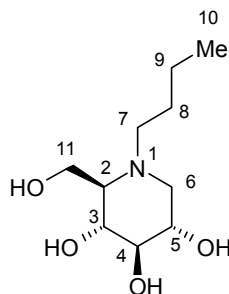


SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Zavesca. This scientific discussion has been updated until 1 April 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Zavesca contains the active substance, miglustat. Miglustat is a synthetic derivative of a family of polyhydroxylated alkaloids or imino sugars extracted from plants and microorganisms. The chemical name for miglustat is 1,5 (Butylimino)-1,5-dideoxy-D-glucitol. Miglustat has a molecular weight of 219 and the following chemical structure:



Miglustat reduces the biosynthesis of glucosylceramide from ceramide through the inhibition of the enzyme glucosylceramide synthase. Glucosylceramide is the first committed step in the synthesis of some 300 to 400 glycosphingolipids. This inhibitory action forms the rationale for substrate reduction therapy in Gaucher disease for which excessive accumulation of glucosylceramide underlies the pathogenesis.

In spite of being ubiquitous components of eukaryotic cells, the exact biological functions of glycosphingolipids have not been clarified. *In vitro* studies have indicated that glycosphingolipids (GSLs) can contribute to cell growth, differentiation, cell to cell and cell to matrix interactions, membrane organisation and signalling. Ceramide, apart from being one of the building blocks for sphingolipids (GSLs and sphingomyelins), is also a potent signalling molecule. Glucosylceramide has been shown to be important in maintaining axonal growth in experimental *in vitro* systems. The consequences of glucosylceramide depletion in human are not well understood.

Miglustat also inhibits the following enzymes at different IC_{50} : α -glucosidase I and II, the disaccharidases sucrase and maltase, lactase (weak inhibition), lysosomal and non-lysosomal glucocerebrosidase. α -glucosidases are *N*-linked oligosaccharide processing enzymes important for protein folding and protein function. The inhibition of disaccharidases probably accounts for the abdominal symptoms and osmotic diarrhoea that complicate miglustat treatment (see pre-clinical and clinical sections of this report). Non-lysosomal glucocerebrosidase may have a role in ceramide mediated signal transduction and the potential effects of this inhibition are unknown.

Gaucher disease is the most common glycosphingolipid lysosomal storage disorder and the first to be treated by enzyme replacement. It is an inherited functional deficiency of glucosylceramidase, alternatively known as glucocerebrosidase, a β -glucosidase. The lysosomal enzyme glucocerebrosidase is responsible for the hydrolysis of glucosylceramide (GlcCer) into free glucose and ceramide. Reduced activity of this enzyme leads to the accumulation of GlcCer in macrophages and underlies the pathogenesis of Gaucher disease.

The inheritance of Gaucher disease is autosomal recessive and is most commonly found among Ashkenazi Jews. It is estimated that the prevalence of Gaucher disease – all types – was less than 0.6 per 10,000 in the EU at the time the application was made. The relationships between the mutant

alleles, consequent enzyme variants, activator proteins and the phenotypes of the disease remain poorly understood.

Classification of Gaucher disease is based on the age of onset and clinical features. Type 1 disease (adult) is characteristically non-neuronopathic and accounts for approximately 99% of cases. Type 2 (infantile) is the most severe neuronopathic form and is generally fatal by 2 years of age.

Type 3 disease (juvenile) is characterised by subacute neuropathological symptoms and is intermediate in severity.

Patients with type 1 Gaucher disease can be affected by visceral enlargement, bleeding tendency caused by thrombocytopenia, recurrent infections and repeated episodes of bone pain caused by infarction. Bone infarction can lead to growth retardation and skeletal deformities. Osteoporosis is nearly universal in these patients. The course of type 1 Gaucher disease is variable. Most patients have a normal life expectancy, though overwhelming sepsis, possibly exacerbated by the loss of the spleen, can be the cause of death. Patients with type 1 Gaucher disease also appear to have an excess risk for the development of malignancies, especially lymphoproliferative disorders.

The management of type 1 Gaucher disease was based on supportive measures until the 1990's. These included orthopaedic procedures and splenectomy. Various dose regimens of recombinant enzyme (Cerezyme) are now used. Although enzyme replacement therapy (ERT) has been successful in alleviating the effects of the type 1 Gaucher disease, the response may be incomplete in some patients with a degree of residual organomegaly, haematological abnormalities or elevated biochemical markers of disease. The skeletal response to ERT is slower and less robust than the response of visceral organs. About 15% of patients develop IgG antibodies to ERT but anaphylactoid reactions are very rare. Pulmonary hypertension has also been observed in patients receiving ERT but that is also a rare feature of the disease independent of ERT. The need for regular intravenous administration is an important consideration for the affected patients.

Zavesca is indicated for the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1 of the SPC). Therapy with Zavesca should be directed by physicians knowledgeable in the management of Gaucher disease. The recommended starting dose for the treatment of patients with type 1 Gaucher disease is 100 mg administered orally three times a day.

2. Chemical, pharmaceutical and biological aspects

Composition

Zavesca contains 100 mg of miglustat as active ingredient and it is presented in the form of hard capsules.

Conventional pharmaceutical excipients (sodium starch glycollate, povidone, and magnesium stearate) have been selected and the rationale for the selection of the individual excipients is also given. The capsule shell contains gelatin and titanium dioxide. The printing ink contains black iron oxide, shellac, soya lecithin and antifoam.

The product is packaged in Aclar/Alu blisters.

Active Substance

Miglustat is a single stereoisomer of an imino sugar. It is a white crystalline material, which is highly soluble in water (greater than 1 g/ml at ambient temperature).

There are 4 chiral centres; miglustat is used in this application in the RRRS-enantiomer. The structure has been established unequivocally by single x-ray crystallography, elemental analysis, IR spectroscopy, UV spectroscopy, NMR spectroscopy, Mass spectroscopy and specific optical rotation.

Various routes of synthesis have been applied in the manufacture of the active substance during the pharmaceutical, pre-clinical and clinical development of the product. The proposed commercial synthesis of miglustat is a 4-stage process starting with (D+)- glucose and n-butylamine. This process has been validated particularly with regard to stereoisomerism.

Batch analysis results indicate that the batches manufactured using all the different synthetic routes are practically identical with respect to quality and, particularly, the impurity profile.

Active substance specification

The active substance specification includes tests for identity (infrared spectroscopy, HPLC, polarimetry), assay (HPLC, 98 – 102%) and a number of purity tests for related substances (HPLC and TLC), residual solvents (GC). The specification also includes a test for microbiological control. The analytical methods used in the routine controls are suitability described. The validation studies submitted are in accordance with the ICH Guidelines.

Impurity limits in the specification are justified by toxicology studies relevant to the chosen method of synthesis.

Batch analyses include eleven batches of active substance. The batch analysis data show that miglustat can be synthesised reproducibly according to the agreed specification.

Stability

Stability studies have been performed on seven full manufacturing scale batches of miglustat. These batches were stored following the guidelines of the ICH at accelerated and long-term storage conditions.

The parameters studied were appearance, colour and clarity, melting point and range, miglustat identity by HPLC, specific optical rotation, HPLC assay of miglustat content, HPLC assay and TLC determination of miglustat related substances, moisture content by LOD and KF, total viable aerobic count (every 12 months). The test methods employed during the stability studies are stability-indicating and the same methods that were used for the control of active substance at release.

The tests carried out in these studies are sufficient to establish the retest period for miglustat.

Other Ingredients

Sodium starch glycollate, povidone, and magnesium stearate are of Ph Eur/USP quality. Certificates of analyses are provided and show compliance with respective monographs.

