug interactions in an animal model of a similar disease, Sandhoff disease.

In Sandhoff mice, the treatment with miglustat (600 mg/kg/day by diet from 6 weeks of age) extended survival of the animals (50% increase in life expectancy compared to the untreated animals), compared to that of mice treated with nonsteroidal antiinflammatory drugs or antioxidants (12–23% increase for each). When the antiinflammatory drug indomethacin (0.8 mg/kg/day dosing from 12–13 weeks of age) was combined with miglustat, survival was extended to 66% increase in life expectancy (6% synergy). Even greater synergy (11%) was achieved by a combination of aspirin (200 mg/kg/day dosing from 8-9 weeks of age) with miglustat (maximum 73% increase in life expectancy).

Pharmacokinetics

No new data were provided. In a published paper (Treiber *et al.*, 2007), the pharmacokinetic profile of ^{3}H-miglustat in rats following administration of a single dose of 160 mg/kg intravenous (IV) (male only) and orally (male and female combined) was similar to that observed in a previous study under the same dosing conditions. In both studies, peak plasma

concentrations of non-volatile radioactivity after oral administration were attained within 0.5 hours post-dose (Treiber *et al.*, 2007) and reached 13.8 μg equivalent/mL, resulting in an oral bioavailability of about 58% with $AUC_{0\text{-}inf}$ of 93-95 h·μg/mL. Its half-life was 4.5 hours (Treiber *et al.*, 2007).

For juvenile animals (12 days of age), plasma concentrations of miglustat were measured in juvenile rats (Crl:CD(SD)) following oral (gavage) administration at doses of 20, 60 and 180 mg/kg/day from Day 12 post-partum to Day 70 of age (once daily to Day 21 post-partum, then in three divided doses for 7 weeks), as part of a repeated dose study for the original application. Although pharmacokinetic/toxicokinetic profile was not analysed in this study, the increase in systemic exposure tended to be less than dose-proportional, compared to approximately dose-proportional in older rats, and there were no sex-related differences.

In addition, in the data provided for the previous submission, there were toxicokinetic studies conducted on young rats (3-4 weeks of age) for repeat dose toxicity (13 and 52 weeks) and carcinogenicity studies. The study data were reviewed for Gaucher disease and pharmacokinetic details were included in the original evaluation report. In general, the absorption parameters of miglustat in young rats were similar to those observed in adult rat studies. In young rats, time to maximal plasma concentration (T_{max}) was generally achieved at 0.5 hours post-dose and increases in serum area under the curve (AUC) values were broadly dose-proportional. Maximal plasma concentration (C_{max}) and AUC values were greater after repeated dosing in Week 13 or 52, compared to the values on Day 1, suggestive of accumulation. There were no sex differences in the pharmacokinetic parameters. Miglustat does not bind to plasma protein.

Metabolism, distribution and excretion

The metabolism, tissue distribution and excretion profiles of miglustat in animals after oral or IV administration were studied previously for Gaucher disease.

In the supplementary information provided, the Treiber group (2007) has reported similar results to those described in the nonclinical evaluation of the original application. According to their experiment, following a single oral administration of ^{14}C-prodrug (^{14}C-OGT 924) at the dose of 137 mg/kg (equivalent to 60 mg/kg of miglustat) to male rats, the maximum concentration (C_{max}) was reached within 1 hour post-dose in most tissues. At this time, the ^{14}C radioactivities in many tissues were equal to or exceeded those in plasma, suggesting good partitioning of miglustat into tissues. The highest tissue concentrations were observed in stomach, small intestine, large intestine, caecum, kidney and urinary bladder, whilst relatively low concentrations were observed in the liver. Based on the radiochromatogram analysis, metabolism of miglustat in rats was limited and, consequently, unchanged miglustat was the most prominent entity in rat urine after IV or oral administration of either ^{3}H-miglustat or ^{14}C-prodrug. For excretion, after oral administration of the ^{14}C-prodrug to rats, radioactivity was rapidly excreted into urine and faeces. Most of the radioactivity (84.5%) was recovered within 24 hours post-dose, with an overall recovery of 88.1% for the 72 hour collection period. During this period, the total radioactivity recovered was greater in urine (57 ± 7%) than in faeces (31 ± 4%).

In relation to NPC disease, it is important that miglustat is able to cross the blood-brain barrier. The tissue/plasma AUC ratio in the brain was 0.4 at T_{max} of 4 hours following oral administration of OGT 924 (Treiber *et al.*, 2007). It has been shown that the prodrug OGT 924 is readily converted to miglustat during gastrointestinal (GI) absorption and first pass metabolism (Treiber *et al.*, 2007). Furthermore, miglustat $T_{1/2}$ in the brain was significantly longer than that in plasma (17 hours vs 3.8 hours, respectively) and consequently brain

concentrations exceeded plasma levels by 2-fold (0.34 vs 0.16 μg equivalent/g) at 24 hours post-dose. This may be relevant to efficacy of the drug for NPC disease, but also suggests accumulation in the brain of rats.

Similarly, miglustat was absorbed in the brain of monkeys after oral administration of ^{3}H-miglustat at a dose of 55 mg/kg multiple times (seven times once every eight hours). The concentrations of miglustat in the cerebrospinal fluid (CSF) were 0.752 and 0.732 μg/mL at 8 hours after the 6th or 7th doses, respectively, whilst the mean plasma concentrations of ^{3}H-miglustat were 8.08 and 9.75 μg/ml. This suggests relatively poor partitioning (< 10% of the plasma concentration) of miglustat into monkey brain.

Relative exposure in young and adult animals

In the clinical data provided, human exposure at 200 mg/day tds in NPC patients resulted in an $AUC_{0–8h}$ of about 16.3 μg.h/mL (C_{max} = 2.7 μg/mL). This AUC value is about 1.8 times that (AUC_{0-8h} 9 μg.h/mL) in Gaucher patients after oral administration at a half dose (100 mg tds). This suggests that the systemic exposures of miglustat in humans are roughly dose-proportional, based on the values of AUC_{0-8h}. For this reason, the exposure ratios (ERs) (animal:human) of miglustat for the dose (600 mg/day: 200 mg tds) proposed for NPC disease were recalculated by dividing the ERs calculated in the Gaucher disease application by 1.8 (AUC_{0-8h} 16.3 μg.h/mL/9 μg.h/mL) for an AUC basis, and by 2 for a BSA basis. Table 1 summarises the ERs of miglustat estimated in animal studies for the clinical dose proposed for NPC disease.

Table 1: Relative exposure of miglustat in repeated dose oral toxicity studies (mean for the combined males and females)

Species	Study duration; route	Dose (mg/kg/day)	ER based on AUC		ER based on BSA		Study
			Gaucher disease	NPC disease	Gaucher disease	NPC disease	
Mouse	13 weeks, PO	100, 420, 840	1, 7, 17	0.6, 4, 9	2, 6, 13	1, 3, 6	455869
	2 years, PO	210, 420, 840/500	3, 5, 7	1, 3, 4	3, 6, 8	2, 3, 4	23296
Rat	13 weeks, PO	90, 180, 420, 840	2, 5, 9, 19	1, 3, 5, 10	3, 5, 13, 25	1, 3, 6, 13	PSA-90C-3476
	13 weeks, PO	20, 60, 180	1, 2, 5	0.4, 1, 3	0.6, 2, 5	0.3, 1, 3	WVC/001
	52 weeks, PO	180, 420, 840, 1680	4, 7, 10, 23	2, 4, 6, 13	6, 13, 26, 51	3, 6, 13, 26	PSA-91C-3490
	2 years, PO	30, 60, 180	0.7, 2, 4	0.4, 1, 2	1, 2, 6	0.5, 1, 3	23254
Beagle dog	2 weeks, PO	20, 40, 80, 85, 165, 240, 495, 825	3, 5, 10, 11 21, 30, 62, 104	1, 3, 6, 6, 12, 17, 35, 58	2, 4, 8, 9, 17, 24, 50, 83	1, 2, 4, 4, 8, 12, 25, 42	Various studies
Rhesus monkey	4 weeks, PO	165, 495, 1650			10, 30, 100	5, 15, 50	PSA-89C-3346

- The ER values for Gaucher disease in each study can be referred to the 'Relative exposure' section in 'Assessment' of the original evaluation report.
- For the ER on a BSA basis, conversion factors from mg/kg to mg/m^2 for mouse, rat, dog, monkey and human (50 kg BW) are 3, 6, 20, 12 and 33, respectively. PO=oral

Toxicology

No new study was provided. As indicated previously, there are no changes expected regarding the product-related safety. However, in the current application, the dose (200 mg tds) proposed for the treatment of NPC disease was increased to twice that (100 mg tds)

registered for the treatment of Gaucher disease. This will result in reduced safety margins (approximately halved) for the toxicities expected in NPC patients if treated with Zavesca. The proposed patient population is also extended to paediatric (age not specified) and adult patients for NPC disease from adult patients only for Gaucher disease. For these reasons, this assessment will discuss risks of the drug toxicities due to the increase in dose and safety of the drug for paediatric use (based on the toxicity study conducted in juvenile animals).

Acute toxicity

In the data provided for the original submission, the highest doses tested in mice and rats were 2 x 5000 mg/kg orally and 106 mg/kg/h IV infusion for 24 hours (about 2500 mg/kg), respectively. At these doses, all animals survived with minimal clinical signs of toxicity. Especially in the mouse study, the loose stools or diarrhoea commonly seen in repeated dose studies was not observed.

Repeat dose toxicity

The following describes brief summaries of the drug toxicities extracted from the previous nonclinical evaluation report, with revised safety margins based on the maximum recommended human dose (MRHD, 600 mg/day) proposed for NPC disease.

Effects on the Gastrointestinal Tract (GIT)

GI effects including diarrhoea/soft or watery stools and GI inflammation/lesions were a major toxicity of miglustat after repeated oral (gavage) administration to all species investigated (mouse, rat, dog and monkey) and were associated with reduced food consumption and body weight gain. Vomiting was common in dogs. At high doses, severe GI intolerance resulted in death.

The ERs for the miglustat-induced GI effects in animals calculated based on AUC, BSA or mg/kg are included in Table 2. The GI intolerance may be a local effect (ER comparison is more applicable based on mg/kg than based on AUC), but there were insufficient data to confirm this. The diarrhoea has been reported as an adverse reaction in clinical trials, suggesting humans are also susceptible to GI effects.

Table 2: Relative exposures of miglustat at various toxicities in the GIT for young and adult animals based on the MRHD (600 mg/day) proposed for NPC disease

Effect	Species	Study duration (weeks)	Dose at which effect observed (NOEL, mg/kg/day)	ER (based on AUC or BSA[#])	ER (based on mg/kg)
Diarrhoea/soft stools	Mouse	104	210	2	18
		13	(NOEL 100)	(0.6)	(8)
	Rat	13	90	1	8
		13	(NOEL 60)	(1)	(5)
	Dog	2	20[*]	1	2
			(No NOEL)	(NA)	(NA)
	Rhesus monkey	4	165[*]	5[#]	14
			(No NOEL)	(NA)	(NA)
Bloody diarrhoea	Mouse	2	Not observed at 2400[**]	18[#]	200
	Rat	52	1680	13	140
		52	(NOEL 840)	(5)	(70)
	Dog	2	80	6	7
		2	(NOEL 40)	(3)	(3)
	Rhesus monkey	4	165[*]	5[#]	14
			(No NOEL)	(NA)	(NA)
GI inflammation/lesions	Mouse	104	210	2	18
		13	(NOEL 100)	(0.6)	(8)
	Rat	52	1680	13	140
		52	(NOEL 840)	(5)	(70)
	Dog	2	80	6	7
		2	(NOEL 40)	(3)	(3)
	Rhesus monkey	4	495	15[#]	41
		4	(NOEL 165)	(5[#])	(14)

[*] The lowest dose tested; [**] The highest dose tested; [#] ER calculated based on BSA; NA, not applicable; Note: human body weight of 50 kg was considered for the calculation of ERs based on BSA or mg/kg

The lowest ERs for No Observable Effect Level (NOEL) of GI effects in mice, rats, dogs and monkeys are 8, 5, < 2 and < 14, respectively.

Supplementation of the diet with 65% dextrose did not consistently ameliorate the GI toxicity induced by miglustat. There was a lower incidence of GI intolerance when miglustat was administered in the form of the pro-drug, OGT 924.

In mice, there were dose-related increases in the incidence of tumours in the large intestine

Effects on the male reproductive tract

The male reproductive system was affected in rats orally (gavage) administered miglustat. In a 4 week study, the changes included seminiferous tubular atrophy, arrested spermatogenesis and epididymal hypospermia. Following longer period of treatments, similar lesions were observed and these are summarised in Table 3. NOELs could not be established in any of those studies. The effects of miglustat on the male rat reproductive tract were reversible.

Table 3: Summary of incidences in the rat male reproductive system following repeated oral (gavage) administration of miglustat or prodrug

Miglustat/prodrug; dosing duration	Incidence	LOEL (mg/kg/day)	ER (based on AUC)	Study
Miglustat; 2 years	Testicular tubular atrophy	30	0.4	23254
Miglustat; 52 weeks	Testicular aspermatogenesis and seminiferous tubule atrophy	180	2	PSA-91C-3490
Prodrug; 26 weeks	Low sperm concentration and increase of sperm with altered morphology	300	2	P30S4085
Miglustat; 4 weeks	Seminiferous tubular atrophy, arrested spermatogenesis and epididymal hypospermia	180	2	PSA-89S-3341

LOEL: Lowest Observable Effect Level

In association with the above changes in the male rat reproductive system, treatment-related interstitial cell adenomas (Leydig cell tumours) were found in the male testes.

While miglustat or prodrug was toxic in the rat male reproductive system, the above incidences were not found in dogs administered miglustat at doses of up to 140 mg/kg/day orally (ER 7 on a BSA basis), or in rhesus monkeys given up to 1650 mg/kg/day miglustat orally (ER 50 on a BSA basis) tested for the same duration (4 weeks).

From the above observations, it can be concluded that the miglustat effects in the male reproductive system appears to be reversible and may be species-specific.

Neurotoxicity

As indicated in the *Metabolism, distribution and excretion* section above, miglustat crosses the blood-brain barrier, with a longer half-life in the brain than that in plasma. Nevertheless, there were no signs of neurotoxicity or CNS-related pathological effects of miglustat in the safety pharmacology study in mice (NOEL at 600 mg/kg: ER 5 based on BSA) or in the repeated dose toxicity studies conducted on mice (including juveniles), rats, dogs and monkeys, respectively. However, in the sponsor's Clinical Overview, there were neurological symptoms, such as tremors and headaches observed in NPC or Gaucher patients treated with miglustat. Therefore, the statement '*the lack of any relevant neurotoxic effects of miglustat in humans*' in the nonclinical overview does not seem to reflect the clinical results of miglustat.

Effects on haemostasis

Treatment-related reductions in platelet counts were observed in rats and dogs, while an increase was seen in rhesus monkeys. Dogs treated at 85 mg/kg/day orally (ER 6 based on AUC) for 7 days resulted in a 50% reduction in platelet counts and a 23% increase in partial thrombin time (PTT). In rats, reductions in platelet counts generally occurred at about ≥ 420 mg/kg/day (ER 5). In humans, mild reductions in the platelet count without association to bleeding were also observed in some patients with NPC disease treated with Zavesca. However, there was no indication of progressive platelet count reduction over time or in patients on long-term treatment. A caution related this effect was noted in the Precautions section of the draft Product Information.

Immunotoxicity

In the studies conducted for effects of miglustat on lymphoid tissue and on immune function, there were no significant effects on lymphocyte subsets in blood or spleen of mice (miglustat 90-900 mg/kg/day intraperitoneally (IP) for 10 days), rats (prodrug 300-1200 mg/kg/day orally for 26 weeks: ER about 2-8 on a BSA basis), or cynomolgus monkeys (60-600 mg/kg/day miglustat IV for 4 weeks).

Other toxicities

There were also treatment-related other effects in various organs and/or tissues. Reductions in red blood cell parameters were observed in rats, dogs and rhesus monkeys treated (gavage) with miglustat, and this effect might be associated with blood loss in the GIT. The aspartate transaminase (AST) and/or alanine transaminase (ALT) values were elevated in all species investigated, but there was little evidence of an effect of miglustat on the liver. Other tissues/organs affected included the mammary gland (active secretion and galactocoele), heart (cardiomyopathy, inflammation), bone marrow (hypocellularity), thyroid (follicular cell vacuolation), eyes (cataracts), pancreas (acinar cell vacuolation, reduced zymogen granules and/or staining) and kidney (mainly mineralisation) in some studies. However, the findings in these organs were either not observed consistently across studies and/or species or were only observed at high doses. Detailed information can be found in relevant sections of the original evaluation report.

Genotoxicity

Miglustat is a relatively simple iminosugar and there was no indication of genotoxic potential for either miglustat or its perbutylated pro-drug (OGT 924) in a range of standard tests *in vitro* and *in vivo*.

Carcinogenicity

GIT tumours

In the 2 year mouse carcinogenicity study testing with miglustat at doses of 210, 420 and 840/500 mg/kg/day orally (gavage), there were dose-related increases in the incidences of combined benign (adenoma) and malignant (adenocarcinoma) neoplasia in the large intestine (that is, caecum, colon and rectum) of animals for both sexes. The incidences were higher in males than in females. For all treatment groups and sexes combined, incidences of adenocarcinoma were higher than incidences of adenoma (2.7-8.2% and 0.3-5.1%, respectively, in the combined initial and final study reports), and the tumours were associated with inflammatory or ulcerative lesions. In this study, no NOEL was established. At the lowest dose of 210 mg/kg/day tested, the ERs are 2 and 18 based on AUC (for systemic effect) and mg/kg (for local effect), respectively.

Since miglustat is not genotoxic and GIT tumours are localised and associated with inflammatory or ulcerative lesions, the sponsor has argued that the development of the neoplastic lesions in the mouse was probably associated with 'lifelong persistence' of ulcerations/inflammatory lesions and associated regenerative cell proliferation. While such a mechanism is plausible, the exact mechanism of tumour induction is not known without mechanistic studies.

The intestinal tumours seen in mice above were not observed in the rat 2 year carcinogenicity study tested up to 180 mg/kg/day (ERs 2 and 15 based on AUC and mg/kg, respectively). In this species, although the GI intolerance included mainly soft and watery stools, they were not particularly susceptible to GIT inflammation/lesions. In dogs and rhesus monkeys, GIT inflammation/lesions were observed following oral administration of miglustat. Further, miglustat is associated with GI intolerance, such as diarrhoea in patients, indicating that humans are also susceptible to at least some GI effects of miglustat. Therefore, the intestinal carcinogenic risk in humans following long-term treatment with miglustat cannot be discounted, based on a number of reasons. These include:

i) the presence of a drug-related carcinogenic effect in the large intestine of the mouse, with no NOEL established,
ii) no mechanistic data available for the tumours which indicate that mice, but not humans, are susceptible to intestinal tumours,
iii) the fact that humans are sensitive to the GI effects of miglustat and large intestinal carcinogenicity is common in humans, and
iv) some difficulty in determining the 'correct' metric for calculation of exposure ratio and no certainty as to whether the effect is a local one, therefore no accurate estimate of exposure ratio. If miglustat is registered for the new indication at the higher dose, any inflammatory bowel disease in patients should be closely monitored.

Testicular tumours

In the rat carcinogenicity study, a treatment-related carcinogenic response was observed in the male testes. The total incidence of interstitial cell adenomas (Leydig cell tumours) was 2.0%, 18.0%, 18.4%, and 20.0% at dose levels 0, 30, 60 and 180 mg/kg/day respectively. A NOEL was not established and the ER at 30 mg/kg/day was 0.4 based on AUC. It is important to note that in repeat dose toxicity studies, testicular tubular atrophy and spermatogenic arrest/aspermatogenesis were seen in male rats. Testicular tumours were not seen in the mouse carcinogenicity study.