The Magnesium stearate is of vegetable origin, and statements concerning the absence of risk for TSE transmission are provided. Certificates of Suitability by the EDQM on minimising the risk of transmission of TSE for the gelatine are also supplied. Specifications of the capsule shells are provided, including an identification test for titanium dioxide.

The printing ink used for the capsules is a proprietary mixture and its specification includes an identification test for black iron oxide.

Zavesca capsules are supplied in Aclar/Alu blister packs. The suppliers have provided technical specifications, which comply with the current EU requirements.

Finished Product

The development pharmaceuticals have taken into consideration the physicochemical characteristics of the active drug substance, such as high aqueous solubility, hygroscopic properties, stability, particle size, polymorphism and biopharmaceutical issues such as dissolution rate.

The compatibility of the active drug substance with excipients, content uniformity and chemical stability in the presence of excipients was also examined. Conventional pharmaceutical excipients have been selected and the function of each individual excipient is standard and well-known.

The process for the manufacturing of the finished product follows conventional pharmaceutical practices, which utilise a blending step, granulation, encapsulation, and packaging. The manufacturing process has been adequately validated and is satisfactory. The in process controls are adequate for this capsule preparation. Based on data presented it is concluded that the blending and granulation processes have been satisfactorily qualified according to the parameters conventionally applied to a product of this type.

The batch analysis data show that the capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product Specification

The specification includes tests by validated methods for identification (IR and HPLC), assay (standard limits, i.e. 95-105% by HPLC of the labelled quantity of miglustat), degradation products and impurities (HPLC and TLC), uniformity of mass and uniformity of contents.

The tests and limits of the release and shelf life specification for the finished product are appropriate to control the quality of Zavesca 100 mg capsules for their intended purpose.

Stability of the Product

In total three batches of Zavesca 100 mg capsules were evaluated for stability using a range of challenge ICH stability conditions (25 °C/60% RH, 30 °C/60% RH and 40°C/75% RH) stored for up to 12 months in Aclar/Alu packs.

Supportive stability data are also available for three batches of Zavesca 100 mg capsules and Zavesca 50 mg capsules stored at ICH conditions in double aluminium blisters for up to six months, and three batches of Zavesca 50 mg stored in Aclar packs for up to 12 months.

As a conclusion from the stability studies, the results indicate satisfactory stability and support the shelf life stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Zavesca 100 mg is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for the marketing authorisation. There are no major deviations from EU and ICH requirements.

In general, this is a standard oral formulation of a very soluble active substance, and no problems of bioavailability may arise from pharmaceutical quality aspects of the product.

The active substance is well characterised and documented. The excipients are commonly used in this kind of formulation; the packaging material is well documented and meets Ph Eur requirements. The manufacturing process of finished product has been adequately described. The quality defined is supported by all data provided in the dossier.

The stability data of the finished product in the proposed packaging has been adequately demonstrated and supports the proposed expiry date.

3. Toxicopharmacological aspects

Pharmacodynamics

In vitro studies

The proposed mode of action of miglustat in the treatment of Gaucher disease is based on its inhibitory activity against glucosylceramide synthase, an enzyme in the first synthetic step of numerous glycosphingolipids and a key component in the regulation of intracellular levels of ceramide and glycosphingolipids. *In vitro*, IC₅₀s of 20-40 µM against glucosylceramide synthase have been reported. The proposed clinical dosing regimen is related to plasma C_{max} values of approximately 9 µM. The IC₅₀ values for miglustat with respect to glucocerebrosidase, the lysosomal enzyme deficient in Gaucher disease and a non-lysosomal glucosylceramidase activity, an integral membrane protein, were 520 and 0.31 µM, respectively. The potential physiological/pathological responses to an inhibition of the latter enzyme are not known.

Possible biochemical consequences of an inhibition of glycosphingolipid synthesis include increased levels of ceramide and diversion of glycosphingolipid synthesis into the galactosylceramide pathway. One literature study reports increased levels of sphingomyelin in mouse liver, suggesting conversion of excess ceramide along this axis. Under conditions where the galactosylceramide pathway is inhibited, diversion into the glucosylceramide synthase route has been shown, but the opposite reactions seem less likely although there are indications that this is possible.

The pharmacological studies conducted with miglustat are rather limited. The lack of studies with respect to the desired target enzyme is explained by its specific intracellular localisation in the Golgi apparatus. Studies on the specificity and selectivity with respect to cell types and enzymes could have been valuable. In the literature it is reported that miglustat inhibits the glycogen debranching enzyme 4- α -glucanotransferase with an IC₅₀ of 4.5 µM. Miglustat is also a potent inhibitor of glucosidases with an, IC₅₀ for α -glucosidases in porcine and rat liver of 0.36 µM. Limited experimental data indicates that the difference in potency against glucosylceramide synthase and glucosidase *in vitro* may not translate to the *in vivo* situation possibly in part depending on different subcellular sites of location of the two enzymes. Miglustat also has inhibitory activity against the intestinal disaccharidases sucrase and maltase. The lack of specificity and the fact that the enzyme targeted is the first in an extensive synthetic pathway may provide an explanation for some of the adverse reactions associated with miglustat therapy. A correlation between the extent of enzyme inhibition, changes in glycosphingolipid synthesis and pathological reactions is not possible. In mouse, depletion of approximately 50% of liver and spleen glycosphingolipids, achieved after about 4 months of treatment, was tolerated without any overt signs of toxicity, but body weight decreased.

In vivo studies

In normal mice, miglustat administration in the diet was well tolerated without diarrhoea, but body weights were significantly lower compared with control mice. Ganglioside GM₂ depletion measured after 10 days treatment was about 25% in liver at a dose of 600 mg/kg/day. There are no animal models of Gaucher disease. In mouse embryos, survival was not compatible with homozygosity for the glucosylceramide synthase gene, indicating that activity is essential for normal development and differentiation. In mouse models of related diseases, such as Tay-Sachs and Sandhoff, miglustat treatment seemed to ameliorate disease progression. The doses in these studies, up to 4800 mg/kg for up to 12 weeks, were near maximum possible doses. In Tay-Sachs mice, with central nervous system storage of glycosphingolipids, brain levels of abnormally stored glycosphingolipids were reduced after oral doses of miglustat. Small spleens and thymuses were noted, but no overt toxicity. In Sandhoff mice treated with up to 4800 mg/kg/day, life expectancy was increased by approximately 40%. Miglustat treatment in Niemann-Pick C mice, in which the gene defect is associated with defective intracellular trafficking and accumulation of cholesterol in the liver and spleen, and gangliosides (GM₂

and G_{M3}), lactosylceramide and glucosylceramide in neuronal tissue, prolonged the life-span of mice and decreased the storage of lipids. Type 1 Gaucher disease is considered to have no involvement on the central nervous system (CNS).

Pharmacodynamic drug interactions

Recombinant glucocerebrosidase given by intravenous injection is a current treatment for type 1 Gaucher disease. Potential interactions with miglustat were studied in mice treated for 5 weeks with miglustat and then given 5-10 U/kg of glucocerebrosidase intravenously and activity and enzyme half-life were determined. Data indicated enhanced activity of the enzyme as well as increased half-life (2.1 min in controls and 3.36 min in treated mice).

General and safety pharmacology programme

General pharmacology studies were limited and functional effects on the CNS, cardiovascular system and the gastrointestinal system, only, were investigated. Single doses of up to 27 mg/kg iv in dog, 700 mg/kg ig in rat and 600 mg/kg ig in mouse had no remarkable effect on the parameters studied. Effects on renal and respiratory systems were not studied. The potential for immunotoxicity was considered in relation to repeated dose toxicity studies. Only the perbutyrate analogue was tested and the study was rather limited. The limited scope of general pharmacology studies is accepted, as acute effects are unlikely and repeated dose toxicity studies overall covered relevant aspects.