In consideration of Leydig cell hyperplasia and adenomas in male rats commonly produced by treatments which modify luteinising hormone (LH) secretion, reductions in testosterone levels and associated increases in LH levels might be expected. However, miglustat (up to 1 mM) had no effect on testosterone production in isolated or cultured rat Leydig cells *in vitro*. Therefore, the sponsor has argued that an indirect mechanism, through a disrupted hypothalamus-pituitary-testes hormonal axis, could also lead to reductions in testosterone levels. However, the mechanism of the tumour induction is not known, since no mechanistic studies were conducted for this tumour.

Although the exposure ratios were low (no NOEL and LOEL at ER < 1) and the underlying mechanism has not been elucidated, it is unlikely that these tumours are of clinical relevance, due to a number of reasons including the non-genotoxic property of miglustat, benign tumours, no evidence of Leydig cell tumours in mice (ER up to 3), and the fact that this is a rare tumour in humans.

Other tumours

In the mouse carcinogenicity study, there were also dose-related but weak signals for malignant fibrous haemangiosarcoma of the skin and granulocytic leukaemia in males, The incidences were 4% at 840/500 mg/kg/day (ER 4 on a BSA basis) for each finding. However, these findings are deemed to be of equivocal toxicological significance, in consideration of inconsistent findings across genders and non-genotoxic property of miglustat.

Reproductive toxicity

Males

The male reproductive tract was a significant target for miglustat in the rat repeated dose toxicity studies, showing various effects on rat sperm with no NOEL. Nevertheless miglustat had no effect on mating and only a small effect on fertility at doses of up to 180 mg/kg/day orally (ER 3 based on AUC) when administered from 2-10 weeks prior to mating to during mating. In the male fertility study, there was only a small effect on live fetuses/litter with an increase in pre-implantation loss, possibly associated with an increase in the number of unfertilised eggs. There was no evidence that the abnormal sperm resulted in abnormalities in fetuses/pups but no studies were conducted to confirm this. The caution that "*Male patients should maintain reliable contraceptive methods whilst taking Zavesca and for 3 months thereafter.*" was included in the 'Male fertility' section of the draft Product Information, and is appropriate.

The above observations were confirmed by two published papers reporting studies on mouse sperm. In these papers, it was reported that the treatment (oral) with miglustat resulted in changes in the morphology of mouse spermatozoa (NOEL at 1 mg/kg/day: ER < 1 based on AUC) (Van der Spoel *et al*., 2002) and lower motility unable to enter or activate oocytes, but unaltered genetic integrity for offspring (Suganuma *et al*., 2005).

Females – rat

Fertility was also affected in female rats following oral administration of miglustat. Increased resorptions/post-implantation loss with a subsequent reduction in fetuses or pups/litter was a consistent finding in rats dosed over the period of organogenesis (prior to mating to early gestation or early gestation period) at doses of ≥ 60 mg/kg/day orally (ER 1 based on AUC). The dose of 300 mg/kg/day orally was associated with increases in resorptions and reductions in live fetuses/dam. All fetuses died at a maternal dose of ≥ 1200 mg/kg/day. Implantation was only affected at very high doses (that is 2400 mg/kg/day). In general, the doses at which there were increases in post-implantation loss were maternotoxic as evidenced by a decrease in body weight/body weight gain of dams, an exception being 60 mg/kg/day in the female fertility study.

An increase in gestation length was observed at doses ≥ 60 mg/kg/day (ER 1 based on AUC) and fetal/pup weights were reduced at a dose of 180 mg/kg/day orally (ER 3) in a fertility/embryofetal developmental study (dosing from prior to mating until 5 weeks after) and in the pre-postnatal development study (dosing from Day 6 of gestation to Day 20 post-partum), respectively. The dose of 180 mg/kg/day was maternotoxic in both studies. At this dose, dystocia was observed in 2/24 females (incidence < 10%) that littered in the pre-postnatal study. These effects may be clinically relevant. In addition, the pre-postnatal study in rats revealed a reduction in survival index at doses of 60 and 180 mg/kg/day (87% and 71%, respectively, compared with 94% in the control group). The latter dose was maternotoxic and associated with a significant reduction in pup birth weight, while food consumption of dams was significantly reduced at the former dose over days 7 to 14 post-partum.

In spite of the incidences above, there were no teratogenic effects (external, visceral and skeletal) on fetuses in the female fertility study and pre-postnatal study. There were increased incidences of non-ossified or incompletely ossified bones at all doses (20, 60 and 180 mg/kg/day), especially at HD; fewer bones were affected at MD and LD. At HD, the findings are consistent with a reduction in fetal weights and maternal toxicity as evidenced by a decrease in maternal body weight/body weight gain. In the pre-postnatal study, there was a

slight increase in the incidence of ‘innominate artery absent’ (5.4% compared with 1.8% in controls) at the HD (180 mg/kg/day) and this was consistent with the increased incidence of cardiovascular variations observed in rabbits.

Females – rabbit

As in rats, miglustat was fetotoxic in rabbits, causing an increase in resorptions/post-implantation loss and consequent reduction in fetuses/doe at doses of ≥ 45 mg/kg/day orally. Two embryofetal development studies were conducted in rabbits (doses of 15-45 and 3-30 mg/kg/day orally for dosing duration of Days 6-18 of gestation) with consistent findings of increases in fetal blood vessel variations: additional blood vessel arising from the aortic arch, left subclavian branching variation and/or 'brachiocephalic missing'. In both studies, reductions in ossification/non-ossification of some bones were also observed, resulting in a NOEL of 10 mg/kg/day. All doses were maternotoxic (reduced maternal body weight gain). Although there were no toxicokinetic data available for rabbits, the ER at 10 mg/kg/day is estimated to be < 1 based on BSA.

In relation to the reproductive toxicity of miglustat, a caution stating that "Zavesca *should not be used during pregnancy. Effective contraceptive measures should be used by women of childbearing potential.*" was included in the 'Use of Pregnancy' section of the draft Product Information. This is considered appropriate.

Paediatric use

Very limited nonclinical data was provided to support the extended indication to the paediatric population. There was only one repeat dose toxicity study conducted in juvenile rats following oral (gavage) administration of miglustat from Day 12 post-partum to Day 70 of age (necropsy on Days 21, 35 and 70 of age) with a 10 week recovery period. The dose levels tested were 0, 20, 60 and 180 mg/kg/day. In this toxicity study, the mean group bodyweight gain and food consumption were reduced in all dose groups during treatment. These effects were also observed in adult rat repeat dose studies. However, there were no differences in the food consumption in the treated groups (male and female) at the end of dosing on Day 70. Distended abdomens were recorded in a majority of animals at the HD from Day 37, which may indicate a GIT effect similar to that observed in adults.

Miglustat had no effects on eyes at any doses in the ophthalmoscopy examination. At these doses, locomotor activity, learning, righting reflex and behaviour were not affected in the behavioral and functional tests. However, treatment-related increases in the absolute number of circulating leukocytes, specifically the numbers of lymphocytes (27-37%) and monocytes (30-66%) were observed in both males and females receiving 60 or 180 mg/kg/day when sampled on Day 70. The clinical chemistry changes that were attributed to drug treatment were observed in serum alkaline phosphatase (ALP), glucose, triglyceride, calcium, potassium, sodium and albumin, mostly in the MD and HD groups of both males and females. However, cholesterol and globulin changes were seen mainly in females from all treated dose groups. The changes ranged from -13% to +50% (compared to control values), except for triglyceride in female HD (+109%).

For organ weights, liver weight (relative to body weight) was increased in a dose-related manner in both males up to 14% at HD and females up to 28% at HD on Day 70. The changes in other organ weights might not be directly related to treatment but could be due to the lower body weight in treated groups. The changes in the organ weight during the treatment were reversible.

In the histopathology observation, there was an increased incidence of basophilic cortical tubules in the kidneys of treated males on Days 35 and 70, suggestive of early tubular changes. However, these findings were mainly minimal to slight in nature and also reversible, and were therefore toxicologically insignificant. There were no other treatment-related findings.

For sexual development, there was a delay in the day of balanopreputial separation for males and vaginal perforation for females in all test groups. Nevertheless, no treatment-related effects were observed in the number of offspring born per litter and subsequent litter survival. Physical development of the offspring from all treated groups was unaffected. In the male reproductive system, there were significant reductions in the sperm concentration and homogenization resistant spermatid counts, and increases in abnormal sperm (headless sperm or sperm with reduced hook) at all dose levels (no NOEL). The ER at the lowest dose (20 mg/kg/day orally) tested is considered to be about 0.3 based on BSA.[2] However, the incidences of abnormal sperm were reversible after the recovery period, although 'miscellaneous abnormalities' were not reversed. As discussed previously, the reductions in the sperm concentration and increases in the abnormal sperm were also seen in young (3-4 months of age) and adult rats in the repeat dose toxicity studies above.

In summary, administration of miglustat to juvenile rats elicited toxicity at dose levels from 20 mg/kg/day (ER < 1), with no NOEL established. The toxicities of miglustat observed in juvenile rats were also seen in older rats and therefore there were no toxicities specific for juvenile rats.

Local tolerance

The mouse ear swelling test showed that miglustat did not cause sensitisation at concentrations up to 30%. A Draize test using rabbits showed that miglustat was mildly irritating to skin with application of 250 mg in 0.25 mL aqueous solution.

Nonclinical Summary and Conclusions

Gastrointestinal (GI) effects, including soft stools/diarrhoea and GI inflammation/lesions, were a major toxicity of miglustat, which were observed in all species tested (the lowest ER for NOEL: 8, 5, < 2 and < 14 for mouse, rat, dog and monkey, respectively) and were associated with reduced food consumption and body weight gain. GI events (i.e. diarrhoea) and weight loss were also observed in the juvenile and adult populations in clinical studies.

The male reproductive tract was a target organ following repeat dose administration in rats. The reversible changes included, but were not limited to, testicular or seminiferous tubular atrophy, arrested spermatogenesis and epididymal hypospermia. An increase in abnormal sperm, decrease in sperm concentration and reduction in sperm motility were also observed. No NOEL was established (the lowest dose tested: ER 0.4 on an AUC basis).

In carcinogenicity studies, there was a dose-related increase in the incidence of large intestinal hyperplasia and tumours (adenomas and adenocarcinomas) in mice (no NOEL established and ERs *ca* 2 and 18 for LOEL based on AUC and mg/kg, respectively), but not in rats. These tumours might be relevant to humans, since they were associated with GI inflammation/lesions and humans are sensitive to the GI effects of miglustat. In rats, a treatment-related increase in the incidence of interstitial (Leydig) cell adenomas was observed (no NOEL and ER < 1 for LOEL based on AUC), associated with testicular tubular atrophy. However, given their benign nature, absence in mice, and rare occurrence in humans, the Leydig cell adenomas in rats are unlikely to be of clinical relevance.

[2] The BSA-based ER in juvenile rats was calculated based on a conversion factor (from mg/kg to mg/m^2) of 3 for 20 mg/kg in 20-35 g BW rats on Day 12 post-partum and the clinical dose for the minimum BSA (100 mg/day for 0.47 m^2) recommended in the draft Product Information [(3 x 20)/(100/0.47) = 0.3].

Oral administration of miglustat induced reproductive toxicity in rats and rabbits. In rats, post-implantation loss, increased gestation length, decreases in pup survival and fetal body weight, and dystocia were seen at doses of ER 1-3 (on an AUC basis). In rabbits, there were increases in post-implantation loss and fetal blood vessel abnormalities at doses of ER ≤ 2.

Miglustat has been registered for 2 years in Australia for the treatment of Gaucher disease and has Orphan Drug designation for treatment of NPC disease. The main toxicity issue, previously identified and described, is treatment-related GI lesions/carcinogenicity in mice (inflammatory lesions, hyperplasia, adenomas, adenocarcinomas). Should the product be registered for the NPC indication, it should be noted that the previously-accepted safety margins for these lesions are halved by the higher dose proposed for the new indication, a no-effect dose level was not determined, and relevance to humans has not been discounted by the experimental data. This carcinogenicity occurred in the presence of an inflammatory effect in the mouse large intestine, so it may be prudent to provide relevant cautionary advice in the event that inflammatory bowel disease develops in patients. Other nonclinical toxicity issues are addressed in the PI (male fertility, female reproduction, delayed clotting times and sexual maturation). Further information on the clinical safety of miglustat may be available from post-registration data, since the drug was approved for the treatment of NPC disease in EU in January 2009, and has been registered for up to 6 years in Australia, USA and EU for the treatment of Gaucher disease. Limited nonclinical data suggest that the toxicity of miglustat in the paediatric population is expected to be similar to that in adults.

IV. Clinical Findings

Introduction

The submission essentially comprised a single study in NPC - OGT 918-007; a 12 month randomised, standard care controlled, open-label study of efficacy and safety that was followed by a prospective, non-controlled 12 month extension period, after which there was a further extension going out to 42 months from the start. As part of Study OGT 918-007 there was a pharmacokinetic (PK) analysis and a non-controlled paediatric sub-study.

Also in the submission were studies of miglustat used in other disorders; study: OGT 918-006 in Gaucher disease and OGT 918-009 in G_{M2} Gangliosidosis.

A schematic diagram for the study, OGT 918-007, is shown on the following page.

Pharmacokinetics

There were pharmacokinetic (PK) studies associated with studies OGT 918-007, OGT 918-006 and OGT 918-009.

The results from study OGT 918-007 were used to calculate the PK parameters shown in Table 4.

Table 4: PK parameters study OGT 918-007 (NPC).

Parameters - geometric mean (coefficient of variation)	Age > 12y Range 12-39y	Age < 12y Range 5-11y		
	200 mg tds N = 6	200 mg tds N = 1	200 mg TDS N = 2	200mg am + 100mg pm N = 1
AUC_{0-8h} (ng.h/mL)	16412 (19.5)	11975 (NA)	18792 (13.9)	15866 (NA)
C_{max} (ng/mL)	2698 (22.9)	2075 (NA)	3289 (9.03)	2223 (NA)

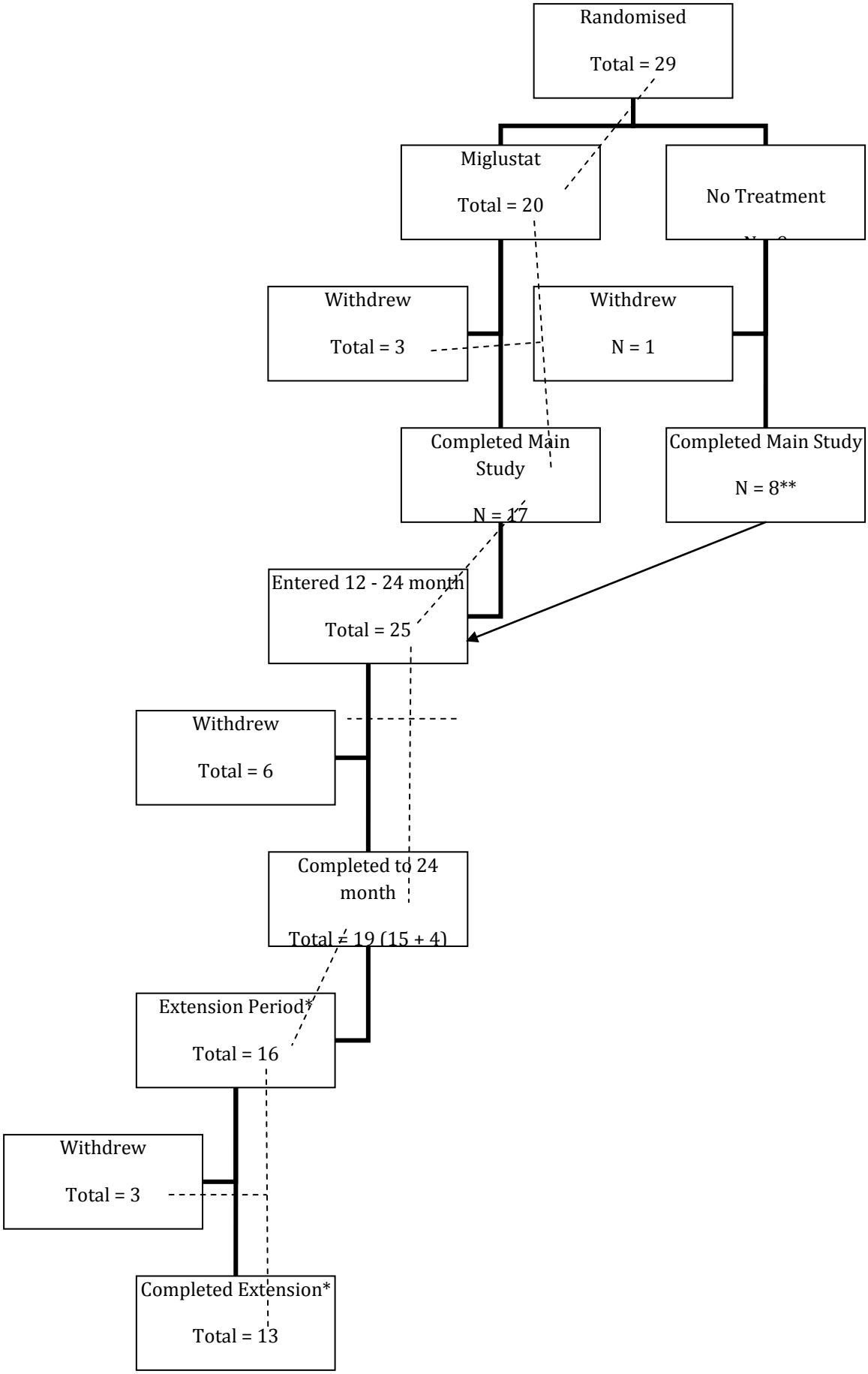
C_{trough} (ng/mL)	1427 (18.3)	962	NA	NA
t_{max} - median (h) (range)	3.00 (0.750-4.00)	4.00 (NA)	3.54 (3.08-4.00)	4.00 (NA)

Absorption

T_{max} (median) was approximately 3-4 hours for all groups. There appeared to be a lag time in absorption of approx 0.75 hours especially when the outlier 104 was ignored.

Distribution

The composite (mean) plasma concentration/time curves from study 007 can be seen in Table 5.


Randomised
Total = 29
Miglustat
Total = 20
No Treatment
Withdrew
Total = 3
Withdrew
N = 1
Completed Main Study
N = 17
Completed Main Study
N = 8**
Entered 12 - 24 month
Total = 25
Withdrew
Total = 6
Completed to 24 month
Total = 19 (15 + 4)
Extension Period*
Total = 16
Withdrew
Total = 3
Completed Extension*
Total = 13

Multiple dose kinetics

In patients on 200mg tds C_{trough} was approximately half $C_{max,}$ that is, accumulation occurred. While the ranges for individual plasma concentrations were given, the time sequence of concentrations was not, so that the extent of accumulation could not be assessed, however on the basis of similarity of mean pre-dose and 8 hour concentrations it was claimed steady state was achieved.

Excretion

In Study 007 the apparent terminal half-life could not be estimated because the blood sampling scheme did not extend beyond the dosing interval of 8 hours. That is, the terminal phase was not well characterised in this study.

Pharmacokinetics in special populations

Effect of age

The doses for < 12 years of age were calculated on the basis of an adjustment for body surface area (BSA) so that relation to age is not readily apparent except to say that results for 200 mg tds suggest a slower absorption with children and with lower T_{max} and AUC.

Patients with N-C

Absorption was slower than for 100 mg in healthy volunteers (t_{max} 2.5 hours vs. 3-4 hours in study 014). No data on repeated dosing in volunteers.