In vitro studies using foetal fibroblasts and peritoneal macrophages indicated that miglustat at levels up to 6 mg/ml did not affect PGE₂ synthesis. No anti-inflammatory activity was thus evident.

Pharmacokinetics

The pharmacokinetics of miglustat and its perbutyrate analogue were studied. Tritium-labelled miglustat was used in part of these studies and results are based on radioactivity measurements. In other studies on metabolism and disposition, ¹⁴C-labelled compound was used.

Pharmacokinetic data are available for most species used in toxicology studies, but are somewhat limited. There are no data on excretion into breast milk. Distribution studies have not been conducted with miglustat, but with the perbutyrate prodrug, only. Systemic bioavailability of total radioactivity, the majority of which was accounted for by miglustat, was approximately 82% in rat and 64% in rhesus monkey after administration of ¹⁴C-labelled perbutyrate analogue. At molar equivalent doses systemic availability of miglustat from the perbutyrate analogue in monkey was about 38% of that of the active substance. However, at equimolar doses in dogs, maximum plasma levels of miglustat after administration of the prodrug, were 5% of levels obtained with the parent compound. In monkey and dog there was some evidence of partially de-esterified intermediates in plasma, faeces or urine. These data indicate that miglustat toxicity after administration of the prodrug may be better characterized in rat and monkey models than in dog.

Pharmacokinetics of miglustat seem overall fairly uncomplicated with essentially no or very limited metabolism, no protein binding and excretion predominantly into urine. Less than 10% of a radioactive dose was found in faeces in mouse and rat. Renal clearance in mouse and rat was greater than creatinine clearance, consistent with active renal secretion. This was not seen in rhesus monkey or dog. The volume of distribution (V_d) was 0.76 and 0.71 l/kg in dog and monkey, respectively. In mouse and rat, V_d was greater. Distribution of label after administration of the prodrug at 137 mg/kg was extensive with high levels detected in the GI-tract, urinary bladder and kidney. Tissue to plasma ratios of AUC ranged from 10 to 50. Maximum plasma levels were reached in 1 to 2.7 hours in rat and monkey, respectively. Corresponding value in human was 2 hours. The AUC in brain in a mouse study accounted for about 20% of the plasma AUC and 35% in a rat study in which the perbutyrate analogue was administered. Overall, these characteristics indicated that species used in toxicology studies could all be considered as relevant models. In rat and monkey, there was evidence of accumulation of miglustat. In rat, steady-state values appeared to be reached in 26 weeks. In general

there were no significant difference in systemic exposure of males and females, but in the 52-week rat study males tended to have values higher than females.

Toxicology

Single dose toxicity

Single dose toxicity studies with miglustat comprise of 2 mouse and 1 rat study and were not conducted according to current practices. Nevertheless, the studies allow the conclusion that the compound has a low potential for acute toxic effects by the oral route.

Repeated dose toxicity

The toxicity of miglustat and the perbutyrate analogue was investigated in studies in mouse, rat, rabbit, dog and monkey. Doses of 20-4200 mg/kg/day in rat, 20-825 mg/kg/day in dog and 60-1650 mg/kg/day in monkey were tested. The NOEL was 20-60 mg/kg/day in a rat 13-week study and 60 mg/kg/day in a 5-week intravenous monkey study, corresponding to AUCs approximately x1 and approximately x5 the expected clinical value, respectively. Exposure at the low dose in other studies ranged from approximately x2-x5 the expected clinical level and it seems clear that no significant margins of exposure will exist at a NOEL. Chronic toxicity studies are available in the rat only, but a 12-month toxicity study in monkey using the prodrug has been submitted. Toxicokinetic data in the monkey study showed exposure to the active substance and the study could be accepted as the non-rodent chronic toxicity study.

Severe toxicity, deterioration of clinical condition and/or gastrointestinal toxicity, was apparent in rats at repeated doses of over 840 mg/kg/day and in dogs at approximately 85 mg/kg/day, corresponding to AUC levels x8-x18 the expected clinical levels. Severe gastrointestinal toxicity with bloody stools, congestion of the mucosa of small/large intestine, hyperaemia and occasional necrosis of villus tips was most prominent in dogs. Tolerance was better towards the perbutyrate analogue. Gastrointestinal adverse effects are also reported in the clinic and may be related to the inhibitory activity of miglustat on disaccharidases. In most repeated dose toxicity studies decreased body weight gain was recorded. The gastrointestinal effects of miglustat are reflected in section 5.3 of the SPC.

Serum chemistry changes e.g. increases in AST and ALT were noted in rat studies, and also in dog and monkey. A histopathological correlate in the liver was evident only in rare cases. In rhesus monkey, single cell necrosis was noted after 4 weeks and doses of 1650 mg/kg/day. In a dose-escalating study in dogs as well as in the 10-week rat study ALP increased while in most other studies decreases were reported. A potential for hepatotoxicity at high doses cannot be excluded. Toxicity may be secondary to other effects such as gastrointestinal toxicity. The effects on transaminase levels of miglustat are adequately addressed in the SPC.

Haematological examinations showed decreases in red blood cell parameters. White blood cells, neutrophils and lymphocytes were also decreased. Platelets were lowered in most studies. In rat, the appearance of giant platelets was reported. In the 52-week monkey study, 2 high dose animals exhibited depletion of granulocytic cell line storage pool. *In vitro* studies in human bone marrow cells indicated effects of miglustat on neutrophils.

Decreased thymus and spleen weights were reported in several studies in the rat, and in one monkey study (4-week, gastric intubation study). Lymphocyte depletion in submaxillary and mesenteric lymph nodes, thymus and spleen was reported in the rat and in the thymus and spleen in the monkey. The data indicate that miglustat may have a potential for interaction with the immune system, but the findings were likely secondary to debilitation after long-term, high-dose miglustat treatment. This has been considered in the SPC.

Cardiovascular and autonomic parameters were not remarkably affected after a single intravenous infusion of miglustat in dogs. In the 52-week study in rat, cardiac myopathy, or myocardial degeneration and fibrosis complex, was considered an exacerbation of a strain specific pathology. Myocarditis was noted in some monkeys (rhesus) in a 4-week study. In the 52-week monkey

(cynomolgus) study at the high dose that provided systemic exposure levels of miglustat of approximately x 4-7 the expected clinical exposure, males exhibited prolonged QRS and one animal had a second degree AV block. No *in vitro* electrophysiological studies have been performed. Literature data show that ceramide may inhibit L-type calcium channels. Taken together the results suggest a potential for myocardial changes cannot be excluded and this is reflected in the SPC.

Tail lesions, scaly tail and acanthosis/hyperkeratosis, were noted in 3 rat studies after oral dosing. Literature data report that sphingolipid content and ratios in the stratum corneum are essential for maintenance of epidermal permeability barrier. Effects on the tail were not seen in other studies in e.g. mice, and taken together the data do not indicate any generalised effect on skin function. A difference in rodent and human skin barrier biology suggests that skin changes and consequent reactions may not be expected in humans.

Equatorial cataracts were noted in the 1-year rat study. Changes were transitory at AUC levels x 6-7 the expected clinical AUC, indicating a lower level of cause for concern. The reason for the transitory nature of cataracts in the rat is not clear. The finding seems coupled to high doses and prolonged exposure. The cataracts have been addressed in section 5.3 of the SPC.

An increased incidence of chronic progressive nephropathy was also reported for treated rats in the six-month toxicity study with the perbutyrate analogue. Furthermore, kidney changes were seen at the microscopic examination in all treatment groups in one 13-week study in male rats. Although effects on the kidneys did not appear consistent over studies it is difficult to exclude a possible treatment-related effect. A statement on the potential nephropathy has been included in the SPC.

Effects on the CNS were not evident in short-term tests. The potential for long-term effects is difficult to assess from available repeated dose toxicity studies. Brain is rich in glycosphingolipids. Distribution studies showed that penetration into brain occurs and progressive depletion of gangliosides may take place. Given the nature of the compound and the diverse pathways involved, a theoretical potential for adverse neurological effects is difficult to exclude. Relevant sections in the SPC consider these aspects (also see clinical discussion).

Vacuolation of various organs, thyroid, pancreas and the GI-tract, was reported both with miglustat and its perbutyrate analogue. According to the literature, vacuolation seen with the perbutyrate analogue resembles that seen in humans with genetic glycogenosis Type II or Pompe's disease, conditions where 1,4- α -glucosidase is lacking. Inhibition of host α -glucosidase may lead to altered glycoprotein processing and accumulation of incompletely metabolised oligosaccharides in the rough endoplasmic reticulum of affected cells. The consensus appears to be that it is likely these kinds of changes can be accommodated and are not coupled to functional effects.

Reproduction toxicity

A range of reproduction toxicity studies was conducted in rat and rabbit. None of the studies included toxicokinetic measurements. If systemic exposure data from repeated dose toxicity studies are extrapolated to these studies, the high dose of 180 mg/kg/day in some studies would correspond to approximately 2-3 times the expected clinical exposure. A major target organ in rat was the male reproductive tract, with impairment of fertility and specific studies addressed the issue. A NOEL could not be identified, but effects were apparent at the low dose of 20 mg/kg/day. In repeated dose toxicity studies the effects were characterised by decreased spermatogenesis, hypospermia in the epididymides, decreased sperm concentrations and increased incidence of abnormal sperm morphology. The pivotal reproduction toxicity studies were conducted in accordance with GLP principles. In the male fertility study, the velocity, morphology and concentration of sperms were adversely affected, but the ability to fertilise an ovum was unchanged. Ova that were fertilised seemed to develop normally. A "bell-shaped" dose-response was noted with an increase in number of headless sperm and sperms with reduced hook. Specific studies showed that in rat, 13-weeks of treatment followed by a similar treatment free period was sufficient to reverse the effects on male fertility. Reversibility after long-term treatment is not clear. Sections 4.4, 4.6 and 5.3 of the SPC include appropriate warnings on the potential reproduction toxicity.

Reproductive effects in females included increased post-implantation loss and early embryonic death, increased duration of gestation and dystocia. There is thus a potential that teratogenicity may be superseded by toxicity at high doses. Studies indicate that miglustat crosses the placenta. An increase in incomplete ossification was seen in embryotoxicity studies. In rabbits, a dose-dependent increase in foetuses with an additional blood vessel arising from the aortic arch was noted. This was categorised as a variant and stated to be a common observation in rabbits. Offspring from dams treated with miglustat exhibited lower body weights and survival and tended to perform less well in the rotarod test. Delayed maturity was evident in development of female reproductive systems. These findings have been adequately reflected in the SPC.

Genotoxicity

The potential for genotoxicity was evaluated in gene mutation tests in bacteria, tests for chromosomal aberration in human lymphocytes and in an *in vivo* mouse micronucleus study. Cytotoxic levels were reached with the perbutyrate analogue, but not with miglustat. Both compounds gave overall negative results in the tests.

Oncogenic/Carcinogenic Potential

Studies on the potential for genotoxicity were negative. No carcinogenicity studies have been conducted in accordance with a CPMP scientific advice. However, the applicant is currently conducting a 104-Week Rat Carcinogenicity Study as part of an agreement with the FDA.

Local Tolerance

The sensitisation potential of miglustat was studied in a mouse ear-swelling test. Miglustat dissolved in distilled water was non-irritating at 10% to abdominal skin and 30% was non-irritating to the ear. Miglustat was not a sensitiser in this test.

Primary dermal irritation of miglustat was investigated in an exploratory rabbit study. Miglustat was classified as "very mildly irritating".

Special Toxicity Studies

In female mice treated with miglustat for 118 days at 600, 1200 and 1800 mg/kg/day as escalating doses, spleen and thymus weights were reduced by treatment and this was coupled to reduced cellularity. Plasma levels ranged from 18 to 57 μM , levels considerably higher than expected clinical levels. The cellular composition was altered such that cells positive for T-cell markers were increased and B-cells reduced. The changes showed reversibility. The mechanism of these changes is not known. Potential effects on the immune system were considered particularly during the development of miglustat as an anti-HIV therapy. Miglustat reduced CD4 levels in human lymphoid cell line H9. Treatment for 10 days by intraperitoneal injection of 300 mg/kg did not affect splenocytes. The studies concluded that there were no direct toxic effects on the immune system.

In vitro, miglustat inhibits the glycogen debranching enzyme 4- α -glucanotransferase ($\text{IC}_{50}=4.5 \mu\text{M}$) and related compounds have been shown to inhibit α -1,6-glucosidase. At doses of 2400 mg/kg/day miglustat may impair glycogen breakdown as shown in studies in mice where glycogen content in starved treated mice was more than twice as high as in control starved mice. However, apparently there is no progressive accumulation and no associated pathology in mice treated over 6 months.

Ecotoxicity/Environmental Risk Assessment

An environmental risk assessment has been considered. Due to the rarity of the disorder and the doses proposed to be used no toxic hazard to the general population can be anticipated and the dilution in normal domestic waste stream ensures that biota in the environmental media will not be at risk.

GLP Status

Pivotal studies on repeated dose toxicity, reproduction toxicity and genotoxic potential were conducted in accordance with GLP principles. Studies on general pharmacology were limited and not in compliance with GLP principles; the Company provided an acceptable justification for this deficiency.

Discussion on toxico-pharmacological aspects

The documentation on the pharmacology of miglustat is somewhat limited while toxicology studies overall provide an adequate characterisation of the toxic effects that the compound can produce. Miglustat has shown *in vitro* activity against an enzyme in a pathway relevant for Gaucher disease. The inhibitory activity is not specific for glucosylceramide synthase. The target enzyme is a key component in the regulation of intracellular levels of ceramide and glycosphingolipids and this as well as the non-selectivity, may be related to toxic effects seen at high doses. There is no *in vivo* animal model for Gaucher disease. Efficacy in *in vivo* animal models has been shown in related models of lysosomal storage diseases, including those with a neurological involvement.

Repeated dose toxicity studies showed a wide range of potential targets both with the active substance and the perbutyrate analogue. Severe gastrointestinal toxicity was evident in dogs. Serum chemistry changes, haematological changes and decreased body weights were noted in other studies. Vacuolation of various organs including thyroid, pancreas and liver were recorded. Reproduction toxicity studies showed embryo/foetotoxic potential and impaired fertility in males, which showed reversibility after a treatment free period. Organ weight changes occurred. Cardiomyopathy, nephropathy, possible exacerbations of an underlying pathology, were other findings in rat studies. Equatorial cataracts were noted at high doses in the 1-year rat study. A potential for interference with the immune system has been discussed. Miglustat did not seem to have any genotoxic activity. A NOEL, corresponding to x1 to x5 the expected clinical AUC could only be identified in 2 repeat dose toxicity studies of 13 and 5 weeks duration, respectively. Margins of exposure at doses associated with pathophysiological findings can be expected to be modest in general, but as studies were conducted in healthy/normal animals, higher values might be expected under conditions of glycosphingolipid storage in cases where toxicity can be coupled to an exaggerated pharmacological effect.