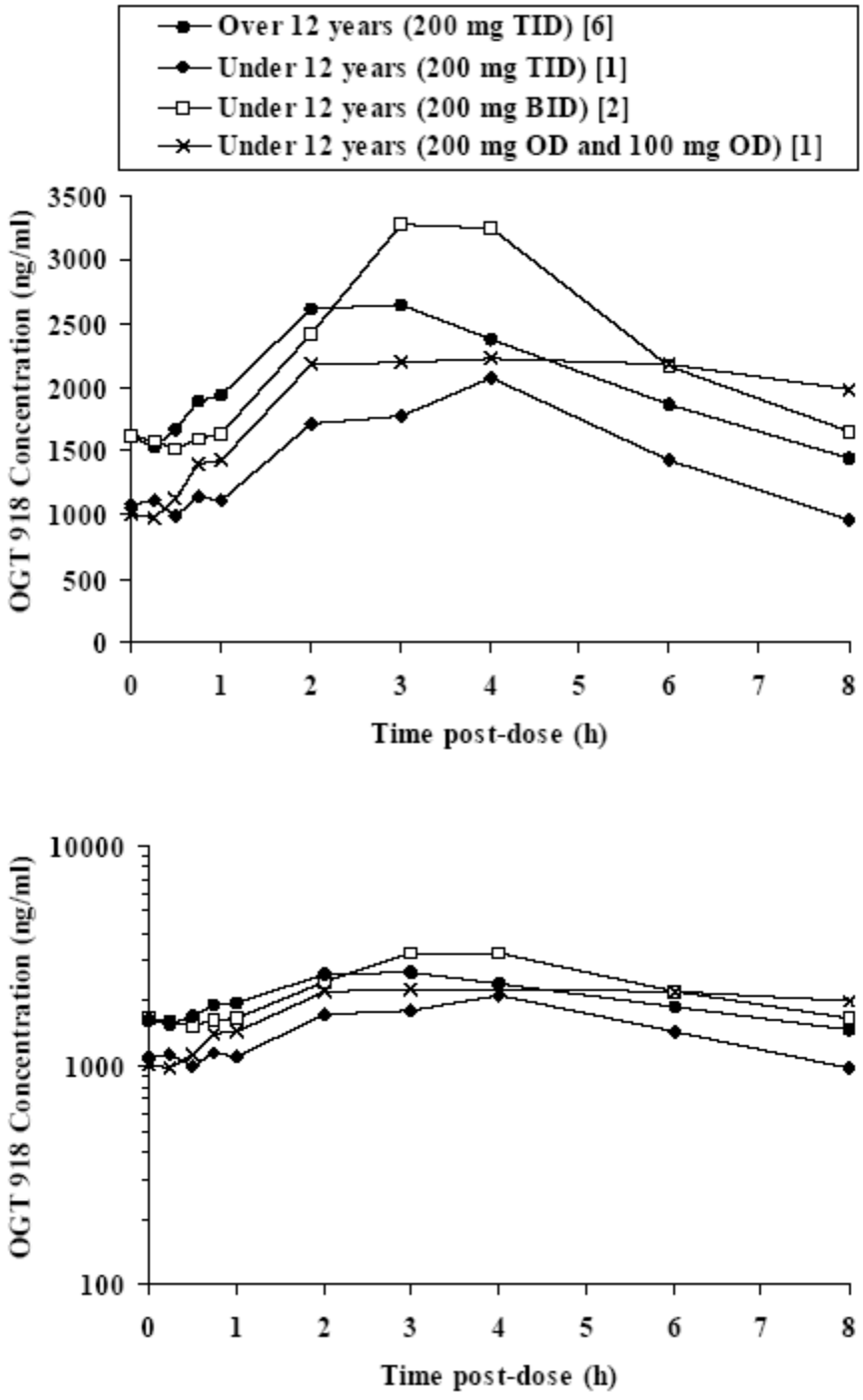
Other special populations

While patients with G_{M2} Gangliosidosis had only slightly higher C_{max} and AUC, with T_{max} faster, on 200mg tds compared to NPC results, patients with Neuronopathic Gaucher Disease had C_{max} almost double and AUC 1.5 times that of NPC, with a T_{max} of 2.0 hours. Concentrations of miglustat in CSF were approximately 37 % to 42 % (>12 years) and 31 % to 67 % (<12 years) of that in plasma for Gaucher patients, while they were approximately 46 % and 29 % that seen in plasma for with G_{M2} Gangliosidosis.

Summary

The variation in PKs across disease states and in healthy volunteers in part may reflect the small numbers involved and the lack of repeated dosing PKs in volunteers. There have been previous discussions on bioavailability and the lack of a specific study.

Table 5: Mean plasma concentrations of miglustat vs. time following repeated oral administration of miglustat to patients aged over and under 12 years.



[n] = Number of patients included in arithmetic mean.

Pharmacodynamics

There were no new data submitted in the application.

Efficacy

Pivotal study OGT 918-007 was a 12 month randomised, standard care controlled, open-label study of efficacy and safety, which was followed by a prospective, non-controlled 12 month extension period, after which there was a further extension going out to 42 months from the start. As part of Study OGT 918-007 there was a PK analysis (see above) and a non-controlled, paediatric sub-study. The initial 12 months of study was referred to as the Main Study.

The primary objective was:

To evaluate miglustat as a treatment for NPC by assessing changes in saccadic eye movement[3] velocity (SEMV) and other markers of the disease. The measurement of saccadic eye movement was selected because supranuclear gaze palsy (saccadic initiation failure) is often the earliest neurological sign in NPC and because saccadic eye movement failure is associated with definite visual, learning and social handicap. Horizontal saccadic eye movement (HSEM) was considered to have the greatest potential for improvement with miglustat treatment, although less affected than vertical supranuclear gaze palsy.

The secondary objectives were to assess the clinical safety and tolerability of miglustat therapy with particular regard to any changes in the neurological assessments.

Inclusion criteria were:

- Patients ≥ 12 years were included in the main study, with < 12 years old treated as a paediatric sub-group.
- Patients with NPC confirmed by abnormal cholesterol esterification and filipin staining.
- Patients who could ingest a capsule.

Exclusion criteria were:

- Patients currently undergoing therapy with other investigational agents or patients taking drugs or food supplements that could interfere with gastrointestinal absorption or motility.
- Patients suffering from clinically significant diarrhoea (more than three liquid stools per day for > 7 days) without definable cause within 3 months of the screening visit, or with a history of significant gastrointestinal disorders.
- Patients with an intercurrent medical condition that would render them unsuitable for the study, for example, human immunodeficiency virus (HIV), hepatitis infection.
- Patients with an adjusted creatinine clearance < 70 ml/min/1.73m^2 (creatinine clearance < 70).

This randomised, controlled study in adults and juveniles with NPC compared treatment with miglustat versus no treatment in adults and juveniles with NPC. A placebo control group was not chosen because:

- Of the association of diarrhoea with miglustat, placebo would not achieve blinding.
- Since patients with NPC have swallowing difficulties, it was considered unethical to administer placebo for a continuous 12-month period with no potential benefit.

[3] The amplitude and velocity characteristics for saccadic data from each patient were plotted using MATLAB/REX or associated software. The outcome data comprised a graph of saccadic peak duration (amplitude/peak velocity) versus saccade amplitude, with a linear regression fitted to these data points. The slope (α, ms/deg) and intercept (β, ms) of the regression line were estimated using ordinary least squares. A four degree (4°) threshold for the amplitude was implemented in order to calculate the α and β, since the regression is not considered linear below this 4° threshold.

Thus there was a No Treatment control group that received the standard clinical care that would normally have been available. Outcomes were assessed blindly.

The highest well-tolerated dose in previous clinical studies in patients with the type 1 Gaucher disease, that is, 200mg tds was selected as the initial dose. If a patient had an adverse event (AE) that was considered to be treatment-related, the dose was reduced to 200mg twice daily (bd), and could be further reduced if AEs continued. Loperamide could be added for diarrhoea.[4]

There were numerous protocol amendments - most after the study started - but with no impact on the primary variables except for the 18 April 2005 decision that was made to retain HSEM-α as primary endpoint and downgrade HSEM-β to a secondary endpoint. The sample size could not be justified statistically, but based on data from Gaucher disease 30 patients were expected to provide adequate power to detect a meaningful change in vertical saccadic α between treatments

The **primary efficacy endpoint,** HSEM-α (baseline to Month 12) was considered to have a more straightforward and clinically meaningful interpretation, and was expected to be less variable than HSEM-β. Horizontal-Left and Horizontal-Right saccadic eye movement was to be combined for the analysis, with only one eye being selected.[5] Eye movement was assessed by different methods in each centre - an infrared system was used in one centre while a scleral search coil was used in the other centre.

As well as a PK analysis and haemoglobin and platelets (see Safety), there were multiple secondary efficacy endpoints including:

1. At baseline, Month 12 and last value:

- Horizontal saccadic β.
- Vertical saccadic parameters.
- Swallowing ability (also at Month 6).
- Liver and spleen organ volumes.
- Cerebellar volume.

2. At baseline, Months 3, 6, 9, 12, and last value:

[4] In type 1 Gaucher disease studies indicated that the GI AEs were not dose dependent and were largely self-limiting (in 50 mg to 200 mg tds doses). The data suggested that incremental increases in dose could transiently exacerbate GI AEs, so an initial 200 mg tds with no dose increase was planned.

[5] For each patient, the duration at peak velocity (Dp) can be related to amplitude (A) using the following linear equation

$$Dp = \beta + \alpha A$$

This equates to $Vp = 1/(\alpha + \beta/A)$, where Vp is peak saccadic eye velocity, and is derived from amplitude and duration ($Vp = A/Dp$). According to this model, Vp saturates as A approaches infinity with a maximum value of $1/\alpha$ (deg/ms), and decreases (to 0) as A approaches 0 with slope $1/\beta$ (1/ms). Note that the estimates of the parameters α and β are negatively correlated and are therefore not independent. As such, α was selected as primary efficacy endpoint, while β is a secondary endpoint. A four degree (4°) threshold was implemented on the amplitude in order to calculate the α and β, since the regression is not considered linear below this 4° threshold (i.e. values of < 4° were not used to calculate the α and β). All the regression results were flipped to the first quadrant such that a reduction in α and β represented an improvement.

- Neurological examination tests. (Gait Examination, Standard Ambulation Index Value, reflex assessments, muscle assessments were assessed for bulk, tone and power, auditory and visual acuity examination, Snellen test).
- Neuropsychological tests (Purdue Peg Board Test and the mini-mental state examination (MMSE)).
- Tremor (Archimedes spiral score for spirals 1 and 2).
- Chitotriosidase activity.
- Quality of life. (CHQ-PF50 questionnaire [patients ≤ 13y] domains Global Health, Physical Functioning, Role/Social Limitations-Emotional/Behavioural, Role/Social Limitations-Physical, Bodily Pain/Discomfort, Behaviour, Global Behaviour Item, Mental Health, Self-Esteem, General Health Perceptions, Change in Health, Parental Impact-Emotional, Parental Impact-Time, Family Activities and Family Cohesion and summary scores Physical Summary and Psychosocial Summary or SF-36 questionnaire[≥ 13y] domains Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health and summary scores Physical Component Summary and Mental Component Summary).

All hypothesis tests were 2-sided superiority hypothesis tests undertaken at the 5% significance level. Confidence intervals (CIs) were 2-sided with 95% coverage. For continuous endpoints, ANCOVA was used in order to detect a difference between the treatment groups. In general, the model was to include terms for baseline and treatment group. For each ANCOVA model, the data were investigated to determine whether the distributions were unimodal and not highly skewed. If the data were not normally distributed, then the data were ranked prior to performing the ANCOVA. Both the main analysis of the primary efficacy variable, and all analyses on secondary and exploratory efficacy variables, were based on the efficacy set.[6]

20 patients received miglustat and 9 no treatment. There was no accurate assessment of treatment compliance. The means and ranges of the demographics were reasonably evenly distributed except that the no treatment group contained a higher percentage (44% vs. 25%) of juveniles. The sponsor suggests this may account for the generally greater incidence in NPC complications seen at baseline in the treatment group (with more adults).

Primary efficacy results

Two patients on miglustat and one on no treatment had no post baseline observations and one patient had assessment on withdrawal but not at month 12.

There were no statistically significant differences between the miglustat and the no treatment groups, nor could an effect by centre be shown. However excluding 6 patients from the miglustat group and 1 on no treatment who were taking benzodiazepines produced a p-value = 0.028. It was argued that since fatigue can slow saccades, the sedative effects could have confounded the results.

A qualitative examination of the main sequence scatter plots and visual comparison of the regression slopes for the plots of saccades from 26 patients who provided useable data at both baseline and Month 12 (or last visit) showed in the miglustat group, 15/19 patients (79%) were stable or improved (7 improved, 8 with no change), 2 deteriorated, and 2 had ambiguous results, while in the no treatment group, 2/7 patients (29%) were stable or improved (1

[6] **Efficacy set**: Those patients who received at least one dose of study drug and who had at least one post-baseline efficacy assessment for the given parameter.

improved, 1 with no change), 3 deteriorated, and 2 had ambiguous results. Results are presented in tables 6-9.

Table 6: Summary of actual values and changes from baseline for HSEM-α (ms/deg) (efficacy set, Main Study Juveniles/Adults)

	Miglustat(N = 20)				No Treatment (N = 9)			
	N	Baseline value (SD)	Actual value (SD)	Change from Baseline (SD)	N	Baseline value (SD)	Actual value (SD)	Change from Baseline (SD)
Month 12	17	2.976 (2.225)	2.587 (1.634)	−0.389 (0.950)	8	2.483 (1.425)	2.558 (1.734)	0.074 (0.823)
Last value	18	3.021 (2.167)	2.590 (1.585)	−0.431 (0.938)	8	2.483 (1.425)	2.558 (1.734)	0.074 (0.823)

Table 7: Analysis of change from baseline in HSEM-α (efficacy set Main Study Juveniles/Adults)

Parameter		Adjusted mean change from baseline		Estimated treatment difference	95% CI	p-value
		Miglustat	No Treatment			
Horizontal saccadic-α (ms/deg)	Month 12	–0.329	–0.055	–0.274	(–0.959, 0.411)	0.414
	Last value	–0.376	–0.050	–0.326	(–1.000, 0.348)	0.327

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Table 8: Change from baseline in HSEM-α including centre in the model (Exploratory analysis, efficacy set Main Study Juveniles/Adults)

Parameter		Adjusted mean change from baseline		Estimated treatment difference	95% CI	p-value
		Miglustat	No Treatment			
Horizontal saccadic-α (ms/deg)	Month 12	–0.450	0.066	−0.515	(–1.149,0.118)	0.105
	Last value	–0.463	0.055	−0.518	(–1.125,0.089)	0.091

Table 9: Change from baseline in HSEM-α excluding benzodiazepine taking patients (Exploratory analysis efficacy set Main Study Juveniles/Adults)

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Parameter		Adjusted mean change from baseline		Estimated treatment difference	95% CI	p-value
		Miglustat	No Treatment			
Horizontal saccadic-α (ms/deg)	Month 12	–0.485	0.234	–0.718	–1.349,–0.088	0.028
	Last value	–0.485	0.234	–0.718	–1.349,–0.088	0.028

6 patients on miglustat and 1 on No Treatment received benzodiazepines during the study) and were excluded from this analysis.

The ANCOVA model used for all analyses includes terms for baseline, centre and treatment group.

Secondary and post-hoc efficacy outcomes

At baseline, Month 12 and last value:

- Only 2 patients had Vertical saccadic parameters measured (due to the severity of the disease).
- Swallowing ability – all patients could swallow all foodstuffs. No significant differences between treatments in improvement or deterioration.
- Cerebellar volumes were only assessed at 1 centre.

At baseline, Months 3, 6, 9, 12, and last value:

- Neurological examination tests. Of the parameters assessed - olfaction, light touch, vibratory sense, temperature, pharyngeal sensation, pharyngeal gag, sternocleidomastoid muscles, trapezius muscles, tongue muscles and plantar reflex- only the tongue muscles showed a statistically significant difference between the groups (5% on miglustat vs. 33% on No Treatment p = 0.023; Fisher's Exact test).
- Gait Examination showed very little change.

- Auditory acuity showed decreased abnormalities for miglustat and increased for No Treatment, the groups showed similar changes in the Snellen test from baseline to last value.
- Neuropsychological tests (Purdue Peg Board Test and the Mini Mental State Examination (MMSE) - the latter showed a trend in favour of miglustat) (Table 10)

Table 10: Summary of mean change for Purdue Peg Board & MMSE neuropsychological assessments (efficacy set Main Study Juveniles/Adults) baseline to last value

Parameter	Miglustat(N = 20)				No Treatment (N = 9)			
	N	Baseline value (SD)	Last value (SD)	Change from Baseline (SD)	N	Baseline value (SD)	Last value (SD)	Change from Baseline (SD)
Purdue Peg Board (Total Score)[a]	19	16.7 (9.4)	15.1 (6.8)	1.7 (5.9)	9	21.8 (12.2)	21.9 (14.7)	0.1 (3.8)
MMSE (Total Score)[b]	19	22.8 (5.2)	24.0 (5.6)	1.2 (2.5)	9	23.4 (4.9)	23.1 (5.7)	–0.3 (2.8)

[a] A higher score indicates better dexterity. Total Score is the sum of the standard scores for dominant hand, non-dominant hand and both hands.
[b] A higher score indicates better mental status; a total score of 24 or above is considered normal.

- Tremor (Archimedes spiral score for spirals 1 and 2) – no significant difference
- Quality of life (CHQ-PF50 questionnaire) - showed a trend in favour of miglustat (Table 11)

Table 11: Summary of mean change for SF-36 Quality of Life questionnaire (efficacy set Main Study Juveniles/Adults) from baseline to last value

Domain[a]	Miglustat(N = 20)				No Treatment (N = 9)				p-value*
	N	Baseline value (SD)	Last value (SD)	Change from Baseline (SD)	N	Baseline value (SD)	Last value (SD)	Change from Baseline (SD)	
Physical functioning	17	60.3 (34.5)	57.4 (35.4)	–2.9 (31.1)	8	81.3 (24.6)	83.8 (20.0)	2.5 (20.0)	0.255
Role-physical	17	75.0 (35.4)	67.2 (40.2)	–7.8 (43.7)	8	87.5 (26.7)	75.0 (40.1)	–12.5 (35.4)	0.965
Bodily pain	17	77.7 (23.1)	84.4 (20.7)	6.7 (15.4)	8	90.0 (17.0)	83.4 (20.0)	–6.6 (21.9)	0.268
General health	17	53.7 (26.4)	63.1 (25.3)	9.4 (18.1)	7	71.7 (19.5)	69.1 (10.3)	–2.6 (15.1)	0.478
Vitality	17	54.4 (25.7)	53.5 (19.8)	–0.9 (21.4)	8	62.5 (16.5)	61.0 (18.8)	–1.5 (14.6)	0.535
Social functioning	17	76.5 (27.9)	77.9 (24.0)	1.5 (26.5)	8	89.1 (14.1)	82.8 (17.6)	–6.3 (23.2)	0.911
Role-emotional	17	74.5 (36.4)	66.7 (47.1)	–7.8 (61.8)	8	75.0 (38.8)	95.8 (11.8)	20.8 (39.6)	0.125
Mental health	17	66.4 (22.8)	70.8 (15.9)	4.4 (21.1)	8	80.5 (12.6)	77.5 (13.7)	–3.0 (15.1)	0.781
Physical component	17	44.0 (11.2)	44.7 (11.0)	0.6 (6.0)	7	51.2 (6.5)	47.6 (9.1)	–3.6 (6.4)	0.292
Mental component	17	48.1 (12.7)	48.5 (9.5)	0.5 (12.4)	7	49.9 (7.2)	52.4 (6.8)	2.5 (8.6)	0.396

[a] Scores are expressed on a scale of 0 to 100, where higher scores indicate better health and well-being.

*The ANCOVA model used for all analyses included terms for baseline, centre and treatment group.

Other secondary variables are tabulated in Table 12.