The available experimental data are not sufficient to allow any definitive conclusion on the relationship of all toxic effects and treatment with miglustat. In this context additional studies on target organ toxicity in relation to the planned long-term studies would be valuable. The applicant has committed to conduct a preclinical study to further assess the neurotoxic potential of miglustat and will also conduct a Juvenile Growth Study in the Rat. Until the results have been evaluated, the use in children cannot be recommended (see clinical discussion). In addition, the applicant is conducting a further pre-clinical dose range finding study in the mouse to support the planned mouse carcinogenicity study.

It is possible that some of the findings, e.g. nephropathy and cardiac myopathy may not be clinically relevant and represent artefactual changes, chance occurrences or exacerbation of underlying pathology. General debilitation of animals may also be a factor. However, a direct relation to treatment considering the biochemical pathways involved cannot be excluded. These effects appeared at the high doses, but in terms of systemic exposure margins to clinical, levels were not that high. Other factors to consider are that changes can be expected to exhibit progressive development as depletion of glycosphingolipids is expected to occur progressively and that the capacity of homeostatic mechanisms to counteract intracellular disturbances may be unpredictable.

The extent of enzyme inhibition as well as the amount of residual enzyme activity likely exhibits considerable interindividual differences. This together with individual variations in general sensitivity suggests that until additional data becomes available the safety of the compound should be carefully monitored (see clinical discussion). Pre-clinical findings have been appropriately considered in the SPC based on currently available data.

4. Clinical aspects

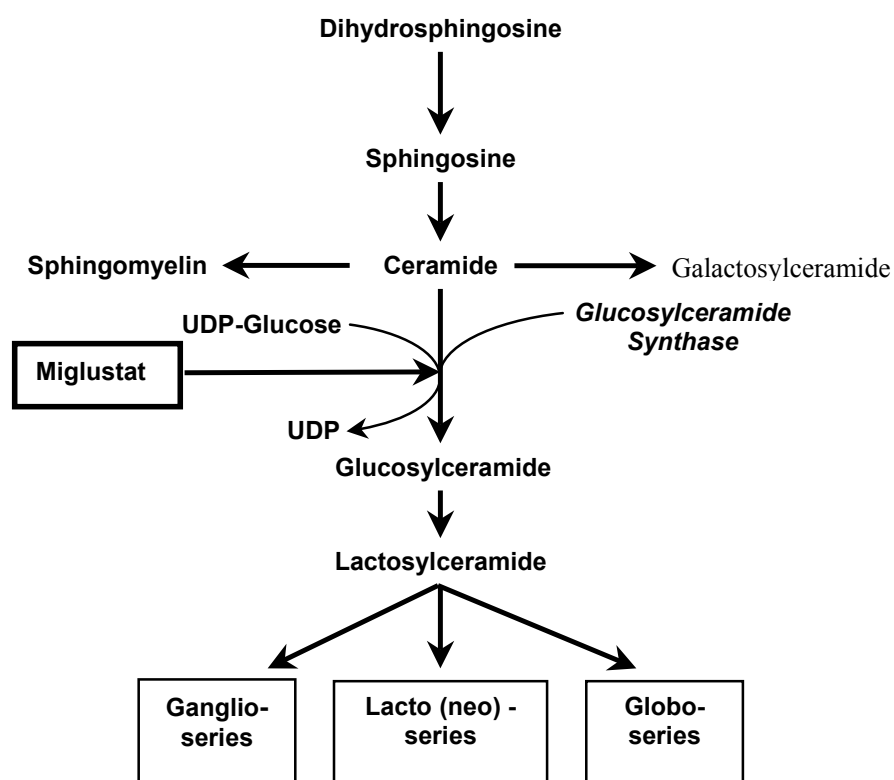
Clinical pharmacology

The rationale for the investigation of miglustat in clinical trials in glycosphingolipid storage diseases is based on *in vitro* data showing that miglustat reduces glycosphingolipid synthesis by inhibiting glucosylceramide synthase (GCS).

The Zavesca capsules proposed for marketing are identical to the formulation used in clinical studies.

Pharmacodynamics

The site of action of miglustat in the biosynthetic pathways of glycosphingolipids:



Glycosphingolipids (GSL)

The human pharmacodynamic data are limited. The effects of miglustat on glycosphingolipids were shown using estimation of G_{M1} ganglioside and plasma glucosylceramide in a small number of patients. G_{M1} ganglioside on leukocytes is the main source of stored glycolipids. These limited data lend support to an *in vivo* effect of miglustat in reducing plasma glucosylceramide but there is no information on the amount of inhibition of the enzyme glucosylceramide synthase at the proposed dose.

G_{M1} analysis on leukocytes was performed for 7 subjects and there was no notable change from baseline in G_{M1} at Month 6, with a mean percentage increase of 0.5% ($p=0.981$). At Month 12, however, there was a statistically significant mean percentage decrease of 4273 binding sites per cell or 38.5% from baseline ($p=0.006$). This decline in cell surface G_{M1} expression on leukocytes confirmed the ability of miglustat to lower the rate of glycolipid biosynthesis. The results showed consistency between reductions in cell surface G_{M1} in the clinical setting and the results of the pre-clinical studies given that, during treatment, miglustat serum concentrations ranged approximately between trough levels of 0.8 $\mu\text{g/ml}$ and peak levels of 1.6 $\mu\text{g/ml}$.

Plasma concentrations of glucosylceramide were measured in a subgroup of eight subjects on miglustat. The mean GlcCer concentration at baseline was 14.2 nmol/ml. There were mean decreases from baseline of 2.2 and 2.8 nmol/ml at Months 6 and 12 respectively (p=0.074 and p=0.172, respectively).

Plasma oligosaccharide analysis was carried out in 6 patients on miglustat to assess the effect of miglustat on α -glucosidase. There was no notable increase in the percentage of *N*-linked glycosylated glycan and it was concluded that there was no major inhibitory effect on *N*-glycan-processing α -glucosidases at the concentration used.

No formal dose-finding studies have been performed for miglustat. The justification for a dose regimen in humans aiming at a plasma level of 1-2 μ g/ml is based on data obtained from a human cell line.

Pharmacokinetics

The pharmacokinetics of miglustat has been characterised in three clinical studies in 82 Gaucher subjects (studies OGT 918-001, -003, and -004), one clinical study in 16 Fabry subjects (study OGT 918-002), and five clinical studies in over 100 HIV positive or AIDS subjects (studies NS8-93-06-001, NS8-93-06-004, NS8-94-06-009, NS8-93-06-010, and NQ3-94-06-101). A relative bioavailability and food effect study has been performed in healthy volunteers. Data from patients with Gaucher and Fabry diseases were included in a population pharmacokinetic evaluation to assess the influence of demographic characteristics and renal and hepatic function on miglustat pharmacokinetics. In Gaucher disease single and multiple doses (TID) of 50 and 100 mg were used and in HIV/AIDS patients doses up to 1000 mg TID.

In study OGT 918-001 and the studies in HIV patients, miglustat was determined in plasma and urine by HPLC and electrochemical detection. In studies OGT 918-002, 3 and 4 an LC-MS method was used. Linearity in plasma and urine was demonstrated for miglustat over the range 30-5000 ng/ml for the HPLC-EDT method and 5-400 ng/ml for the LC-MS method.

Non-compartmental analysis was usually used for calculation of pharmacokinetic parameters. Population pharmacokinetics was performed using NONMEM. Descriptive statistics were used.

Miglustat was shown to be rapidly absorbed and maximum plasma concentrations are reached on average 2-2.5 h after dose. The absolute bioavailability has not been determined.

Mean pharmacokinetic variables (coefficients of variation as %) of miglustat in Gaucher patients after administration of 100 mg TID. (Study OGT 918-001), n=5

Sampling time	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-6h} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	t _{1/2} (h)
Day 1	862 (16)	2.5 (2-4)	3746 (23)	9502 (22)	7.30 (17)
Month 1	1922 (9)	2.0 (1-2.5)	8911 (22)	-	6.39 (22)

t_{max} values are median with range of values in parentheses
The dosing interval was 6/6/12 h

The apparent volume of distribution (V/F) was estimated to be 83 ± 22 l. Miglustat does not bind to plasma proteins. Apparent oral clearance (CL/F) is 230 ± 39 ml/min. The average half-life is 6-7 h.