Table 12: Tabulation of some secondary variables

Parameter		Adjusted mean change from baseline		Estimated treatment difference	Ratio[a]	95% CI	p-value
		Miglustat	No Treatment				
Horizontal saccadic-β (ms)	Month 12	1.714	2.747	–1.033	-	(–8.349, 6.283)	0.772
	Last value	0.960	2.353	–1.393	-	(–8.271, 5.485)	0.679
Liver volume (L)/height (cm) (*100)[b]		0.813	0.719		1.130	(0.911, 1.403)	0.252
Liver volume (L)/BMI (kg/m^2) (*100)[b]		6.135	4.945		1.241	(1.013, 1.519)	0.038
Liver volume (L)/BSA (cm^2) (*100)[b]		0.801	0.681		1.176	(0.962, 1.438)	0.108
Spleen volume (L)/height (cm) (*100)[b]		0.291	0.295		0.987	(0.774, 1.260)	0.914
Spleen volume (L)/BMI (kg/m^2) (*100)[b]		2.157	2.136		1.010	(0.795, 1.283)	0.934
Spleen volume (L)/BSA (cm^2) (*100)[b]		0.283	0.283		0.997	(0.786, 1.264)	0.979
Cerebellar volume (cm^3)	Month 12	137.158	129.200		1.062	(0.906, 1.244)	0.393
	Last value	133.922	126.351		1.060	(0.934, 1.203)	0.32
Ambulatory Index Value[c]	Month 12	0.023	0.793	–0.770		(–1.610, 0.071)	0.071
	Last value	0.087	0.802	–0.715		(–1.438, 0.007)	0.052[f]
Chitotriosidase (nmol/mL.h)	Month 12	60.0	–3.0	58.0[d]		(9, 136)	0.036[e]
	Last value	54.0	5.0	49.0[d]		(–1, 127)	0.066[e]

[a] Ratio of geometric means (miglustat/No Treatment).
b Adjusted geometric mean. Due to the fact that weight loss is expected with miglustat treatment, it was considered uninformative to analyse organ volume/weight; however, as the study involves adolescents, it was also important to take into account expected organ growth in these patients. For these reasons, organ volume/height, organ volume/BMI and organ volume/BSA were analysed.
[c] Scores range from 0 (fully active) to 9 (restricted to wheelchair). A lower score indicates better ambulation. For confirmatory purposes, p-values were also obtained using a Wilcoxon test stratified by baseline severity (p = 0.070 at Month 12 and p = 0.039 at last value).
[d] Hodges-Lehman estimate for difference in means.
[e] Wilcoxon rank sum test and t-approximation.
[f] Wilcoxon test stratified by baseline severity gives p = 0.039.
The ANCOVA model used for analyses includes terms for baseline, centre and treatment group.

Extension of Study OGT 918-007 12-24 months

17 patients received miglustat for a further 12 months (total 24 months) and 8, previously on no treatment, received miglustat for an initial 12 months, that is, the trial was no longer controlled. Of the 12-24 month group, 2 withdrew, while of the previous no treatment group, 4 withdrew.

Primary efficacy results

The last value HSEM-α showed a mean increase (that is, a worsening) from baseline for both the 12 (N = 6) and 24 (N = 15) months miglustat groups, (0.227 ± 1.756 ms/deg in the 24 months group vs. 0.742 ± 1.279 ms/deg in the 12 months group). At month 12 of the extension only 4 of the 12 month treatment group were assessed. The estimated mean difference between treatment groups at last value was −0.594 ms/deg with 95% CI of −2.078 to 0.889 ms/deg (p = 0.410).

When patients taking benzodiazepines were excluded there was a larger difference between the two groups at last value (−1.076 ms/deg with 95% CI of −4.315 to 2.164 ms/deg, p = 0.472).

The qualitative evaluation of both the 'raw' peak velocity/amplitude data and the peak duration regressions on amplitude showed that 11/15 patients (73%) in the 24 Months miglustat group, compared with 3/6 patients (50%) in the 12 Months miglustat group had stabilized or improved at the last assessment, that is, disease progression for SEM was slower in the patients treated with miglustat for 24 months. This is shown in Tables 13-16.

Table 13: Summary of actual values and change from baseline for HSEM-α (ms/deg) (efficacy set)

	24 Months Miglustat (N = 17)				12 Months Miglustat (N = 8)			
	N	Baseline value (SD)	Actual value (SD)	Change from baseline (SD)	N	Baseline value (SD)	Actual value (SD)	Change from baseline (SD)
Baseline	17	-	– 2.976 (2.225)	–	8		– 2.483 (1.425)	–
Month 12	17	2.976 (2.225)	2.587 (1.634)	−0.389 (0.950)	8	2.483 (1.425)	2.558 (1.734)	0.074 (0.823)
Month 24[a]	15	3.040 (2.353)	3.267 (3.687)	0.227 (1.756)	4	2.940 (1.662)	4.056 (2.495)	1.116 (1.464)
Last value[b]	15	3.040 (2.353)	3.267 (3.687)	0.227 (1.756)	6	2.975 (1.294)	3.717 (2.016)	0.742 (1.279)

Baseline is the last value up to and including final day of Screening Visit 2 and Last Value is the last post-baseline value recorded in the 12-month extension period (excluding the Month-12 visit) up to and including the final day of the Month-24 visit. Only patients with a baseline value are summarized.

[a] 2 Patients in the 24 Months miglustat group and 4 Patients in the 12 Months Miglustat group did not have SEMV data at Month 24.
[b] 2 Patients in the 24 Months Miglustat group and 2 Patients in the 12 Months Miglustat group did not have SEMV data at Month 24 or withdrawal.

Table 14: Analysis of change from baseline in HSEM-α (ms/deg) (efficacy set 12-24 month Study Juveniles/Adults)

Visit	Adjusted mean change from baseline		Estimated Treatment difference	SE	95% CI	P-value
	24 Months Miglustat	12 Months Miglustat				
Month 12	−0.450	0.066	−0.515	0.305	−1.149, 0.118	0.105
Month 24	0.155	1.150	−0.994	0.845	−2.796, 0.808	0.258

Last value	0.166	0.761	−0.594	0.703	−2.078, 0.889	0.410

ANCOVA model used for all analyses included terms for baseline, centre and treatment group.

Table 15: Change from baseline in HSEM- α excluding benzodiazepine taking patients (ms/deg) (Exploratory analysis efficacy set 12-24 month Study Juveniles/Adults)

Visit	24 Months Miglustat	12 Months Miglustat	Estimated Treatment difference	SE	95% CI	P-value
Month 12	−0.448	−0.286	−0.162	0.345	−0.913, 0.589	0.647
Month 24	0.156	1.572	−1.416	1.697	−5.329, 2.498	0.428
Last value	0.154	1.230	−1.076	1.432	−4.315, 2.164	0.472

ANCOVA model used for all analyses included terms for baseline, centre and treatment group.

Table 16: Summary of mean change for SF-36 Quality of Life questionnaire (efficacy set 12-24mth Study Juveniles/Adults) from baseline to last value

Domain[a]	24 Months Miglustat (N= 17)				12 Months Miglustat (N = 8)			
	N	Baseline value (SD)	Last value (SD)	Change from Baseline (SD)	N	Baseline value (SD)	Last value (SD)	Change from Baseline (SD)
Physical functioning	8	54.4 (39.5)	77.9 (30.3)	23.5 (38.4)	3	63.3 (32.2)	60.0 (35.0)	−3.3 (10.4)
Role-physical	8	90.6 (12.9)	78.1 (36.4)	−12.5 (29.9)	3	100.0 (0.0)	83.3 (14.4)	−16.7 (14.4)
Bodily pain	8	84.8 (19.1)	92.0 (15.0)	7.3 (16.6)	3	100.0 (0.0)	83.7 (28.3)	−16.3 (28.3)
General health	7	71.4 (24.2)	68.6 (21.2)	−2.9 (17.0)	3	77.0 (13.2)	64.7 (19.7)	−12.3 (6.4)
Vitality	8	60.0 (18.5)	61.5 (14.3)	1.5 (28.6)	3	75.0 (10.0)	61.7 (16.1)	−13.3 (10.4)
Social functioning	8	82.8 (14.9)	70.3 (25.8)	−12.5 (25.9)	3	87.5 (12.5)	83.3 (19.1)	−4.2 (7.2)
Role-emotional	8	95.8 (11.8)	79.2 (30.5)	−16.7 (25.2)	3	77.8 (38.5)	88.9 (19.3)	11.1 (19.3)
Mental health	8	75.6 (18.3)	68.0 (16.1)	−7.6 (19.2)	3	84.0 (14.4)	72.0 (10.6)	−12.0 (8.0)
Physical component	7	46.3 (10.6)	51.6 (10.1)	5.3 (7.1)	3	51.0 (6.0)	45.6 (11.1)	−5.4 (8.3)
Mental component	7	53.9 (7.4)	50.5 (7.1)	−3.4 (8.2)	3	54.5 (7.8)	52.5 (2.2)	−2.1 (5.8)

[a] Scores are expressed on a scale of 0 to 100, where higher scores indicate better health and well-being.
Baseline is the last value up to and including final day of Screening Visit 2 and Last Value is the last post-baseline value recorded in the 12-month extension period up to and including the final day of the Month-24 visit. Only patients with a baseline value are summarized.

Other efficacy results

Table 17: Tabulation of some secondary variables (12-24 months)

Parameter		Adjusted mean change from baseline		Estimated treatment difference	SE	95% CIs	p-value
		24 months Miglustat	12 months Miglustat				
Horizontal saccadic-β (ms)	Month 12	2.146	2.588	−0.442	3.617	−7.964, 7.080	0.904
	Month 24	5.734	6.427	−0.693	5.138	−11.645, 10.259	0.895
	Last value	5.778	4.976	0.802	3.992	−7.621, 9.225	0.843
Ambulatory Index Value[c]	Month 12	0.023	0.793	−0.770		−1.610, 0.071	0.071
	Month 24	0.233	1.615	−1.382		−2.836, 0.072	0.061
	Last value	0.194	1.571	−1.377		−2.720, -0.034	0.045

ANCOVA model used for all analyses included terms for baseline, centre and treatment group.
[c] For confirmatory purposes, p-values were also obtained using a Wilcoxon test stratified by baseline severity (p = 0.070 at Month 12, p = 0.025 at Month 24 and p = 0.007 at last value).

- VSEM-α and β at Months 12, 24 and last value. Saccades were abnormal for all except for two of eight patients in the 12 Months miglustat group at baseline and were abnormal for all patients at the last visit.
- Assessments of swallowing produced complex results with the difference between 12 and 24 month miglustat treatment only achieving significance for swallowing 5 mL water (p = 0.028, last value).
- Neurological examinations at Months 12, 24 and last value. No statistically significant difference was observed between the groups, the difference between the groups for tongue muscles showed a positive trend (p = 0.053; Fisher's Exact Test). There was very little change in gait from screening to last visit.
- Neuropsychological assessments at Months 12, 24 and last value. Very few patients (8 & 9) were assessed.
- Tremor assessments at Months 12, 24 and last value. Only 4 patients had Archimedes spiral assessment.
- Quality of life assessments at Months 12, 15, 18, 21, 24 and last value - only 10 patients assessed.

Results for some of the parameters assessed with treatment can be interpreted to indicate not just a comparative improvement in some patients, but also a lack (or relative lack) of progression in others including HSEM-α, ability to swallow,[7] and ambulatory index score.

Extension of Study OGT 918-007 beyond 24 months

16 patients entered the Continued Treatment Extension Period, 9 completed the month 48 visit. Comparison of the manifestations of NPC in the group at start of this extension shows little difference with all randomised patients at baseline, that is, no particular manifestations affected survival in the trial.

[7] At the last value, the ability to swallow water, puree, soft lumps and one-third of a cookie had improved or remained stable compared to baseline for 13 (87%), 12 (80%), 11 (73%) and 13 (87%) of the 15 patients in the 24 months miglustat group. Improved or stable ability to swallow water, puree, and one-third of a cookie were seen for 2/5 patients (40%) in the 12 months miglustat group and improved or stable ability to swallow soft lumps in 2/4 patients (50%).

Study objectives were not specified and only safety assessments were performed after 3 February 2006. Primary efficacy endpoint was not assessed, however some of the secondary endpoints were:

- Assessment of swallowing ability,
- Neurological examinations (ambulatory index and auditory acuity),
- Neuropsychological assessments (MMSE).

More than 75% of patients showed improvement or stability for all swallowing assessments. At the last assessment, seven patients (58%) had normal auditory acuity in both ears and five had abnormal results (1 patient changed from normal to abnormal in both ears at last assessment). Mean ambulatory index score fell from baseline to last value by -0.6, 8/12 patients, (67%) showed no change in score, 2 patients showed a deterioration ≥ 2.

Other studies

Paediatric sub-study

The Paediatric sub-study was performed to evaluate the safety and tolerability of miglustat in children < 12 years as approximately two-thirds of cases of NPC are diagnosed before the age of 10 years.

The inclusion criteria for the Paediatric sub-study were the same as for the main OGT 918-007 study with the exception of the age limits (patients above 4 years and under 12 years of age).

There was no control group. It was thought to be ethically inappropriate to use a control group in children, as NPC can be a severe progressive disease in this age group. It was also expected that recruitment would be limited if parents thought that their children might be randomized to a non-treatment group. Thus the study was non-randomised and open, with no control.

Dose was calculated as Body Surface Area (BSA) / 1.8 of the adult dose (200mg tds). The study included PKs in 4 children. The neuropsychological tests used to assess these patients were the Wechsler Scale, the Child's Memory Index and the Vineland Adaptive Behaviour Scale (data from these studies was not available). The Quality of Life questionnaire used was the Child's Health Questionnaire-PF50 (CHQ).

Two patients were accepted though they did not have NPC confirmed by abnormal cholesterol esterification and abnormal filipin staining. The children ranged in age from 4 to 11 years with a higher incidence of splenomegaly and hepatomegaly than in the adult/juvenile main study. Auditory acuity was normal for all except one patient who had abnormal hearing at baseline.

There was a mean decrease in HSEM-α of -0.465 ms/deg (to last value). The ratio of this to SE indicates that this within-patient comparison is statistically significant using the t-distribution. In the qualitative assessment most patients showed improvement.

HSEM-β increased (that is, deteriorated) by 4.533 ms (to last value). The ratio of mean change to SE indicates that this within-patient comparison is not statistically significant using the t-distribution.

Swallowing deteriorated in some patients; of the 2 already with some deterioration 1 showed some improvement. One patient had abnormal pharyngeal gag and 2 patients had abnormal tongue muscles results at baseline and at last visit, otherwise all neurological assessments were normal.

The Standard Ambulation Index for 8/11 patients had no change in value to last visit, and 3 patients worsened by two grades. Reflex and muscle assessment showed no clinically relevant changes. The proportion of patients with ptosis remained unchanged. Only 3 patients completed the CHQ-PF50 QoL questionnaire.

12-24 month Extension of Paediatric Sub-study

Ten patients entered the 12-24 month extension. Over the 12-24 months mean HSEM-α increased by 0.414ms/deg although the result was still a slight (-0.075ms/deg) improvement on baseline (3/10 patients improved, 1 was stable and 6 deteriorated). Ambulation Index showed 8/11 had no change and 3 deteriorated.

The *Continued Treatment Extension Period* was to permit all patients to continue with therapy if it was considered by the Investigator to be in the best interests of the patient. This was also to enable the collection and assessment of further safety data. There was no efficacy data collected except Brainstem Auditory Evoked Potentials in some patients.

The individual patient efficacy analysis is shown in Table 18

Table 18: Summary of efficacy - Individual Patient Efficacy Analysis.

Subject	Days on drug	Disease severity at baseline	Response				
			HSEM-α	Swallowing	Ambulation index	MMSE	OVERALL
Study OGT 918-007 Main study							
007-104	387	moderate	improved	improved	stable	stable	stable
007-105	1667	mild	deteriorated	stable	stable	stable	stable
007-106	2056	moderate	deteriorated	improved	stable	stable	stable
007-107	2056	severe	deteriorated	improved	stable	stable	stable
007-110	1846	severe	stable	deteriorated	deteriorated	deteriorated	deteriorated
007-111	1526	mild	improved	deteriorated	stable	stable	deteriorated
007-112	825	minimal	stable	stable	stable	stable	stable
007-114	1419	severe	deteriorated	deteriorated	stable	deteriorated	deteriorated
007-202	1488	moderate	deteriorated	stable	stable	improved	stable
007-203	1534	moderate	stable	stable	stable	deteriorated	stable
007-204	1462	mild	stable	stable	stable	improved	stable
007-206	1467	mild	deteriorated	stable	deteriorated	stable	deteriorated
007-207	737	moderate	stable	stable	stable	deteriorated	deteriorated
007-209	1086	moderate	deteriorated	stable	stable	stable	stable
007-210	937	mild	stable	stable	improved	stable	stable
007-211	1143	moderate	stable	stable	stable	stable	stable
007-212	585	severe	——	deteriorated	stable	——	deteriorated
007-214	1079	moderate	stable	stable	stable	improved	stable
007-215	1069	mild	improved	stable	stable	stable	stable
Study OGT 918-007 Pediatric sub-study							
007-121	1604	mild	deteriorated	stable	stable		stable
007-122	1290	mild	——	stable	deteriorated		deteriorated
007-123	1547	minimal	stable	stable	stable		stable
007-124	1541	minimal	stable	stable	stable		stable
007-222	1071	minimal	stable	stable	stable		stable
007-223	1075	mild	stable	stable	stable		stable
007-224	1057	mild	deteriorated	stable	stable		stable
007-225	760	mild	deteriorated	stable	stable		stable
007-226	733	moderate	improved	deteriorated	deteriorated		deteriorated
007-228	725	mild	improved	stable	stable		stable

For the overall response analysis, each patient was defined as stable if none of the variables swallowing function, ambulation index and MMSE was deteriorated. Patients were considered stable also if only deterioration of HSEM-α occurred whilst the other three clinical parameters were either stable or improved. Alternatively, patients were defined as deteriorated.

The analysis of the relationship between disease severity at baseline and treatment response was not conclusive.

Retrospective Treatment Case Survey

This was based on a questionnaire for each NC-P patient treated with miglustat. 36 paediatric and 30 adult/juvenile patients; mean age at diagnosis was 9.7 (range 0 – 32) years, mean age at treatment start was 12.8 (range 0.6 – 43) years. 7 patients commenced at age 3 years, 4 at 2 years and 2 at 1year. 12 patients discontinued (4 deaths, 6AEs, 2 lack of efficacy, 1 lost to follow up, 3 other).

Outcomes

Mean duration of treatment was 543 days (18 patients received treatment for > 24 months). Dosage varied (based on 61 patients) - adult mean 535mg/day (29.5% were on 200mg tds- the rest less), paediatric mean 260mg/day. During treatment with miglustat it was reported:

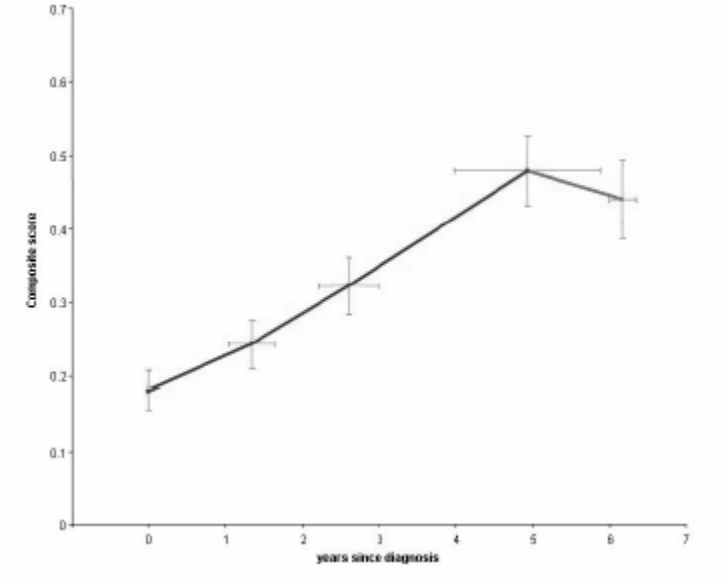
- Ambulation was improved in 9/64 patients (14%) and was stable in 40/64 patients (62%);
- Manipulation improved in 8/63 patients (13%) and was stable in 40/63 patients (64%);
- Language articulation was improved in 7/61 patients (11%) and was stable in 40/61 patients (66%);
- Swallowing function was improved in 12/63 patients (19%) and was stable in 39/63 patients (62%).