Miglustat displays dose-proportional pharmacokinetics. Results from between study comparison in Gaucher subjects have shown that the pharmacokinetics is approximately proportional following dosing with 50 mg and 100 mg (single doses and TID dosing), see table below. Additionally, data from a study in AIDS subjects have shown that miglustat pharmacokinetics is dose proportional in the dose range 2 to 16 mg/kg (approximately 140-1120 mg total dose). AUC_{0-τ} at steady-state (TID dosing) is comparable to AUC_{0-∞} following a single dose, see table below, which is a rough indication

that miglustat exhibits linear, time-invariant pharmacokinetics. Approximate C_{\max} (concentration at 2.5 h after dose) and C_{\min} measured for up to 12 months on TID dosing are stable, further supporting pharmacokinetic linearity.

The inter-individual variability in AUC is 22% and in C_{\max} about 10-15%.

Mean (CV%) C_{\max} and AUC after single and TID dosing of 50 and 100 mg miglustat (n=5-6)

	50 mg Single dose	50 mg Steady state	100 mg Single dose	100 mg Steady state
C_{\max} (ng/ml)	382 (34)	827 (25)	862 (16)	1922 (9)
AUC* (ng·h/ml)	3222 (18)	3668 (22)	9502 (22)	8911 (22)

* Single dose: $AUC_{0-\infty}$; Steady state: AUC_{0-6h}

The data provided regarding urinary excretion suggest that about 50% of an oral dose is excreted unchanged in urine. Without information regarding the bioavailability of miglustat these data cannot be properly assessed. Data from preclinical studies and a mass balance study of the prodrug of miglustat strongly indicate renal elimination of miglustat. Thus, there is no major concern regarding the elimination of miglustat, but further data are needed and the Company has committed to perform appropriate studies to elucidate the elimination of miglustat in man.

Renal clearance is about 150 ml/min, suggesting that the renal elimination is mainly through filtration and that the risk for interactions with drugs eliminated by active secretion is low.

Several markers of efficacy (liver response, spleen response, platelet response, and haemoglobin response, measured at the 6-month time point in the Gaucher population) and two adverse events of interest (diarrhoea and tremor) were evaluated using logistic regression, to determine if plasma concentrations were predictive of any particular adverse event or efficacy outcome.

A relationship between the efficacy marker reduction in spleen volume and plasma concentration of miglustat was demonstrated. Data from the extension studies have shown that significant improvements in haemoglobin and platelets take longer time to develop (up to 18 months); consequently the 6-month analysis was probably at a too early time point to discern a significant effect.

No significant relationship was found between steady-state concentrations and the incidence of tremor. However, subjects with higher steady-state concentrations were more likely to experience a greater intensity of diarrhoea than subjects with low concentrations.

Interaction studies

Limited information is available regarding potential pharmacokinetic interactions.

A food effect study performed in healthy volunteers showed that concomitant administration of food decreases the rate of absorption of miglustat (C_{\max} was decreased by 36% and t_{\max} delayed 2 h) but has no statistically significant effect on the extent of absorption. (AUC decreased by 14%). A moderate effect of carbohydrate intake on the rate and extent of absorption of miglustat (approximate 36% decrease in mean C_{\max} and 32% decrease in mean $AUC_{(0-\tau)}$) was observed in HIV patients at a high miglustat dose (1000 mg TID).

Data from *in vitro* studies indicate a low potential for clinically relevant drug-drug interactions with CYP450 isoenzymes.

An *in vivo* interaction study with Cerezyme (recombinant glucocerebrosidase) suggested decreased absorption rate (t_{\max} increased to 4 h) and extent (C_{\max} and AUC decreased 22 and 14%, respectively). However, there does not seem to be any reasonable rationale for the pharmacokinetic interaction

between recombinant glucocerebrosidase and miglustat. The study was a parallel group study in a small number of subjects, and interpretation of the results should be made with caution. This study also indicates that Zavesca has no or limited effect on the pharmacokinetics of Cerezyme. Relevant information has been included in section 4.5 of the SPC.

Special groups

Limited data in patients with Fabry disease and impaired renal function showed that CL/F decreases with decreasing renal function. The data suggest an approximate decrease in CL/F of 40% and 60%, respectively, in mild and moderate renal impairment. Data in severe renal impairment are limited to two patients with creatinine clearance in the range 18-29 ml/min and suggest a decrease in CL/F by at least 70% in such patients, but cannot be extrapolated to below creatinine clearance of 18 ml/min. In response to questions raised, the applicant recommends a reduction of the dosage interval to administration twice daily in mild renal impairment (creatinine clearance 50-70 ml/min/1.73 m²) and once daily in moderate renal impairment (creatinine clearance 30-50 ml/min/1.73 m²), which is acceptable. Data are too limited to give dosage recommendations in severe renal impairment. Relevant information has been included in sections 4.2 and 4.4 of the SPC.

There is no pharmacokinetic information in decreased hepatic function. Population pharmacokinetic analysis demonstrated no influence of gender, age (18 to 69 years), weight, body mass index or race on the pharmacokinetics of miglustat. The pharmacokinetics of miglustat has not been evaluated in children and adolescents, or in elderly above the age of 69 years.

The lack of pharmacokinetic data in children, adolescents (<18 years) and elderly (>70 years) is sufficiently reflected in the SPC.

Clinical efficacy

The efficacy of Zavesca in type 1 Gaucher disease was investigated in three studies with extension phases, consisting of two open non-comparative trials (OGT 918-001 and OGT 918-003) and one open randomised study in comparison with enzyme replacement given as Cerezyme and as combination therapy of Zavesca and Cerezyme (OGT 918-004). Efficacy analyses were performed primarily on the evaluable population, that is, subjects with non-missing values.

Dose response studies

No dose-response studies have been performed although a comparison of the results from OGT 918-001 and OGT 918-003 using different doses would suggest that 100 mg TID could be more effective than 50 mg TID based on larger reductions in organ volumes. The effectiveness of doses below 50 mg TID has not been explored.

MAIN CLINICAL STUDY

OGT 918-001 and extension

Description of the study

Study OGT 918-001, the main efficacy study, was a multi-centre, non-comparative, Phase I/II study of open-label Zavesca in adult subjects with type 1 Gaucher disease. The trial was exploratory and a large number of variables were measured. An exploratory statistical analysis was performed on the key efficacy measures and changes were compared with baseline values. The applicant justified the use of a non-comparative design because the trial was designed to study subjects unwilling or unable to receive ERT.

The inclusion criteria were designed to select patients with at least moderate disease, eligible for ERT according to current standards: (1) Gaucher disease confirmed by a glucocerebrosidase assay; (2) 18 years of age or older; (3) measurable organomegaly (liver or spleen); (4) Haemoglobin <11.5 g/dl or

platelets $<100 \times 10^9/l$ for those with intact spleen or; hepatomegaly with liver weight $>2.5\%$ of body weight for splenectomised subjects.

Among the exclusion criteria were treatment with Ceredase/Cerezyme within 3 months of screening, clinically significant diarrhoea or lactose intolerance.

Among the withdrawal criteria were Ceredase/Cerezyme therapy, unacceptable treatment-related toxicity or other adverse events and disease progression.