A composite score was calculated for each patient as the mean of the four individual scores (ambulation, manipulation, language and swallowing). The difference between mean age of onset and mean age of initiation of treatment is 3.1 years, double the mean duration of treatment of 1.5 years, thus progression rates before and after treatment were adjusted for the time intervals between the three time points: diagnosis, treatment initiation and last contact. The progression rate decreased significantly from 0.11 score units/year between diagnosis and treatment start to −0.01 units/year after miglustat initiation (paired sample test comparison by Wilcoxon signed rank test $Z = -3.03$; $p = 0.002$).

Analysis of progression on treatment showed that lower age at diagnosis and treatment start and higher progression rate prior to treatment were more likely to be associated with unchanged progression rate on treatment (“poor responders”). A multivariate stepwise logistic regression analysis indicated that age at diagnosis was the most significant predictor of response. When adjusted for age at diagnosis, age at treatment start, severity at diagnosis and at treatment start, progression rate (annual composite score change prior to initiation of miglustat treatment) was not anymore a significant predictor of response.

Among the 57 patients included in the following Natural History survey were 19 patients included in this survey evaluating miglustat treatment in NPC patients. In this sub-group of 19 patients, both the composite score at diagnosis and at start of treatment and its annual progression rate were not different from the other 38 patients in the Natural History survey, and nor from the other 47 patients in the Treatment survey. This suggests that this cohort can be considered representative of the overall population. The progress of the disease in this sub-group before and after treatment can be seen in Figure 1.

Figure 1: Progression of the composite score before and after miglustat treatment (n = 19) (Retrospective Survey)



Y-axis error bars represent the 95% confidence interval of the mean score at diagnosis and at each of the following.
X-axis error bars represent the 95% confidence interval of the mean time interval (years) between each visit and diagnosis.
darker line displays the period between diagnosis and treatment start, the lighter line the treatment period.

Retrospective Case Survey – Natural History

A retrospective questionnaire-based survey was conducted to assess, from the medical records, the progression of neurological outcomes in the natural history of the disease, at diagnosis and at following visits (up to 4). 22 paediatric and 35 adult/juvenile patients; mean age at diagnosis was 10.7 (range 0 – 41) years, follow up time mean 5.5 (range 0.2-29.9) years.

The composite score increased from 0.15 at the time of diagnosis to 0.58 at the last visit, mean scores of all four parameters increased substantially between the time of diagnosis and last visit (between 3- to 6-fold). The annual progression rate of all parameters according to age at diagnosis was consistently highest in the early childhood group and lowest among juveniles-adults. Over the natural course of the disease, the progression rate appears continuous without any apparent spontaneous decline, the highest rate of progression was observed for the swallowing score and the lowest for the language articulation score.

At the time of diagnosis of NPC disease, seizure activity was present in only 3 patients (5%), < 1/3months (2 partial, 1 global). By last visit, this rose to 32% (18 patients; 4 partial, 8 global, 6 both). 5 patients had < 1 seizure /3months, 2 had < 1/month, 3 patients had < 1/week and 7 patients had > 1/week.

Among those patients (N = 49) with a time interval ≥ 1 year between diagnosis and the last visit, only 14% of patients showed 'stable' disease and 86% 'progressed' disease[8] This proportion was 86% in the early childhood group, 82% in the late childhood group, and 94% among juveniles-adults.

[8] Subjects were classified either as having 'stable' disease if none or only one out of four parameters had worsened during the course of the disease, or as having 'progressed' disease if at least two parameters had worsened.

Case Studies

16 case studies were provided, 2 of them were from a publication, all but 1 had received miglustat, their ages ranged 4-43 (mean: 12) years.

Conclusions regarding efficacy

With an estimated worldwide diagnosed population of 500, NPC is always fatal and the vast majority of children die before age 20 (and many die before the age of 10). Late onset of symptoms can lead to longer life spans but it is extremely rare for any person with NPC to reach age 40. There is as yet no effective treatment for NPC and current treatment options have been restricted to supportive therapies only.

The evaluator believed that the submission demonstrates sufficient efficacy (as shown by a decrease in the rate of progression of the disease) to a level required to meet that described in the European Medicine Agency's *CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations Effective: December 2006* for which the proposed indication for this drug qualifies.

In deficiency diseases for 'substitution studies', well characterised short- and long-term consequences of the deficiency, and a clear understanding of the pharmacokinetics and pharmacodynamics of the compound, provide guidance for designing studies.

Regulatory requirements for licensing 'substitution products' may deviate from those for other compounds provided that symptoms related to the deficiency are clearly understood and that the pharmacokinetics and pharmacodynamics of the product are well documented in clinical studies.

PD were not demonstrated in clinical studies , but are well described from *in vitro* and animal studies, and while not exactly a substitution for a defective transport mechanism, the competitive inhibition decreases the necessity for it.

Within-patient comparisons in a relentlessly and predictably progressive disorder might provide sufficient data to support a benefit–risk assessment. However, in other situations comparative trials may be needed/expected.

The retrospective surveys showed the progressive nature, Main Study OGT 918-007 provided a comparison with no and delayed treatment, the paediatric sub-study gave adequate explanation for omitting a comparator, an historical comparison in 19 patients was made. There is no currently approved treatment to use as an active comparator.

In very rare disorders, it is important that every patient participating in a study contributes as much information as possible to make a benefit–risk assessment possible. Therefore, the well-planned use of the best available techniques to obtain and analyse information is crucial.

Study OGT 918-007 data was subjected to a qualitative as well as the usual quantitative assessment, the sponsors point out the problem of assessing the results of treatment in the absence of previously published data.[9]

Time to disease progression is an endpoint of intermediate level and it requires a measure of disease severity or of disease progression. Ideally, this should be validated as a tool for use in clinical trials, but it is recognised that there might be too few patients to use some for

[9] There is no recognized clinical endpoint in the assessment of NPC disease. In the absence of previous experience or health authority guidelines, the decision was taken to evaluate a number of parameters relevant to pharmacological rationale and characteristics of disease involvement in NPC.

validating endpoints and others for testing treatments. In studies whose endpoint is time to progression or time to remission, adequate length of follow up of the patients is important; this can be done in 'open-label extensions' or randomised studies. It is preferable to be able to identify a causal relationship between treatment and a particular (beneficial) outcome.

Quality of life data should ideally be considered as supportive evidence. It may be important to assess any influence of the observed study effect on activities of daily life and social functioning.

The appropriate clinical endpoint may not be known or widely agreed or a validated clinical endpoint may not exist. In other cases, the mode of action of the test treatment may not be well enough known to predict which of several possible outcomes will be affected. In such circumstances, the usual approach of pre-specifying the primary endpoint may be too conservative and more knowledge may be gained from collecting all sensible/possible endpoints and then presenting all the data in the final study report. Still, every effort should be made to identify an appropriate hierarchy in the endpoints.

The sponsor did produce some QoL data, however it was limited. The Composite Disability Score (ambulation, manipulation, language and swallowing) covers some major social difficulties and, used in the retrospective surveys, showed a decrease in rate of progression.

In relation to paediatrics, analysis of progression on treatment showed that lower age at diagnosis and treatment start, and higher progression rate prior to treatment, were more likely to be associated with unchanged progression rate on treatment. A multivariate stepwise logistic regression analysis indicated that age at diagnosis was the most significant predictor of response. There appeared to be 13 patients aged < 4 years, and of the 26 patients in the aged < 6 years group in the analysis 9 were poor responders. Could these all have been under 4 years? Possibly 7. In the case report summaries of 12 responses < 4 years only 1 had a good response, 5 had a fair response and 6 had poor, none or worse.

Safety

Extent and Duration of Patient Exposure

Overall, the mean exposure in the safety report (which looked at trials in lipid storage disorders) was 2.2 years (SD 1.5; range: 0 – 6.6 years) for a total of 206 patients.

Adverse events

98.5% (203 patients) had at least one treatment-emergent adverse event (AE). The total number of AEs was 3,051. The most frequently reported events were diarrhoea 84.5% (174 patients), weight decrease 62.6% (129 patients), tremor 46.1% (95 patients), and flatulence 44.2% (91 patients). The prevalence of diarrhoea was 77.7% within the first 6 months, and then decreased to range 46% - 58%. The highest prevalence of weight decrease (60.1%) was between 6 - 12 months, and then decreased to 39% -58%. The highest rate of tremor (35%) was within the first 12 months, and then decreased to 26% - 32%.

Pivotal study OGT 918-007

40 patients with NPC disease received ≥ 1 dose of miglustat. Overall mean exposure duration is given as 1233.5 days (3.4 years); 1282 days in patients enrolled in the Main study, 1140.3 days in patients enrolled in the Paediatric sub-study; and overall mean duration of treatment was 2.6 years (SD ± 1.6; range: 0.0 – 5.4 years): 35 patients (87.5%) were exposed for at least 6 months, and 2 (5.0%) for at least 5 years. In the Main Study only 14/17 patients (82%) were taking the full 200mg TID at 12 months, 3 patients were on lower doses.

39 patients (97.5%) had 809 AEs; the most frequently occurring were diarrhoea 82.5% (33 patients), weight decrease in 60.0% (24 patients), tremor in 57.5% (23 patients), and flatulence in 55% (22 patients) (Table 19).

Table 19: Summary of AEs with frequency > 10% in patients with NPC (including unrelated) Safety set

Preferred Term	Miglustat N=40 n	%
ALL SYSTEM ORGAN CLASSES		
Total patients with at least one AE	39	97.5%
DIARRHOEA	33	82.5%
WEIGHT DECREASED	24	60.0%
TREMOR	23	57.5%
FLATULENCE	22	55.0%
FATIGUE	18	45.0%
HEADACHE	17	42.5%
NASOPHARYNGITIS	16	40.0%
VOMITING	14	35.0%
ABDOMINAL PAIN UPPER	13	32.5%
COUGH	12	30.0%
DYSPHAGIA	11	27.5%
DYSTONIA	11	27.5%
ATAXIA	10	25.0%
FALL	10	25.0%
GAIT DISTURBANCE	10	25.0%
NAUSEA	10	25.0%
ABDOMINAL PAIN	9	22.5%
DEAFNESS	9	22.5%
DYSARTHRIA	9	22.5%
GAZE PALSY	9	22.5%
INSOMNIA	9	22.5%
CONFUSIONAL STATE	8	20.0%
NERVE CONDUCTION STUDIES ABNORMAL	8	20.0%
DEPRESSION	7	17.5%
GAIT SPASTIC	7	17.5%
PARAESTHESIA	7	17.5%
SLEEP DISORDER	7	17.5%
URINARY INCONTINENCE	7	17.5%
ABDOMINAL DISCOMFORT	6	15.0%
CONTUSION	6	15.0%
DECREASED APPETITE	6	15.0%

In the 35 patients with 145 miglustat-related AEs, most common were diarrhoea [33 (82.5%)], flatulence [21 (52.5%)], weight decreased [15 (37.5%)], abdominal pain upper [11 (27.5%)] and tremor [11 (27.5%)] (Table 20). Nine patients had 18 AEs that lead to discontinuation (of which 9 AEs were related to miglustat). There were 11 patients with 23 serious adverse events (SAEs). Three patients died after stopping miglustat treatment. None of the deaths was considered to be related to the treatment with miglustat.

There have been 3 patients reported with Crohn's disease on miglustat (one reporter stated awareness of 3 other cases of Crohn's in NPC patients not on miglustat).

Most common marked laboratory abnormalities involved neutrophils 10/38 (26.3%) and platelets 4/39 (10.3%). 39% of the patients (38% of the juvenile/adults and 42% of the paediatric patients) already had platelet counts below the lower limit of normal at screening. Reduced platelet count is a common finding in NPC disease and is likely related to residual splenomegaly.

Table 20: Summary of Miglustat related AEs in patients with NPC disease.

Preferred term	N (%)
Total patients with at least 1AE	35 (87.5)
Total no. AEs	145
Diarrhoea	33 (82.5)
Flatulence	21 (52.5)
Weight decreased	15 (37.5)
Abdominal pain upper	11 (27.5)
Tremor	11 (27.5)
Abdominal pain	7 (17.5)
Nerve conduction studies abnormal	5 (12.5)
Abdominal discomfort	4 (10.0)
Abdominal distension	4 (10.0)
Decreased appetite	4 (10.0)
Vomiting	4 (10.0)
Anorexia	2 (5.0)
Lethargy	2 (5.0)
Nausea	2 (5.0)
Paraesthesia	2 (5.0)
Amnesia	1 (2.5)
Ataxia	1 (2.5)
Axonal neuropathy	1 (2.5)
Depression	1 (2.5)
Diarrhoea haemorrhagic	1 (2.5)
Dysarthria	1 (2.5)
Energy increased	1 (2.5)
Eructation	1 (2.5)
Faecal incontinence	1 (2.5)
Fatigue	1 (2.5)
Gastroenteritis	1 (2.5)
Headache	1 (2.5)
Lactose intolerance	1 (2.5)
Pollakiuria	1 (2.5)
Polyneuropathy	1 (2.5)
Rash maculo-papular	1 (2.5)
Tearfulness	1 (2.5)
Thirst	1 (2.5)

Other studies

The sponsor's Summary of Clinical Safety reviewed data from several studies and their extensions:

- Type 1 Gaucher disease: OGT 918-001, OGT 918-003, OGT 918-005, OGT 918-004 and OGT 918-016.
- Type 3 Gaucher disease: OGT 918-006.
- Niemann-Pick type C disease: OGT 918-007.
- GM2 gangliosidosis: OGT 918-009.
- Fabry disease: OGT 918-002.
- Neuronopathic glycospingolipidoses: OGT 918-007, OGT 918-006, OGT 918-009.

The most frequently reported related AEs included diarrhoea [assessed as related in 168 patients (81.6%)], decreased weight [assessed as related in 110 patients (53.4%)], flatulence [assessed as related in 88 patients (42.7%)], tremor [assessed as related in 64 patients (31.1%)], abdominal pain [assessed as related in 43 patients (20.9%)] and abdominal pain upper [assessed as related in 31 patients (15%)].

Withdrawals due to adverse events

The total number of AEs leading to discontinuation was 54. The most frequently reported AEs leading to discontinuation were diarrhoea (8 patients, 3.9%), tremor (5 patients, 2.4%), flatulence (4 patients, 1.9%), weight decrease (4 patients, 1.9%).

Deaths and other serious adverse events

41 patients (19.9%) had an SAE. The total number of SAEs was 71. The most frequently reported SAE was viral infection, (3 patients, 2%). Aspiration, constipation, postoperative wound infection, psychotic disorder and tibia fracture were reported in 2 patients each. 9 SAEs led to discontinuation: only one of these was assessed as related to the study medication, i.e. one case of peripheral neuropathy in study OGT 918-001.

Laboratory abnormalities

The major laboratory abnormalities were low haematological values (incidence 4 - 12%) and raised liver enzymes (3 – 5%). Despite the high incidence of diarrhoea there was only 1/201 low potassium reported.

Effect on Vital Signs and Electrocardiogram (ECG)

The weight percentile (adjusted by age and gender in patients aged ≤ 20 years at treatment start) showed a decrease in the first year of treatment; after that median weight remained at the same percentile for the following 2 years.

The height percentile (adjusted by age and gender in patients aged ≤ 20 years at treatment start) showed a decline in height growth rate at 6 months and at 1 year of treatment. After that, median height remained at the same percentile.

Post-marketing experience

Use of miglustat in type 1 Gaucher disease has been registered in the EU since 2002. The sponsor's Clinical Overview refers to 7 Periodic Safety Update Reports to October 2007. Exposure to 19 October 2007 involves 141 clinical trials in which 246 adults, 60 adolescents and 143 children/infants have been treated. The reporting rate for the most commonly reported events was 18.5% (84/454) for diarrhoea, 8.6% (39/454) for tremor, 4.4% (20/454) for unspecified neurological symptoms, 12.3% (56/454) for weight decrease, 3.3% (15/454)

for memory impairment, and 2.6% (12/454) for convulsions. There have been 11 deaths. Of 273 AEs 162 were miglustat related and of these 58 ADR were SAEs.

Conclusions regarding safety

In the 40 NPC patients on miglustat, related AEs were diarrhoea [33 (82.5%)], flatulence [21 (52.5%)], weight decreased [15 (37.5%)], abdominal pain upper [11 (27.5%)] and tremor [11 (27.5%)]. These support that safety data from the trials in the other lipid disorders may apply to NPC. Of the 40 patients – 4 patients discontinued for unrelated AEs, leaving 36 patients of whom 5 patients had 9 AEs related to miglustat that led to discontinuation, a 14% attrition rate from adverse reactions over 2.6 or 3.4 years of a long-term therapy.

Clinical Summary and Conclusions

The evaluator recommended that miglustat be approved for the treatment of adult and paediatric patients aged 4 years and older with Niemann-Pick Type C Disease with progressive neurological manifestations with the following observations:

1. The evidence provided supports that the treatment delays the development of the neurological manifestations; the individual patient analysis did not support overall improvement in patients' neurological manifestations.
2. Given that the onset of symptoms can be delayed until adulthood (in 40% of cases), treatment in the absence of symptom onset has not been justified.
3. The study evidence submitted excluded children aged < 4 years, while the survey evidence suggests that this age group is much less likely than older patients to benefit.
4. The product is a capsule, there are practicalities in the swallowing of which in small children and infants, where swallowing may anyway become impaired (in the retrospective survey the highest rate of progression was observed for the swallowing score).

It was noted that the guideline *CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations Effective: December 2006* states:

If, collectively, the data look compelling, then a Marketing Authorisation may be grantable.

Considerations should include:

- *How closely changes in the surrogate endpoint are causally linked to changes in a clinical endpoint or symptom.*
- *How much risk is associated with the therapy*
- *What other therapies (if any) are available for the same condition.*

Demonstrating that a surrogate endpoint adequately reflects the true clinical endpoint is difficult. Epidemiological data and data from patient registers may provide some help. These data may be limited when there are very few patients.

A risk–benefit assessment may become very difficult, since the size of benefit may be impossible to determine based on a surrogate endpoint.

Also it has to be pointed out that surrogate markers cannot serve as final proof of clinical efficacy or long-term benefit. If they are intended to be the basis for regulatory review and approval then, unless they are properly validated, there should be a predetermined plan to

supplement such studies with further evidence to support clinical benefit, safety and risk/benefit assessment.

The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important.

The sponsor proposes a post-marketing registry for all NPC patients.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted as it was not a requirement at the time this application was submitted.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in an application of this type.

Nonclinical

The toxicology evaluator summarised that:

- No new clinical studies were provided. Some published papers and a few study reports/summaries submitted for the original application were provided. However, the available data were sufficient to evaluate the current application.
- For pharmacodynamics, miglustat inhibited synthesis of glycosphingolipids (GSLs) *in vitro*, by inhibition of activity of ceramide glucosyltransferase and increase in activity of acid β-glucosidase. Miglustat also reduced synthesis of globotriaosylceramide (a glucosylceramide-based lipid) in lymphoblasts extracted from a patient with a similar disease (Fabry disease). *In vivo*, oral administration of miglustat to NPC mice and cats delayed the onset of neurological dysfunction (ataxia and intention tremor), increased the average life span (in mice), and reduced ganglioside accumulation and accompanying neuropathological changes.
- In relation to the extension of treatment to the paediatric population, the pharmacokinetic parameters (that is, absorption and excretion) of miglustat in young (3-4 months of age) rats were similar to those observed in older rats. In juvenile rats (12 days of age), the increase in systemic exposure tended to be less than dose-proportional, compared with approximately dose-proportional for young and adult rats.
- After oral administration to male rats, miglustat is absorbed into most tissues efficiently (within 1h post-dose), with high concentrations in the gastrointestinal tract (GIT), kidney and bladder, and low concentrations in the liver. The drug undergoes limited metabolism and the main excretion route was urinary.
- Gastrointestinal (GI) effects, including soft stools/diarrhoea and GI inflammation/lesions, were a major toxicity of miglustat, which were observed in all species tested (the lowest ER for NOEL: 8, 5, <2 and <14 for mouse, rat, dog and monkey, respectively) and were associated with reduced food consumption and body weight gain. GI events (that is diarrhoea) and weight loss were also observed in the juvenile and adult populations in clinical studies.
- There were minor effects on haematology, clinical chemistry parameters and/or immune function, mainly at high doses. Platelet counts were reduced in rats and dogs but

increased in rhesus monkeys. Mild reductions in platelets (without associated bleeding) were also seen in humans.

- The male reproductive tract was a target organ following repeat dose administration in rats. The reversible changes included, but were not limited to, testicular or seminiferous tubular atrophy, arrested spermatogenesis and epididymal hypospermia. An increase in abnormal sperm, decrease in sperm concentration and a reduction in sperm motility were observed. No NOEL was established (the lowest dose tested: ER 0.4 on an AUC basis).
- Miglustat can cross the blood-brain barrier and the brain/plasma AUC ratio of the drug was 0.4 after a single oral administration to rats. A longer half-life in the brain compared with that in plasma may relevant to efficacy of the drug for NPC disease. There was no neurotoxicity or CNS-related pathological effects in any animal species investigated including juvenile rats, although there were some neurological adverse effects, such as tremors and headaches in humans.
- In carcinogenicity studies, there was a dose-related increase in the incidence of large intestinal hyperplasia and tumours (adenomas and adenocarcinomas) in mice (no NOEL established and ERs about 2 and 18 for LOEL based on AUC and mg/kg, respectively), but not in rats. These tumours might be relevant in humans, since they were associated with GI inflammation/lesions and humans are sensitive to the GI effects of miglustat. In rats, a treatment-related increase in the incidence of interstitial (Leydig) cell adenomas was observed (no NOEL and ER <1 for LOEL based on AUC), associated with testicular tubular atrophy. However, given their benign nature, absence in mice, and rare occurrence in humans, the Leydig cell adenomas in rats are unlikely to be of clinical relevance.
- Oral administration of miglustat induced reproductive toxicity in rats and rabbits. In rats, post-implantation loss, increased gestation length, decreases pup survival and foetal body weight, and dystocia were seen at doses of ER 1-3 (on an AUC basis). In rabbits, there were increases in the post-implantation loss and foetal blood vessel abnormalities at doses of ER $\leq$ 2.
- Only limited data (one repeat dose study in rats) were provided to support the extended (paediatric) patient population. The toxicities observed in juvenile rats were similar to those seen in older animals (mainly reductions in body weight gain/food consumption, distended abdomens, reductions in sperm concentration and increases in abnormal sperm) and were reversible. A delay in balanopreputial separation in males and vaginal perforation in females were noted in all dose groups. No treatment effects were observed in offspring from treated groups (number, survival, physical development). There was no NOEL established in the juvenile study (the lowest dose tested: ER < 1 on a BSA basis).

Clinical

On pharmacokinetics, efficacy and safety**,** the clinical evaluator identified one single study **(OGT 918-007)** in patients with NPC disease. Study OGT918-007 consisted of (1) a 12 month randomised, standard care controlled, open label period followed by (2) a prospective, non controlled, 12 month extension period and (3) a further extension of study for 24 months, that is, up to 48 months from the commencement of the study (for review later). Patients enrolled were aged $\geq$ 12 years and the inclusion criteria were (i) NPC confirmed by abnormal cholesterol esterification and filipin staining and (ii) ability to ingest a capsule. 29 patients (n=20 for miglustat and n=9 for no treatment standard care group). The initial dose was 200mg tds and the dose could be reduced if there were dose related adverse events to 200mg bd or less.

Also included under Study OGT918-007 but with different design is another (4a) age-group (4-11 years old) study of initial 12 months duration followed by (4b**)** 12-24 month Extension period and (4c**)** Continued Treatment Extension Period.

12 month randomised, standard care controlled, open label study period.

The primary objective was to evaluate miglustat as a treatment for NPC by assessing changes in saccadic eye movement velocity (SEMV) and other markers of the disease.

The sponsor claims that the measurement of saccadic eye movement was selected because supranuclear gaze palsy (saccadic initiation failure) is often the earliest neurological sign in NPC and because saccadic eye movement failure is associated with definite visual, learning and social handicap. Horizontal saccadic eye movement (HSEM) was considered to have the greatest potential for improvement with miglustat treatment, although less affected than vertical supranuclear gaze palsy. The secondary objectives were to assess the safety and tolerability of miglustat therapy. Using rather complex mathematical formulae and an appropriate software model, the saccadic peak duration and velocity data were used to derive parameters α and β whose estimates are negatively correlated and dependant. A reduction in α and β represented an improvement. According to the sponsor, HSEM-α has a better clinical interpretation and is less variable than HSEM-β. Analysis was based on the combined horizontal left and right saccadic eye movements' outcome in only one selected eye. Eye movements were assessed by an infrared system in one centre and by a scleral search oil method in the other centre.

The primary efficacy endpoint was the change in HSEM-α from baseline to Month 12.

The secondary efficacy endpoints include:

- Changes in pharmacokinetic, haemoglobin and platelet values
- Changes from baseline to Month 12 or last assessment in HSEM-β, vertical saccadic parameters, swallowing ability (inclusive of 6 month assessment), liver and spleen organ volumes, cerebellar volume, neurological examination tests [at baseline, months 3, 6, 9, 12 and last value for gait examination, standard ambulation index value, reflex assessments, muscle assessments (for bulk, tone and power), auditory, visual acuity, Snellen test, neuropsychological assessments (Purdue Peg Board Test and the MMSE), tremor (Archimedes spiral score for spirals 1 and 2), chitotriosidase activity and quality of life (CHQ-PF50) questionnaire [patients ≤13y] domains Global Health, Physical Functioning, Role/Social Limitations – Emotional/Behavioural, Role/Social Limitation – Physical, Bodily Pain/Discomfort, Behaviour, Global Behaviour Item, Mental Health, Self-Esteem, General Health Perceptions, Change in Health, Parental Impact – Emotional, Parental Impact – Time, Family Activities and Family Cohesion and summary scores Physical Summary and Psychosocial Summary or SF-36 questionnaire [≥ 13y] domains Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role- Emotional, and Mental Health and summary scores Physical Component Summary and Mental Component Summary).

The evaluator stated that all hypothesis tests were 2-sided superiority hypothesis tests undertaken at the 5% significance level. CIs were 2-sided with 95% coverage. For continuous endpoints, ANCOVA was used in order to detect a difference between the treatment groups. In general, the model was to include terms for baseline and treatment group. For each ANCOVA model, the data were investigated to determine whether the distributions were unimodal and not highly skewed. If the data were not normally distributed, then the data were ranked prior to performing the ANCOVA. Both the main analysis of the primary efficacy variable, and all analyses on secondary and exploratory efficacy variables, was based on the

efficacy set. (i.e. those patients who received at least one dose of study drug and who had at least one post-baseline efficacy assessment for the given parameter).

On pharmacokinetics outcomes, the evaluator provided the following and commented that:

Parameters- geometric mean (coefficient of variation)	Age > 12y Range 12-39y	Age < 12y Range 5- 11y		
	200mg TID N = 6	200mg TID N = 1	200mg BID N = 2	200mg am + 100mg pm N = 1
AUC_{0-8h} (ng.h/mL)	16412 (19.5)	11975 (NA)	18792 (13.9)	15866 (NA)
C_{max} (ng/mL)	2698 (22.9)	2075 (NA)	3289 (9.03)	2223 (NA)
C_{trough} (ng/mL)	1427 (18.3)	962	NA	NA
t_{max} - median (h) (range)	3.00 (0.750-4.00)	4.00 (NA)	3.54 (3.08-4.00)	4.00 (NA

- T_{max} (median) was approximately 3-4h for all groups. There appeared to be a lag time in absorption of approx 0.75h especially when an outlier was excluded.
- The apparent terminal half-life could not be estimated because the blood sampling scheme did not extend beyond the dosing interval of 8h, i.e. the terminal phase was not well characterised in this study.
- In patients on 200mg TID, C_{trough} was approximately half C_{max} i.e. accumulation occurred.
- The doses for < 12y were calculated on the basis of an adjustment for body surface area (BSA) so that relation to age is not readily apparent except to say, that results for 200mg TID suggest a slower absorption for children and with lower T_{max} and AUC values.
- Absorption was slower than 100mg in healthy volunteers (t_{max} 2.5h vs. 3-4h study 014). No data on repeated dosing in volunteers.

For the primary efficacy outcomes on the 12 month randomised, standard care controlled, open label period, the evaluator stated that:

- 2 patients on miglustat and 1 on no treatment had no post baseline observations and 1 patient had assessment on withdrawal but not at month 12.
- There were neither statistically significant differences between the Miglustat and the No Treatment groups nor an effect by centre shown. However, excluding 6 patients from the miglustat group and 1 on No Treatment group who were taking benzodiazepines, produced a statistically significant difference (p-value = 0.028). It was argued that since fatigue can slow saccades, the sedative effects could have confounded the results.
- A qualitative examination of the main sequence scatter plots and visual comparison of the regression slopes, for the plots of saccades from 26 patients who provided useable data at both baseline and Month 12 (or last visit), showed in the miglustat group that 15/19 patients (79%) were stable or improved (7 improved, 8 with no change), 2/19 deteriorated, and 2/19 had ambiguous results and in the No Treatment group that 2/7 patients (29%) were stable or improved (1 improved, 1 with no change), 3/7 deteriorated and 2/7 had ambiguous results.

The Delegate noted that there appeared to be a discrepancy in the number (19) of miglustat and no treatment (7) patients quoted as having data for scatter plots of saccades. The Delegate believed that the respective numbers should have been 18 and 8, given that, 2 miglustat patients and 1 no treatment patient did not have post baseline observations / data.

For the secondary efficacy outcomes**,** the evaluator stated that;

At baseline, Month 12 or last observation value

- Only two patients had vertical saccadic parameters assessment performed.
- There were no significant differences between treatments in improvement or deterioration regarding swallowing ability.
- Cerebellar volumes were only assessed at one centre.

At baseline, months 3, 6, 9, 12 or last observation value

- Of the neurological examination parameters (olfaction, light touch, vibratory sense, temperature, pharyngeal sensation, pharyngeal gag, sternocleidomastoid muscles, trapezius muscles, tongue muscles and plantar reflex) assessed, only the tongue muscles showed a statistically significant difference between the groups (5% on miglustat vs 33% on No treatment p=0.023; Fisher's Exact test).
- Gait Examination showed very little change.
- Auditory acuity showed decreased abnormalities for miglustat and increased for No Treatment, the groups showed similar changes in the Snellen test from baseline to last value.
- Neuropsychological tests (Purdue Peg Board Test and the MMSE – the latter showed a trend in favour if miglustat).
- Tremor. (Archimedes spiral score for spirals 1 and 2) – no significant difference
- Quality of life. (CHQ-PF50 questionnaire) - showed a trend in favour of miglustat
- Tabulation of secondary variables in Table 12

(2) Prospective, non-controlled 12 Month extension study period.

In this extension study period, 17 out of the 20 miglustat patients continued medication for a further 12 months period while 8 out of the 9 no treatment patients commenced miglustat for the first time for 12 months. The dose of miglustat, efficacy parameters and data analyses were as previously described.

For the primary efficacy outcomes on the prospective non controlled 12 month extension study period, the evaluator stated that:

- 6 patients (2 from the 17 continuing miglustat patients and 4 from the previous 8 no treatment patients) withdrew before the end of the 12 months extension period (only 4 patients in the previous 8 no treatment group had assessment at 12 months of treatment while some probably had evaluable data along the line before withdrawal).
- The last value HSEM-α showed a mean increase (that is, worsening) from baseline for those newly scheduled for miglustat treatment over 12 months i.e. the 12 months group (data available for n=6) and those continuing for a further 12 months miglustat treatment, that is, the 24months group (data available for n=15). The values are 0.227 ± 1.756 ms/deg in the 24 months group vs 0.742 ± 1.279 ms/deg in the 12 months group. The estimated mean difference between the treatment groups at last value was -0.594 ms/deg with 95% CI of -2.078 to 0.889 ms/deg (p= 0.410).

- When patients taking benzodiazepines were excluded, there was a larger difference between the two groups at last value (-1.076 ms/deg with 95% CI of -4.315 to 2.164 ms/deg, p = 0.472).
- The qualitative evaluation of both the 'raw' peak velocity/amplitude data and the peak duration regressions on amplitude showed that 11/15 patients (73%) in the 24 Months miglustat group, compared with 3/6 patients (50%) in the 12 Months miglustat group had stabilised or improved at the last assessment, i.e. disease progression for SEM was slower in the patients treated with miglustat for 24 months.

For the secondary efficacy outcomes, the evaluator provided Table 17

- VSEM-α and β at Months 12, 24 and last value, Saccades were abnormal for all except for two of eight patients in the 12 Months miglustat group at baseline and were abnormal for all patients at the last visit.
- Assessments of swallowing produced complex results with the difference between 12 and 24 month miglustat treatment only achieving significance for swallowing 5mL water (p = 0.028, last value).
- Neurological examinations at Months 12, 24 and last value. No statistically significant difference was observed between the groups, the difference between the groups for tongue muscles showed a positive trend (p = 0.053; Fisher's Exact Test). There was very little change in gait from screening to last visit.
- Neuropsychological assessments at Months 12, 24 and last value. Very few patients (8 & 9) were assessed.
- Tremor assessments at Months 12, 24 and last value. Only 4 patients had Archimedes spiral assessment.
- Quality of life assessments at Months 12, 15, 18, 21, 24 and last value – 10 patients assessed.

(3) Further study extension for 24 months

16 patients from the prospective, non-controlled 12 month extension study entered this further study extension of 24 months duration. Nine (9) patients completed the further 24 months treatment period. Comparison of the NPC manifestations in these 16 patients apparently revealed little or no differences, to those presented at baseline by all patients randomised at the start of Study OGT 918-007. In this extension study, neither were the study objectives specified nor the primary efficacy endpoint assessed. Some of the secondary endpoints [assessment of swallowing ability, neurological examinations (ambulatory index and auditory acuity) and neuropsychological assessments (MMSE)] were assessed.

For the secondary efficacy outcomes**,** the evaluator stated that:

- More than 75% of patients showed improvement or stability for all swallowing assessments. At the last assessment, seven patients (58%) had normal auditory acuity in both ears and five had abnormal results (1 patient changed from normal to abnormal in both ears at last assessment). Mean ambulatory index score fell from baseline to last value by -0.6, 8/12 patients, (67%) showed no change in score, 2 patients showed a deterioration ≥ 2.

(4a) Paediatric (4 to 11 yrs old) age group

This paediatric age subgroup was performed to evaluate the safety and tolerability of miglustat in children < 12 years as apparently two-thirds of cases of NPC are diagnosed before the age of 10 years. The inclusion criteria were similar to those for the main OGT 918-007 study. The study enrolled 12 patients (2 patients were accepted though they did not have NPC confirmed by abnormal cholesterol esterification and abnormal filipin staining). The children had a higher incidence of splenomegaly and hepatomegaly than in the adult/juvenile main study. Auditory acuity was normal for all except 1 patient who had abnormal hearing at baseline. Dose calculation was based on Body Surface Area (BSA)/1.8 of the adult dose (200mg tds). Initial duration was 12 months.

The efficacy parameters were similar to those for the main OGT 918-007 study. The neuropsychological tests used to assess these patients were; the Wechsler Scale, the Child's Memory Index and Vineland Adaptive Behaviour Scale. (Data from these studies was not available). The Quality of Life questionnaire used was the Child's Health Questionnaire-PF50 (CHQ).

On the efficacy outcomes for this particular paediatric study, the evaluator stated that:

- There was a mean decrease in HSEM-α of -0.465 ms/deg (to last value). The ratio of this to SE indicates that this within-patient comparison is statistically significant using the t-distribution. In the qualitative assessment, most patients showed improvement.
- HSEM-β increased (i.e. deteriorated) by 4.533 ms (to last value). The ratio of mean change to SE indicated that this within-patient comparison is not statistically significant using the t-distribution.
- Swallowing deteriorated in some patients; of the 2 already with some deterioration, 1 showed some improvement. 1 patient had abnormal pharyngeal gag and 2 patients had abnormal tongue muscles findings at baseline and at last visit, otherwise all neurological assessments were normal.
- Little change in gait. The Standard Ambulation Index for 8/11 patients had no change in value to last visit, and 3 patients worsened by two grades. Reflex and muscle assessment showed no clinically relevant changes. The proportion of patients with ptosis remained unchanged. Only 3 patients completed the CHQ-PF50 QoL questionnaire.

(4b) 12-24 months extension period

Ten of the 12 patients previously treated entered this 12-24 month extension study. Regarding efficacy, the evaluator stated that:

- Over the 12-24 months, mean HSEM-α increased by 0.414ms/deg although the result was still a slight (-0.075ms/deg) improvement on baseline (3/10 patients improved, 1 was stable and 6 deteriorated). Ambulation Index showed 8/11 had no change and 3 deteriorated.

(4c) Continued treatment extension period

This continued treatment extension period was to permit all patients to continue with therapy if it was considered by the Investigator to be in the best interests of the patient. This was also to enable the collection and assessment of further safety data. There was no efficacy data collected except Brainstem Auditory Evoked Potentials in some patients.

Surveys

Retrospective treatment case survey

According to the evaluator, the survey was based on a questionnaire for each NPC patient treated with miglustat. There were 36 paediatric and 30 adult/juvenile patients surveyed. The

mean age at diagnosis was 9.7 (range 0-32) years, the mean age at treatment start was 12.8 (range 0.6-43) years. As per the birth years on case report summaries, 7 patients commenced at age 3 years, 4 at age 2 years and 2 at age 1 year. The mean duration of treatment was 543 days (18 patients received treatment for > 24 months). Dosage varied (based on 61 patients) from adult mean dose 535mg/day (29.5% were on 200mg TID- the rest less) to paediatric mean dose 260mg/day.

Regarding outcomes**,** the evaluator stated that:

- 16 patients left (4 died, 6 due to adverse effects, 2 due to lack of efficacy, 1 was lost to follow-up, 3 due to unspecified causes) the study.
- Ambulation was improved in 9/64 patients (14%) and was stable in 40/64 patients (62%); manipulation improved in 8/63 patients (13%) and was stable in 40/63 patients (64%); language articulation was improved in 7/61 patients (11%) and was stable in 40/61 patients (66%); swallowing function was improved in 12/63 patients (19%) and was stable in 39/63 patients (62%).
- A composite score was calculated for each patient as the mean of the four individual scores (ambulation, manipulation, language and swallowing). The difference between mean age of onset and mean age of initiation of treatment is 3.1y, double the mean duration of treatment of 1.5y, thus progression rates before and after treatment were adjusted for the time intervals between the three time points: diagnosis, treatment initiation and last contact. The progression rate decreased significantly from 0.11 score units/year between diagnosis and treatment start to -0.01 units/year after miglustat initiation (paired sample test comparison by Wilcoxon signed rank test

Retrospective natural history case survey

This was a retrospective questionnaire-based survey to assess, from the medical records, the progression of neurological outcomes in the natural history of the disease beginning at diagnosis and at follow-up visits (up to 4). Treaty two and 35 adult/juvenile patients (mean age at diagnosis was 10.7 years, range 0-41 years) were assessed. The follow-up mean time was 5.5 (range 0.2 to 29.9) years.