A starting dose of 100 mg TID of Zavesca was studied. The dose could be increased by increments of 100 mg TID per month up to a maximum dose of 300 mg TID or until the target trough level of $2 \mu\text{g/ml}$ was reached or toxicity (other than Grade 1 gastrointestinal symptoms) were noted. In addition, dose levels could be reduced if a subject experienced any unacceptable side effect that was thought to be related to Zavesca.

The extended use phase of this study (OGT 918-001X) allowed subjects to continue taking Zavesca 100 mg. Data on the same endpoints collected up to Month 24 are reported. In addition, during the evaluation, the applicant submitted additional 36-month data on eleven patients.

Primary endpoints

The primary efficacy endpoints were organ volume response using MRI or CT studied 6-monthly, monthly assessments of haematological and biochemical responses and overall response. The biochemical responses included chitotriosidase, hexosaminidase, acid phosphatase and angiotensin converting enzyme. Elevations of these enzymes have been reported in Gaucher disease but their significance has not been clearly elucidated. Other exploratory variables included leukocyte G_{M1} analysis on a small number of patients. The chosen endpoints were clinically relevant and similar to those used in the assessment of enzyme replacement therapy.

Patients characteristics and disposition

28 patients who were unable or unwilling to be treated with Ceredase/Cerezyme were recruited. 22 of them were treatment naive. They had at least moderate disease as reflected by the inclusion criteria. The mean age was 44.0 years. There were equal numbers of males and females. 54% were Ashkenazi Jews. 26 were genotyped for Gaucher disease and N370S/N370S was found in 11. 6 of these patients had received previous Ceredase/Cerezyme use. 7 patients were splenectomised. 24 subjects had at least one concurrent illness at screening. 10 had unspecified osteonecrosis and 8 had unspecified osteoporosis.

Five subjects withdrew before 6 months and one withdrew after 6 months. Reasons for withdrawals were one serious adverse event, two unacceptable adverse events, and three withdrawals for reasons other than adverse events. There was one protocol deviation, one patient was included for hepatosplenomegaly despite having haemoglobin and platelet counts that were higher than those stated in the inclusion criteria. This patient was believed to suffer from pulmonary hypertension as an explanation for the elevated blood counts despite significant splenomegaly.

OGT 918-001 extension: Eighteen of the 22 subjects who completed OGT 918-001 were enrolled into the extension study. Doses ranged from 100 mg daily to 200 mg TID during this extended treatment period. The most common dose regimen was 100 mg TID. Fourteen subjects were evaluable after 24 months treatment and thirteen of these have data available at 36 months. Two subjects withdrew due to peripheral neuropathy, two due to diarrhoea, and others due to combinations of adverse events and personal reasons or serious adverse events that were unrelated to treatment.

RESULTS

Organ volumes: The pre-specified criteria for assessing liver and spleen volumes response were categorisation of responses into good, moderate or no response based on criteria formulated prospectively by clinicians in the Academic Medical Centre at the University of Amsterdam. A good response was a reduction from baseline organ volume of 30% or greater, a moderate response between 10% and 30% reduction. Reductions of less than 10% were considered within or close to the variability of the method of assessment, and were therefore classified as no response. Either MRI or

CT scan could be used. The study protocol allowed assessments to be made according to the clinical practice of the individual centre.

Liver organ volume: Baseline mean liver organ volume was 2.38 L (1.49-3.7 L) and the excess liver volume factors were 1.1-2.7 times normal. Using the above response criteria for changes in liver volume, a response was seen in 7/22 evaluable patients at 6 months and 8/12 at 24 months. Further reductions in liver volumes in the extension phase were small and the mean reduction in liver volume from baseline was 14.5% (p<0.001) after 24 months and 17.5% after 36 months.

Spleen organ volume: Baseline mean spleen organ volume was 1.658 L (0.68- 3.36 L) and the excess spleen volume factors were 5.44-24.8 times normal. For changes in spleen volumes, a response was seen in 14/19 evaluable patients at 6 months and 16/18 patients at 12 months. The mean reduction in spleen volume from baseline was 26.4% (p<0.001) after 24 months and 29.6% after 36 months.

Haematological parameters: For haemoglobin concentration and platelet count, a response assessment was based on an increase of these indices from baseline as prospectively defined. Good response was defined by an increase of greater than 1.5 g/dl in haemoglobin concentration or $30 \times 10^9/l$ in platelet count. Moderate response was an increase >0.5 g/dl-1.5 g/dl in haemoglobin concentration or increase of >15-30 $\times 10^9/l$ in platelet count.

Baseline mean haemoglobin concentration was 12.28 g/dl (9.30 - 15.05 g/dl). Overall, there were small increases in mean haemoglobin concentration. They were 0.03 g/dl at Month 6 (p=0.769), 0.26 g/dl at Month 12 (p=0.095), 0.39 g/dl (p=0.045) at 18 months and 0.91 g/dl (p=0.007) at 24 months. Values at 36 months were stable with a mean increase from baseline of 0.95 g/dl.

Haemoglobin response category/Time on treatment and number of evaluable subjects	6-month N=23	12-month N=22	18-month N= 15	24-month N= 13
Good	0	2	1	2
Moderate	2	3	6	6
No	21	17	8	5

Anaemic subjects (baseline haemoglobin <11.5 g/dl) had a mean increase of 1.28 g/dl at Month 24 (p=0.007), higher than for the complete cohort.

Baseline means platelet count was $88.1 \times 10^9/l$ ($33.0 - 334.0 \times 10^9/l$). Throughout the 24 month period, there was a small gradual increase in platelet count from baseline. They were $3.6 \times 10^9/l$ (p=0.146) at 6 months, $8.28 \times 10^9/l$ (p=0.014) at 12 months, 11.16 (p=0.009) at 18 months and $13.58 \times 10^9/l$ (p<0.001) at 24 months. At 36 months, the mean increase in patients remaining on therapy was $22.2 \times 10^9/l$.

Platelet response category/Time on treatment and number of evaluable subjects	6-month N=23	12-month N=22	18-month N= 15	24 -month N= 13
Good	0	1	2	0
Moderate	2	4	3	6
No	20	17	10	7

In OGT 918-001, 21 of the evaluable patients were thrombocytopenic at baseline (platelet count < $150 \times 10^9/l$) and the lowest count was $34 \times 10^9/l$. Among the 17 non-responders in platelet responses, five showed a reduction but only two had a reduction greater than or equal to $10 \times 10^9/l$. None of these patients had a platelet count that fell below $30 \times 10^9/l$.

Biochemical parameters: Very high levels of chitotriosidase activity are characteristic of Gaucher disease and are thought to relate to the numbers of abnormal storage cells. Reductions in the levels of chitotriosidase are therefore indicative of improvement in disease severity. Mean decrease of 2,142 nmol/ml.h or 16.4% (p<0.001) from a baseline of 15,105 nmol/ml.h after 12 months compared with a reduction of 21.9% (p<0.001) or 3,713 nmol/ml.h after 24 months was observed.

Other, less specific disease markers, such as hexosaminidase, tartrate-resistant acid phosphatase and angiotensin converting enzyme (ACE) activities showed less significant but favourable changes. For hexosaminidase, the reduction also continued and was 11.9% at Month 24 (p=0.001). Acid phosphatase showed a mean increase of 597.6 nmol/ml.h from baseline to Month 24 (p=0.023). Mean decreases in ACE were seen throughout the study.

Plasma concentrations of glucosylceramide (GlcCer), which represent the storage material that accumulates in Gaucher disease, were measured in a subgroup of eight subjects. The mean GlcCer at baseline was 14.2 nmol/ml. GlcCer analysis showed mean decreases from baseline of 2.2 and 2.8 nmol/ml at 6 and 12 months respectively (p=0.074 and p=0.172, respectively). Analysis of glucosylceramide beyond 12 months was not performed.