On the outcomes**,** the evaluator stated that:

- The composite score increased from 0.15 at the time of diagnosis to 0.58 at the last visit, mean scores of all four parameters increased substantially between the time of diagnosis and last visit (between 3- to 6- fold). The annual progression rate of all parameters according to age at diagnosis was consistently highest in the early childhood group and lowest among juveniles-adults. Over the natural course of the disease, the progression rate appears continuous without any apparent spontaneous decline, the highest rate of progression was observed for the swallowing score and the lowest for the language articulation score.
- At the time of diagnosis of NPC disease, seizure activity was present in only 3 patients (5%), <1/3 months (2 partial, 1 global). By last visit, this rose to 32% (18 patients; 4 partial, 8 global, 6 both). 5 patients had < 1 seizure /3months, 2 had <1 /month, 3 patients had < 1 /week and 7 patients had > 1 /week.
- Among those patients (N=49) with a time interval ≥ 1 year between diagnosis and the last visit, only 14% of patients showed 'stable' disease and 86% 'progressed' disease (Note**:** Subjects were classified either as having 'stable' disease if none or only one out of four parameters had worsened during the course of the disease, or as having 'progressed' disease if at least two parameters had worsened). This proportion was 86% in the early childhood group, 82% in the late childhood group and 94% among juveniles-adults.

The Delegate noted that 19 patients included in the retrospective natural history case survey, with similar composite score at diagnosis and same annual progression rate to those of the other 38 patients in that natural survey, apparently also had retrospective treatment case record review. The evaluator stated that in this subgroup of 19 patients, the composite score at diagnosis and at the start of treatment, and the annual progression rate were also similar to those of the other 47 patients in the treatment survey.

Regarding safety issues**,** the evaluator stated that:

- 40 patients with NPC disease received ≥ 1 dose of miglustat. Overall, mean exposure duration is given as 1233.5 days (3.4 years); 1282 days in patients enrolled in the Main study, 1140.3 days in patients enrolled in the Paediatric sub-study.
- In the 35 patients with 145 miglustat related AEs, most common were diarrhoea in 33 (82.5%), flatulence in 21 (52.5%), weight decreased in 15 (37.5%), abdominal pain upper in 11 (27.5%) and tremor in 11 (27.5%). Nine patients had 18 AEs that lead to discontinuation (of which 9 AEs were related to miglustat).
- There have been 3 patients reported with Crohn's disease on miglustat (one reporter stated awareness of 3 other cases of Crohn's in NPC patients not on miglustat). Most commonly marked laboratory abnormalities were neutrophils 10/38 (26.3%), and platelets 4/39 (10.3%). 39% of the patients (38% of the juvenile/adults and 42% of the paediatric patients) already had platelet counts below the lower limit of normal at screening. Reduced platelet count is a common finding in NPC disease and is likely related to residual splenomegaly.

The evaluator's consideration of the application is as per the conclusions and recommendations below:

- Is it recommended that miglustat be approved for the treatment of adult and paediatric patients aged 4 years and older with Niemann-Pick Type C Disease with progressive neurological manifestations.
    1. The evidence provided supports that the treatment delays the development of the neurological manifestations; the individual patient analysis did not support overall improvement in patients' neurological manifestations.
    2. Given that the onset of symptoms can be delayed until adulthood (in 40% of cases), treatment in the absence of symptom onset has not been justified.
    3. The study evidence submitted excluded children aged < 4 years, while the survey evidence suggests that this age group is much less likely than older patients to benefit.
    4. The product is a capsule, there are practicalities in the swallowing of this in small children and infants, where swallowing may anyway become impaired (in the retrospective survey the highest rate of progression was observed for the swallowing score).
- CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations Effective: December 2006 provides that:
    - If, collectively, the data look compelling, then a Marketing Authorisation may be grantable. Considerations should include:
        1. How closely changes in the surrogate endpoint are causally linked to changes in a clinical endpoint or symptom.
        2. How much risk is associated with the therapy
        3. What other therapies (if any) are available for the same condition.

- Demonstrating that a surrogate endpoint adequately reflects the true clinical endpoint is difficult.
- Epidemiological data and data from patient registers may provide some help. These data may be limited when there are very few patients.
- A risk-benefit assessment may become very difficult, since the size of benefit may be impossible to determine based on a surrogate endpoint.
- Also, it has to be pointed out that surrogate markers cannot serve as final proof of clinical efficacy or long-term benefit. If they are intended to be the basis for regulatory review and approval then, unless they are properly validated, there should be a predetermined plan to supplement such studies with further evidence to support clinical benefit, safety and risk/benefit assessment.
- The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important.

Risk-Benefit Analysis

Apart from the safety concerns (gastrointestinal lesions /carcinogenicity) expressed by the toxicology evaluator, there is a suggestion in the clinical evaluator's considerable conclusions that the suggested approval recommendation for this application is based purely on low level and insufficient efficacy evidence. In what can be termed the pivotal part of Study OGT 918-007 (the 12 months randomised, standard care controlled, open label period), there was no statistically significant difference between the miglustat and no treatment standard care groups in the nominated primary efficacy outcome (change in HSEM-α from baseline to Month 12). Furthermore, the assessed secondary efficacy parameters of swallowing ability, muscle neurological status and gait revealed no significant differences between groups in terms of improvement or deterioration. The latter essentially indicates lack of miglustat treatment effect on most of the key features (dysarthria, dysphagia, dystorisa, saccadic patsy and ataxia) of progression in Niemann-Pick disease, type C.

The prospective, non controlled 12 month extension part of the study, also revealed worsening of the HSEM-α from baseline and the few secondary efficacy parameters assessed, neither had better efficacy outcome overall nor showed major statistically significant differences between the 12 and 24 months treatment groups.

The overall quality of the prospective Study OGT 918-007 is considered unsatisfactory (uneven patient distribution, missing data/ incomplete or missing assessment, open/ non-blinded) and becomes very poor, for the further extension 24 months part of the study (no study objectives, non assessment of the primary efficacy endpoint) and the paediatric (4 to 11 years old) subgroup study [inclusion of patients without NPC disease confirmation, patients with higher incidence of hepato-splenomegaly, open, non controlled, non randomised]. The scanty efficacy assessments in the 24 months extension study and the paediatric subgroup study added little or no supportive evidence that miglustat alters the progression of NPC disease overall.

It is well recognised that the outcomes derived from retrospective questionnaire survey data have their limitations and may not have the same interpretation as those derived from prospective, properly designed study data. Compounding the issue is the fact that the retrospective treatment survey data had to be adjusted to obtain the reported progression rate decrease from 0.11 score unit/year between diagnosis and treatment start to -0.01 unit/year post miglustat initiation. It was noted that no such adjustment can be made when calculating the progression rate (with which comparison is extrinsically being made) from the data derived from the retrospective natural survey data because of the different scenario. Consequently, any impression of decreased progression of the disease from the retrospective

treatment survey data can only be noted as “false positive”, more so, that such finding were not convincingly verified in the prospective long term data analyses.

It is acknowledged that Niemann-Pick Type C disease is a progressive neurological disease leading to disability and premature death in all cases and that there is no known cure or any approved disease modifying treatment. With the above in mind, it is not proper to give official approval for miglustat to be used for the proposed application and to do otherwise, will give a “false promise” to the patients and their carers. Supportive care is essential and remains as the mainstay of management as it substantially improves the quality of life of people affected by NPC.

The Delegate proposed to recommend the rejection of the application.

In its pre-ADEC ssubmission, the sponsor provided a detailed response to the Delegate’s concerns. The sponsor noted that the Delegate indicated that the main issues with the current application are:

i) “…low level and insufficient efficacy evidence”, and

ii) “false-positive” findings regarding disease progression

Considering the gravity of NP-C disease and the current total lack of useful treatment options for these patients, it is therefore appropriate to explore the available data in their entirety, so as not to discount findings supportive of intervention benefit. Given the relentlessly progressive nature of the disease, a tolerable treatment that could favourably modify neurological function, by halting the progression of the neurological disease or reducing the rate of neurological deterioration, would represent a substantial advancement in the clinical management of the disease, which is currently based on supportive measures only. Despite its limitations, Trial OGT 918-007 of miglustat in NP-C disease is the first (and only) controlled study of pharmacological intervention against neurological disease in this rare disorder, the natural history of which is characterised by relentless progression to disability and death. As presented in the application, and discussed by the clinical evaluator, there are multiple and consistent indications that miglustat is active on the progression of neurological involvement in NP-C disease, and that this activity translates into beneficial effects both in individual endpoints of obvious clinical relevance and in responder analyses assessing the benefit at the patient level. Moreover, there are no specific safety concerns associated with miglustat in the target population that could not be monitored in clinical use and that would outweigh a benefit in this disorder.

Taking the totality of the information into account, there is a very reasonable case for stating that miglustat treatment provides clinically pertinent and relevant effects on the progression of CNS involvement in patients with NP-C disease.

In the view of the sponsor, to regard any impression of decreased disease progression from the retrospective treatment survey data as “false positive” is completely incorrect. If the expression "false positive" refers to a concern regarding potential bias in the retrospective survey studies, the fully consistent findings between the two surveys and the prospective study OGT 918-007 should create reassurance that what has been observed is a true treatment effect. The Delegate asserts that supportive care substantially improves the quality of life of NP-C patients. In fact supportive care is a totally ineffective treatment, and is more akin to palliative care in that it has absolutely no impact on the course of disease or outcome in this relentlessly progressive condition. The extent of improvement in a patient’s quality of life that is offered by supportive care is also questionable. To deny patients all hope of receiving treatment with a pharmacological agent that has shown clear clinically relevant (albeit not

statistically significant) benefits over the current standard supportive care, as acknowledged in the granting of an approval by the EMEA/CHMP, would be concerning.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, disagreed with the Delegate's proposal.

ADEC recommended approval of the application for the indication:

for the progressive neurological manifestations in adult and paediatric patients with Niemann-Pick disease Type C

In making this resolution, the Committee acknowledged that Niemann-Pick Type C (NPC) disease is a progressive neurological disease leading to disability and premature death in all cases and that, there is no known cure or any approved disease modifying treatment. Although the study presented a limited evidence of efficacy (the information considered by the Committee demonstrated slight improvements in ambulation, swallowing, hearing and eye movements) the ADEC noted that it would be difficult to establish a randomised clinical trial due to the rarity of the condition, and it would be difficult to obtain more conclusive data.

Furthermore the ADEC noted that the oral administration of miglustat in animal models of NPC resulted in a delayed onset of neurological dysfunction (ataxia and intention tremor), an increase in the average life span and a reduction in ganglioside accumulation and accompanying neuropathological changes. In addition, miglustat has the ability to cross the blood brain barrier. In reflecting that there is a low adverse drug reaction profile for miglustat there remains a positive risk benefit ratio, albeit modest.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zavesca capsules containing miglustat 100mg for the new indication of

Treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick disease Type C

Attachment 1. Product Information

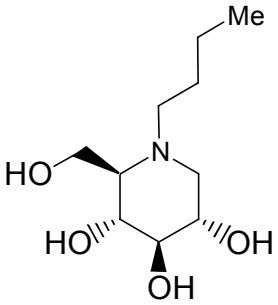
PRODUCT INFORMATION

ZAVESCA® (Miglustat)
100mg capsules

NAME OF THE MEDICINE
Miglustat

DESCRIPTION
Miglustat is an orally active, non-peptide, N-alkylated imino sugar, which is a synthetic analogue of D-glucose. It is a white to off-white crystalline solid and is highly water soluble (›1000mg/mL as a free base). The chemical name of miglustat is 1, 5-(butylimino)-1,5-dideoxy-D-glucitol.

Molecular structure



Molecular formula: $C_{10}H_{21}NO_4$
Molecular mass: 219.28
CAS Number 72599-27-0

Each capsule contains:
Active: 100 mg miglustat
Inactives: sodium starch glycollate, povidone, magnesium stearate
Capsule shell: gelatin, titanium dioxide (E171), black printing ink

PHARMACOLOGY

Pharmacodynamics
Type 1 Gaucher disease
Type 1 Gaucher disease is an inherited metabolic disorder caused by a functional deficiency of β-glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid; glucocerebroside. The failure to degrade glucocerebroside results in the lyosomal storage of this material within tissue macrophages, leading to widespread pathology. Macrophages containing stored glucocerebroside are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney and intestine. Secondary haematogical consequences include severe anaemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. Skeletal complications include osteonecrosis and osteopenia with secondary pathological fractures and associated pain; all of which can cause significant morbidity.

Miglustat acts as a competitive and reversible inhibitor of glucosylceramide synthase, the enzyme responsible for the first and committed step in the synthesis of most glycosphingolipids. The goal of treatment with miglustat is to reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid is reduced to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (substrate reduction therapy).

In vitro and *in vivo* studies have shown that miglustat can reduce the synthesis of glucosylceramide-based glycosphingolipids in a dose-dependent manner

Niemann-Pick type C (NP-C) disease
NP-C disease is a very rare, invariably progressive and eventually fatal neurodegenerative disorder characterised by impaired intracellular lipid trafficking. The neurological manifestations are considered secondary to abnormal accumulation of glycosphingolipids in neurons and glial cells.

Miglustat showed efficacy in relevant animal models of NP-C disease and resulted in a delayed onset of neurological dysfunction (ataxia and intention tremor), an increase in the average life span and reduction in ganglioside accumulation and accompanying neuropathological changes.

Pharmacokinetics
Pharmacokinetic parameters of miglustat were assessed in healthy subjects, in a small number of patients with Type 1 Gaucher disease, and in adults, adolescents and children with Niemann-Pick type C disease.

Miglustat, dosed at 50 and 100 mg in Gaucher patients, exhibits dose proportional pharmacokinetics. The pharmacokinetics were not altered after repeated dosing, three times daily, for up to 12 months.

The kinetics of miglustat appear to be dose linear and time independent. In healthy subjects miglustat is rapidly absorbed. After a 100 mg oral dose, maximum plasma concentrations are reached approximately 2 hours after dosing. Absolute bioavailability has not been determined. The effective half-life of miglustat is approximately 6 to 7 hours, which predicts that steady-state will be achieved by 1.5 to 2 days following the start of three times daily dosing. Food may delay the absorption of miglustat. It is recommended that miglustat be taken away from food to reduce gastrointestinal effects (see Dosage and Administration).

The apparent volume of distribution of miglustat is 83L. Miglustat does not bind to plasma proteins. Miglustat crosses the blood-brain barrier.

The major route of excretion of miglustat is renal with a mean of 82.8% of an administered dose recovered in the urine. Faecal excretion accounted for a mean of 11.9% of the dose. The majority of the material excreted was unchanged miglustat. Minor metabolites were detected in plasma, urine, and faeces. Apparent oral clearance (CL/F) is 230 ± 39 mL/min. The apparent terminal half-life is 6-7 hours.

The pharmacokinetics of miglustat are similar in adult Type 1 Gaucher disease patients and Niemann-Pick type C disease patients when compared to healthy subjects. Pharmacokinetic data were obtained in paediatric patients with Niemann-Pick type C disease aged 5-11 years. Dosing in these children at 200 mg t.i.d. adjusted for body

surface area resulted in C_{max} and AUC_{τ} values which were not appreciably different to those in adolescent/adult patients on 200 mg t.i.d (see Table 1).

Table 1: Comparative Pharmacokinetics in healthy and disease states

Parameters - geometric mean (CV)	NP-C 200mg TID N=6 Age >12 y	Type 1 Gaucher 100 mg TID N=5 Age >12 y	Healthy volunteers 100mg OD
$AUC_{(0-8h)}$ (ng.h/mL)	16412 (19.5)	9071[b] (24)	10622[a]
C_{max} (ng/mL)	2698 (22.9)	1722 (19)	1367 (24.6)
C_{trough} (ng/mL)	1427 (18.3)		
T_{max} - medium (h) (range)	3.00 (0.75 - 4)	1 (1-4)	2.5 (1-4)

a AUC 0-1h
b AUC 0 - 6 to 8h

Renal impairment has a significant effect on the pharmacokinetics of miglustat with an increased systemic exposure associated with a decrease in CL/F, based on observations in patients with Fabry disease and renal insufficiency. These data suggest an approximate decrease in CL/F of 40% and 60%, in mild and moderate renal impairment, respectively. Only very limited data are available in severe renal impairment.

No data are available to evaluate the effects of hepatic impairment on miglustat pharmacokinetics. However, as miglustat is eliminated primarily via the kidneys it is not expected that hepatic impairment will have a clinically relevant effect on the pharmacokinetics of miglustat.

Over the range of data available, no significant relationships or trends were noted between miglustat pharmacokinetic parameters and demographic variables (e.g. age, body mass index, gender or ethnicity). There are currently no pharmacokinetic data available in the elderly (>70 years).

CLINICAL TRIALS

Type 1 Gaucher disease

The safety and efficacy of ZAVESCA® in Type 1 Gaucher disease has been investigated to date in three open-label, non-comparative studies. Efficacy parameters included the evaluation of liver and spleen volume, haemoglobin concentration and platelet count.

In the three non-comparative, monotherapy studies of ZAVESCA®, all patients had mild to moderate Type 1 Gaucher disease, who were unable or unwilling to receive enzyme replacement therapy (ERT), or who had not taken ERT in the preceding 3 months. Mild to moderate Type 1 Gaucher disease was defined as measurable liver or spleen enlargement and Hb<115g/L or platelets <100 x 10^9/L; if splenectomised, liver weight should be >2.5% body weight.

A brief overview of the design and outcome of each of these studies is provided below.

Study 1

In Study 1, ZAVESCA® was administered at a dose of 100 mg, three times daily (t.i.d.). Twenty-eight patients were enrolled in the study, of whom 22 patients completed the initial 12 month phase and 14 patients completed 24 months of treatment. Compared with baseline values, there were statistically significant reductions in hepato- and splenomegaly (measured by magnetic resonance imaging or computed tomography) (Table 2).

Study 2

In Study 2, ZAVESCA® was administered at a dose of 50 mg t.i.d. for 6 months in a total of 18 adult patients. Seventeen patients completed the study. Sixteen patients elected to continue to receive ZAVESCA® in a 6-month extended treatment protocol and 12 patients continued treatment up to 12 months (see Table 2 for a summary of efficacy results).

Study 3

In Study 3, ZAVESCA® was administered at a dose of 100 mg t.i.d. for 12 months, with an optional extended study period of 12 months for a total of 24 months. Eight patients were enrolled in the study, of which 7 patients completed both the initial 12 month phase and the extension up to 24 months (see Table 2 for a summary of efficacy results).

Table 2: Miglustat efficacy in mild to moderate Type 1 Gaucher disease

	6 months	*1 year*	*2 years*
Trial 1 – 100 mg tid			
Liver volume mean Baseline, L *% change* *[95% CI]*	(n=21) 2.4 -7.0 [-10.5, -3.4]	(n=21) 2.4 -12.1 [-16.4, -7.9]	(n=12) 2.5 -14.5 [-19.3, -9.7]
Spleen volume mean Baseline, L *% change* *[95% CI]*	(n=18)* 1.6 -15.1 [-18.4, -11.8]	(n=18)* 1.6 -19.0 [-23.7, -14.3]	(n=10)* 1.6 -26.4 [-30.4, -22.4]
Haemoglobin mean Baseline, g/L *Change (g/L)* *[95% CI]*	(n=22) 119 0.3 [-2, 2]	(n=22) 119 3 [-1, 6]	(n=13) 110 9 [3, 15]
Platelets mean Baseline, x10^{9}/L *Change (*x10^{9}/L *)* *[95% CI]*	(n=22) 77 4 [-1, 9]	(n=22) 77 8 [2, 15]	(n=13) 72 14 [8, 19]
Trial 2 – 50 mg tid			
Liver volume mean Baseline, L *% change* *[95% CI]*	(n=17) 2.5 -5.9 [-9.9, -1.9]	(n=13) 2.4 -6.2 [-12.0, -0.5]	N.D.
Spleen volume mean Baseline, L *% change* *[95% CI]*	(n=11)** 2.0 -4.5 [-8.2, -0.7]	(n=9)†† 2.0 -10.1 [-20.1, -0.1]	N.D.
Haemoglobin mean Baseline, g/L *Change (g/L)* *[95% CI]*	(n=17) 116 -1 [-5, 2]	(n=13) 119 1 [-7, 9]	N.D.
Platelets mean Baseline, x10^{9}/L *Change (*x10^{9}/L*)* *[95% CI]*	(n=17) 116 5 [-6, 17]	(n=13) 122 14 [-3, 31]	N.D.
Trial 3 – 100 mg tid			
Liver volume mean Baseline, L *% change* *[95% CI]*	(n=8) 2.3 -8.4 [-16.1, 0.7]	(n=7) 2.3 -9.4 [-19.5, 0.6]	(n=7) 2.3 -5.6 [-12.1, 1.0]
Spleen volume mean Baseline, L *% change* *[95% CI]*	(n=8) 1.1 -19.0 [-30.4, -7.6]	(n=7) 1.1 -14.4 [-31.9, 3.1]	(n=7) 1.1 -15.4 [-34.4, 3.5]
Haemoglobin mean Baseline, g/L *Change (g/L)* *[95% CI]*	(n=8) 132 2 [-6, 9]	(n=7) 132 0 [-5, 5]	(n=7) 132 -3 [-9, 5]
Platelets mean *Baseline, x10^{9}/L* *Change ((*x10^{9}/L*)* *[95% CI]*	(n=8) 84 4 [-4, 13]	(n=7) 84 14 [2, 26]	(n=7) 84 21 [-30, 73]

* 3 splenectomised. ** 7 splenectomised. †† 5 splenectomised.

Niemann-Pick type C (NP-C) disease

Data to support safety and efficacy of ZAVESCA® in Niemann-Pick type C disease come from a prospective open-label clinical trial (OGT 918-007) and a retrospective survey. The clinical trial included 29 adult and juvenile patients in a 12-month controlled period, followed by extension treatment for an average duration of 3.9 years and up to 5.6 years. In addition, 12 paediatric patients were enrolled in an uncontrolled substudy for an overall average duration of 3.1 years and up to 4.4 years. Among the 41 patients enrolled in the trial, 14 patients were treated with ZAVESCA® for more than

3 years. The survey included a case series of 66 patients treated with ZAVESCA® outside of the clinical trial for a mean duration of 1.5 years. Both data sets included paediatric, adolescent and adult patients with an age range of 1 year to 43 years. The usual dose of ZAVESCA® in adult patients was 200 mg t.i.d., and was adjusted according to body surface area in paediatric patients.

The efficacy variable of primary interest in study OGT 918-007 was the change from baseline to Month 12 and last value in Horizontal Saccade Eye Movements α (HSEM-α), derived from the quantitative measurement of horizontal saccadic eye movement (SEM) velocity, using blinded, centralised assessment. The measure of saccadic eye movement was selected because supranuclear gaze palsy (saccadic initiation failure) is often the earliest neurological sign in NP-C and because saccadic eye movement failure is associated with definite visual, learning and social handicap. There where no statistically significant differences between the ZAVESCA® and the No Treatment groups (see table 3).

Table 3: Analysis of change from baseline in HSEM-α (efficacy set Main Study Juveniles/Adults)

Parameter		Adjusted mean change from baseline		Estimated treatment difference	95% CI	p-value
HSEM-α (ms/deg)		ZAVESCA®	No Treatment			
	Month 12	–0.329	–0.055	–0.274	(–0.959, 0.411)	0.414
	Last value	–0.376	–0.050	–0.326	(–1.000, 0.348)	0.327

The ANCOVA model used for all analyses includes terms for baseline, age and treatment group, CI = confidence interval
Greater mean decreases in HSEM-α (i.e., improvements) from baseline to Month

A qualitative examination of the main sequences scatter plots and visual comparison of the regression slopes for the plots of saccades from 26 patients who provided useable data at both baseline and month 12 (or last visit) showed in the ZAVESCA® group, 15/19 patients (79%) were stable or improved (7 improved, 8 no change), 2 deteriorated, and 2 had ambiguous results while in the No treatment group, 2/7 patients (29%) were stable or improved (1 improved, 1 with no change), 3 deteriorated, and 2 had ambiguous results.

An additional exploratory analysis excluding patients on confounding benzodiazepine medication (a sedative that can slow saccades) demonstrated a significant difference in HSEM- α between treatment groups at 12 months (see table 4)

Table 4: HSEM-α: Analyses of changes from baseline to last value (Efficacy set) – OGT 918-007 Main study, Comparative Phase

HSEM-α (ms/deg)	Adjusted mean change from baseline		Estimated treatment difference	95% confidence interval	p-value
	ZAVESCA®	No Treatment			
Planned analysis[a]					
Last value	–0.376	–0.050	–0.326	–1.000, 0.348	0.327
Including center in the model[b]					
Last value	–0.463	0.055	–0.518	–1.125, 0.089	0.091
Excluding pts on benzodiazepines[c]					
Last value	–0.485	0.234	–0.718	–1.349, –0.088	0.028

[a] The ANCOVA model used includes terms for baseline, age, and treatment group.
[b] The ANCOVA model used includes terms for baseline, centre, and treatment group.
[c] The ANCOVA model used includes terms for baseline, centre, and treatment group. Seven patients received benzodiazepines during the study (6 in the miglustat group, and 1 in the No Treatment group) and were excluded from this analysis.
ANCOVA = analysis of covariance, HSEM = horizontal saccadic eye movement, pts = patients.

Secondary efficacy endpoints: Swallowing function, motor disability, and cognitive ability were also assessed. Swallowing function was assessed on a rating scale, evaluating the patient's ability to swallow water and food substances of varying consistencies. The observed relative risk for any deterioration of swallowing function up to Month 12 with ZAVESCA® vs. No treatment was 0.4 (95% CI 0.13, 1.22, p = 0.17). Motor disability was assessed with the Hauser Standard Ambulation Index (SAI). The observed mean increase (deterioration) in SAI from Baseline to Month 12 was smaller with ZAVESCA® treatment versus No treatment [ZAVESCA®: 0.087 (95% CI -0.287, 0.461), No Treatment: 0.802 (95% CI 0.220, 1.385), treatment effect (ANCOVA with terms for baseline, center, treatment group): -0.715 (95% CI -1.438, 0.007, p= 0.052)]. The assessment of cognitive ability, measured through change from baseline to Month 12 in the Folstein Mini-Mental Status Examination (MMSE) score in adult/adolescent patients, showed a difference in favour of ZAVESCA® [ZAVESCA®: 1.219 (95% CI -0.060, 2.498), No Treatment: -0.352 (95% CI -2.213, 1.510), treatment effect (ANCOVA with terms for baseline, center, treatment group): -1.571 (95% CI -0.692, 3.834, p= 0.165)].
Several other secondary and exploratory endpoints did not indicate clinically relevant effects of ZAVESCA® vs. No Treatment. These included other measures of saccadic eye movements, liver, spleen and cerebellar volumes, standardized neurological examination, additional neuropsychological tests, and quality of life measures.
The data from treatment with ZAVESCA® of paediatric patients with Niemann-Pick Type C disease corroborated the findings in the controlled study in adolescent and adult patients.

In the retrospective survey, disease progression was assessed within the functional domains swallowing, ambulation, manipulation (dysmetria/dystonia), language function/articulation, and overall disability according to a published NP-C disability scale. Across functional domains and for overall disability, ZAVESCA® treatment was

associated with clinically relevant reductions in annualized progression rate, compared with pre-treatment.

The benefit of treatment with ZAVESCA® for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g. every 6 months; continuation of therapy should be re-appraised after at least 1 year of treatment with ZAVESCA®.

INDICATIONS

ZAVESCA® is indicated for the oral treatment of patients with mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option.

ZAVESCA® is indicated for the treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick type C disease.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

General

The efficacy and safety of ZAVESCA® has not been evaluated in patients with severe Type 1 Gaucher disease, defined as haemoglobin concentration <90g/L, platelet count <50 X 10^9/L and active bone disease. Enzyme replacement therapy remains the standard of care for previously untreated patients with Type 1 Gaucher disease.

Neurological Events

Approximately 38% of patients in clinical trials in Type 1 Gaucher disease, and 58% of patients in a clinical trial of Niemann-Pick type C disease reported tremor on treatment. In Type 1 Gaucher disease: these tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month and in many cases resolved during treatment after between 1 and 3 months. Dose reduction may ameliorate the tremor, usually within days, but discontinuation of treatment may sometimes be required. As tremor has also been described in ZAVESCA®-naïve patients with Type 1 Gaucher disease, the presence of pre-existing tremor should be formally investigated prior to the initiation of ZAVESCA® therapy.

Regular monitoring of vitamin B_{12} levels is recommended because of the high prevalence of vitamin B_{12} deficiency in patients with Type 1 Gaucher disease.

Peripheral neuropathy seems to be more common in patients with Type 1 Gaucher disease compared to the general population. Cases of peripheral neuropathy have been confirmed by *ad hoc* electrodiagnostic (EDX) testing in patients treated with ZAVESCA®, primarily in those with relevant concurrent conditions, such as vitamin B_{12} deficiency and monoclonal gammopathy. None of these patients had a formal baseline neurological assessment prior to initiation of therapy to exclude pre-existing disease and further, relevant symptoms, including paraesthesia, and EDX-confirmed peripheral neuropathy have been reported in ZAVESCA®-naïve patients with Type 1 Gaucher disease. Nevertheless, all patients receiving ZAVESCA® should undergo formal baseline and repeat neurological evaluation at 6-month intervals. Patients who

develop symptoms, or who have an exacerbation of pre-existing symptoms, such as numbness and tingling, on treatment should have a careful re-assessment of risk-benefit.

Diarrhoea
Gastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the onset of treatment or intermittently during treatment (see ADVERSE REACTIONS). The mechanism is probably inhibition of disaccharidases in the gastrointestinal tract. The majority of cases are mild and are expected to resolve spontaneously on therapy. In clinical practice, diarrhoea has been observed to respond to diet modification (reduction of lactose and other carbohydrate intake), to taking ZAVESCA® away from meals, and/or to anti-diarrhoeal medication such as loperamide. In some patients, temporary dose reduction may be necessary. Patients with chronic diarrhoea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. ZAVESCA® has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.

Male Fertility
Male patients should maintain reliable contraceptive methods whilst taking ZAVESCA® and for 3 months thereafter. Studies in the rat have shown that miglustat adversely affects spermatogenesis, sperm parameters (in particular, increases in the number of abnormal sperm) and reduces fertility.

Renal impairment
Miglustat is excreted primarily by the kidneys and thus, renal impairment may affect its clearance. Dose adjustment is therefore recommended in these patients (*see Dosage and Administration*). At present, there is insufficient clinical experience with the administration of ZAVESCA® in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) and thus, ZAVESCA® is not recommended in these patients.

Interactions with Other medicines
In vitro data demonstrated that miglustat had no relevant inhibitory effect on the cytochrome P450 (CYP) isoenzymes evaluated (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4). Consequently, miglustat is not expected to increase the plasma concentrations of medicinal products which are metabolised by these isoenzymes.

Limited pharmacokinetic data suggest that co-administration of ZAVESCA® and imiglucerase rch (Cerezyme®) in patients with Type 1 Gaucher disease may result in decreased exposure to miglustat (a reduction of approximately 22% and 14% was observed in C_{max} and AUC, respectively, in a small parallel-group study).

A population pharmacokinetic analysis indicated that loperamide has no effect on the pharmacokinetics of miglustat.

Niemann-Pick type C disease

Neurological events

The benefit of treatment with ZAVESCA® for neurological manifestations in patients with NP-C should be evaluated on a regular basis, e.g. every 6 months; continuation of therapy should be re-appraised after at least 1 year of treatment with ZAVESCA®.

Growth events in paediatric and adolescent patients
Reduced growth has been reported in some paediatric patients with Niemann-Pick type C disease in the early phase of treatment with miglustat where the initial reduced weight gain may be accompanied or followed by reduced height gain. Growth should be monitored in paediatric and adolescent patients during treatment with ZAVESCA®, the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy.

Delayed sexual development was observed in juvenile rats treated with miglustat from prior to weaning to maturity at doses less than the maximal recommended paediatric dose, based on body surface area. The clinical relevance of this finding is unknown.

Haematological events
Mild reductions in platelet counts without association to bleeding were observed in some patients with NP-C treated with ZAVESCA®. In patients included in the clinical trial, 40-50% had platelet count reductions below the lower limit of normal at baseline. Monitoring of platelet counts is recommended in these patients.

***Use in Pregnancy: Pregnancy Category* D**
There is currently no relevant experience with the administration of ZAVESCA® in pregnant women. Miglustat might be expected to cross the placenta and has been shown to be embryotoxic when administered to rats and rabbits. Observed effects included increased post-implantation losses, and decreases in fetal body weights and ossification of various bones. There was an increase incidence of vascular anomalies in rabbits. Increased gestation length and dystocia were observed in rats. Increased post-implantation loss and an increase in gestation length were observed at doses of ≥60 mg/kg/day in rats (relative exposure based on plasma AUC of 1 compared to AUC expected at the maximum recommended clinical dose). Dystocia was observed at 180 mg/kg/day (relative exposure of 3 based on AUC at the maximum recommended clinical dose). In rabbits, increased post-implantation losses were observed at doses of ≥45 mg/kg/day, and the increase in vascular abnormalities occurred at ≥15 mg/kg/day (relative exposure on a body surface area basis of <1 in both instances). In general, reproductive toxicity was observed at doses that were maternotoxic. ZAVESCA® should not be used during pregnancy. Effective contraceptive measures should be used by women of childbearing potential.

Use in Lactation
It is not known if miglustat is excreted in breast milk. ZAVESCA® should not be used during breastfeeding.

Carcinogenicity
In a 2 year carcinogenicity study in rats, miglustat increased the incidence of Leydig cell tumours at all dose levels studied (30-180 mg/kg/day). Based on plasma AUC comparison, the lowest dose represents a relative exposure of only about 0.4 of that expected at the maximum recommended clinical dose. The mechanism of tumour induction and the relevance of these tumours to human risk assessment are unknown, but Leydig cell tumours can occur in male rats by a non-genotoxic mechanism

involving hormonal modulation of testosterone synthesis. The carcinogenic response seen in rats occurred at dose levels which also produced testicular tubular atrophy.

In a 2 year oral carcinogenicity study in mice, miglustat increased the incidence of inflammatory lesions, hyperplasia and tumours (mainly adenocarcinomas) in the large intestine at all doses tested (210, 420 and 840/500 mg/kg/day (dose reduction after half a year)). Exposure to miglustat (mg/kg) was 18-42 times that at the maximal recommended clinical dose. The relevance of these tumors to humans on long term ZAVESCA® therapy cannot be excluded.

Genotoxicity
Miglustat did not show any potential for mutagenic or clastogenic effects in a standard battery of genotoxicity studies.

Ability to drive and use machinery
No studies on the effects of ZAVESCA® on the ability to drive or use machines have been performed. However, dizziness has been reported as a very common adverse event and patients suffering from dizziness should not drive or operate machinery.

ADVERSE REACTIONS

Clinical studies
In nine clinical trials in different indications 206 patients were treated with ZAVESCA® at dosages of 50-200 mg t.i.d. for an average duration of 2.2 years. Adverse events reported in clinical trials of ZAVESCA® in 90 patients with Type 1 Gaucher disease and in 40 patients with Niemann-Pick type C disease are listed below by body system and frequency (very common: >1/10, common > 1/100 and < 1/10). Most events were of mild to moderate severity.

Blood and lymphatic system disorders
Common: Thrombocytopenia

Metabolism and nutrition disorders
Very common: Weight loss
Common: Anorexia, Decreased appetite

Psychiatric disorders
Common: Insomnia, libido decreased

Nervous system disorders
Very common: Tremor
Common: Peripheral neuropathy, headache, dizziness, paraesthesia, hypoesthesia, ataxia

Gastrointestinal disorders
Very common: Diarrhoea, flatulence, abdominal pain,
Common: Nausea, constipation, vomiting, dyspepsia, abdominal distension/discomfort

Musculoskeletal and connective tissue disorders
Common: Muscle spasms

General disorders and administration site reactions
Common: Fatigue, asthenia

Investigations
Common: Nerve conduction studies abnormal

Weight loss has been observed in approximately 60% of patients. The peak was at 12 months with a mean weight loss of 6-7% of body weight and a subsequent trend for the weight to return to baseline levels thereafter.

ZAVESCA® has been studied in several diseases including Type 1 Gaucher disease and Niemann-Pick type C disease where certain events reported as ADRs such as neurological symptoms/signs and thrombocytopenia could also be due to the underlying condition.

Isolated cases of cognitive dysfunction have been reported during clinical trials of ZAVESCA® in type 1 Gaucher disease. A causal relationship has not been established.

DOSAGE AND ADMINISTRATION

Therapy should be directed by physicians who are experienced in the management of Gaucher disease or Niemann-Pick type C disease.

Dosage in Type 1 Gaucher disease

Adults
The recommended starting dose for the treatment of adult patients with Type 1 Gaucher disease is 100 mg three times a day.

As there has been no formal food interaction study performed, it is recommended to take ZAVESCA® without food.

Patients should be instructed to reduce the intake of foods which are high in disaccharides (e.g. lactose or sucrose) or to take ZAVESCA® away from food, as these actions have been shown during the clinical studies to reduce the risk and/or intensity of gastrointestinal adverse events. Also, the use of medications such as loperamide have been demonstrated to be effective in patients experiencing diarrhoea on ZAVESCA®. Temporary dose reduction of ZAVESCA® to 100 mg once or twice a day may be necessary in some patients because of diarrhoea.

Children, adolescents and the elderly
There is currently no relevant experience with the use of ZAVESCA® in patients under the age of 18 and over the age of 70[1].

Dosage in Niemann-Pick type C disease

Adults and adolescents
The recommended dose for the treatment of adult and adolescent patients with Niemann-Pick type C disease is 200 mg three times a day.

Children
Dosing in patients under the age of 12 should be adjusted on the basis of body surface area (BSA, mg/m^2) as illustrated below:

BSA (m^2)*	Recommended dose
> 1.25	200 mg three times a day
> 0.88 - 1.25	200 mg twice a day
> 0.73 - 0.88	300 mg daily divided in 2–3 doses
> 0.47 - 0.73	100 mg twice a day
≤ 0.47	100 mg once a day

* Body surface area (m^2) = 0.007184 x (patient height in cm)$^{0.725}$ x (patient weight in kg)$^{0.425}$

Temporary dose reduction may be necessary in some patients because of diarrhoea

The benefit to the patient of treatment with ZAVESCA® should be evaluated on a regular basis (e.g. every 6 months).

There is limited experience with the use of ZAVESCA® in Niemann-Pick type C disease patients under the age of 4 years.

Renal impairment (GD1 and NP-C)
Pharmacokinetic data indicate increased systemic exposure to miglustat in patients with renal impairment, consistent with the kidneys being the main route of elimination. In patients with an adjusted creatinine clearance of 50-70 mL/min/1.73m^2, administration of ZAVESCA® should commence at a dose of 100 mg twice daily. In patients with an adjusted creatinine clearance of 30-50 mL/min/1.73 m^2, administration should commence at a dose of one 100 mg capsule per day. If necessary the reduced dose can be achieved by dosing twice or once daily respectively. Use of ZAVESCA® in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) is not recommended owing to a lack of clinical experience.

Hepatic impairment (GD1 and NP-C)
ZAVESCA® has not been evaluated in patients with hepatic impairment, although it is assumed that hepatic impairment will not affect the pharmacokinetics of miglustat, as most of the drug is eliminated unchanged, primarily via the kidneys.

OVERDOSAGE
No acute symptoms of overdose have been identified. ZAVESCA® has been administered at doses of up to 3,000 mg/day for up to six months in HIV positive patients during clinical trials. Adverse events observed included granulocytopenia, dizziness and paraesthesia. Leukopenia and neutropenia have also been observed in a similar group of patients receiving doses of ≥ 800 mg/day.

PRESENTATION
ZAVESCA® (miglustat 100mg) is available in blister cartons of 90 hard gelatin capsules

STORAGE
Store below 30°C

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

TGA approved:3 February 2010

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