Overall response: This is determined by a combination of the individual response parameters consisting of organ volume response, haemoglobin response and platelet response. Good response is defined as a good response for at least 2 of the 3 above parameters, moderate response is defined as a moderate response for 2 of the 3 above parameters and no response is neither of the former two. At 12 months, 5 of the 22 subjects had a good response, 10 subjects had a moderate response and 7 had no response.

Skeletal disease assessment: Dual energy X-ray absorptiometry (DEXA) was performed on some patients but the data were not analysed as a 24-month interval was not considered to be sufficient for assessing response by this method. Quantitative chemical shift imaging (QCSI) was assessed for two subjects at Centre 2 in three vertebrae of the spine (L3-5). The results showed an improvement in bone marrow fat fraction from baseline to 12 months and a further improvement at 24 months, with values returning to the normal range.

Supportive studies

OGT 918-003 and extension

Description of the study

Study OGT 918-003 was a non-comparative study of 6-month duration that examined a dose of Zavesca 50 mg TID. The study was conducted in two centres. Dose levels of miglustat were to be reduced to 50 mg twice daily if a subject experienced any unacceptable adverse event that was thought to be related to the study medication or if their trough plasma concentrations exceeded 2 µg/ml. Quality of life was also assessed as a secondary variable. Organ volume assessment was based on CT scan.

In total, 16 subjects continued into the extended treatment phase and treatment was increased up to a maximum of 100 mg TID in the majority, although many of these dose increases did not occur until Month 9 or Month 12. Data up to Month 12 are reported for 13 subjects.

Patient demographics

18 subjects were enrolled in OGT 918-003. The mean age was 42.4 years, 13 (72%) subjects were female and 15 (83%) subjects were Ashkenazi Jews. 17 of the 18 subjects were genotyped for Gaucher disease and the most frequent amino acid genotype was N370S/N370S reported in 7 of the patients. Two reported previous Ceredase/Cerezyme use. 50% had undergone surgery for Gaucher disease. 7 were splenectomised. 89% had at least one manifestation of Gaucher disease at screening. The commonest symptoms were fatigue, bone and joint pain/stiffness.

Patient disposition

Seventeen (94%) subjects completed OGT 198-003. One subject withdrew at his own request after 13 weeks because of diarrhoea and flatulence. Sixteen subjects entered the extension study. Four withdrew. There was one unacceptable GI side effect, one case of progressive hepatosplenomegaly (subsequently found to have lymphoma), one lack of improvement and fatigue, and one dissatisfaction and desire for childbearing.

RESULTS

In comparison with the results of OGT 918-001 at 6 months, subjects who received 50 mg Zavesca TID showed smaller reductions in liver organ volumes and spleen organ volumes than those who received 100 mg Zavesca TID. The mean decrease in liver organ volume was 5.9% and the mean decrease in spleen organ volume was 4.5% at 6 months. Only small mean changes from baseline in haemoglobin concentration were seen at both dosage levels and responders were few. In total, six (35%) subjects had a moderate overall response and 11 (65%) subjects had no overall response at Month 6. Six of the 17 subjects had a moderate response or at least 2 moderate responses for organ volume and any of the two haematological parameters. The rest was classified as no response. The efficacy of an even lower dose than 50 mg TID has not been investigated.

Biochemical responses: There were mean decreases from baseline in chitotriosidase (15.3%, $p=0.001$) and hexosaminidase at 6 and 12 months.

Quality of Life (QoL): Clinically significant improvements were seen from baseline to Month 6 in physical function, enhanced role limitations due to physical problems, general health perceptions, vitality and social function. The improvement in mean score for vitality was 16.5% ($p=0.004$) and the improvement of in physical functioning was 9.4% ($p=0.052$). There were no other changes of note.

OGT 918-004 and extension

Description of the study

In study OGT 918-004, a single centre, open-label, comparative study, 36 patients currently maintained on a minimum of 2 years of Cerezyme therapy were recruited and randomised to switch to either Zavesca (100 mg TID), or continuation of Cerezyme regimen or a combination of Zavesca and current Cerezyme regimen for a period of 6 months. The randomisation was done according to a minimisation procedure, which included a random component and was implemented to achieve balance across gender, age, splenectomy, avascular necrosis and length of time on ERT, as these factors were thought to have an impact on Gaucher disease. No formal sample size calculation was performed. Subjects were eligible if they had Gaucher disease (confirmed by a glucocerebrosidase assay), had received continuous Ceredase/Cerezyme therapy for a minimum of 2 years prior to screening and had received their current dose for a minimum of 6 months; and were 18 years of age or older at the time of consent.

The exclusion criteria and withdrawal criteria were similar to those for the non-comparative studies.

29 subjects entered the optional extended treatment phase of 6 months to receive Zavesca monotherapy. Therefore data on switching to Zavesca from enzyme or combination therapy were available in 19 subjects for 6 months and in 10 subjects for 12 months and. During the evaluation the applicant submitted additional 18-month data.

Patient characteristics and disposition

36 subjects were enrolled in the study and were included in the safety population; 33 were included in the efficacy population. 92% of the patients were Ashkenazi Jews. 97% of the patients were genotyped for Gaucher disease and 23 of the 35 subjects had N370S/N370S amino acid genotype. The mean age was 37.2 years. The mean duration of ERT in this population was 5.8 years. The mean baseline organ volumes, haematological parameters and biochemical markers were in keeping with stabilised disease on treatment.

Thirty-three (92%) subjects completed the study; three subjects withdrew due to unacceptable adverse events. One patient developed tremor in the right hand than both hands and expressed desire to have children. One patient was dissatisfied with her quality of life since commencing Zavesca and had unacceptable symptoms from concomitant infectious mononucleosis. One withdrew due to diarrhoea. There was no withdrawal from the Cerezyme treatment arm.

RESULTS

The changes at 6 months were small for organ volume responses and haematological parameters. Of note was a reduction in platelet count upon switching to Zavesca from enzyme replacement. The extension study also showed a fall in platelet count and a rise in chitotriosidase upon switching to Zavesca, while the changes in liver and spleen organ volumes and haemoglobin concentrations were small. Mean hexosaminidase, acid phosphatase and ACE levels all increased numerically on switching to Zavesca monotherapy although there was a large variability in these results.

Summary of changes from baseline in key response variables in Study OGT 918-004 and comparisons between treatment groups at 6 months.

Variable	Change from baseline in treatment group:			Significance
	Zavesca	Cerezyme	Combination: Zavesca/Cerezyme	
Liver volume (%)	-2.9	3.6	-4.9	p=0.047 for Cerezyme vs. combination comparison
Spleen volume (%)	-4.8	-2.1	-8.5	NS
Haemoglobin (g/dl)	-0.31	-0.15	-0.10	NS
Platelet count ($\times 10^9/L$)	-21.6	15.3	2.7	p=0.035 for Zavesca vs. Cerezyme comparison
Chitotriosidase activity (%)	33.0	-0.3	-3.9	p=0.004 for Zavesca vs. Cerezyme & p=0.001 for Zavesca/combination comparisons

NS = differences between treatment groups not statistically significant p-values refer to Analysis of Covariance model (ANCOVA) which included the five minimisation factors in addition to treatment group and the baseline value of the corresponding efficacy variable

OGT 918-004 Extension Study

29 subjects who completed the initial 6-month treatment period entered the 6-month extension phase to receive Zavesca monotherapy. Approximately half of these subjects received 100 mg TID whilst the other half received a reduced dose of 100 mg BID. No subject required re-institution of Cerezyme treatment during the extended treatment period due to deteriorating disease. No subject withdrew due to lack of efficacy and 28 subjects continued on Zavesca monotherapy beyond the extension phase. A summary of the changes in organ volumes and haematological parameters at 12 months compared to baseline is provided in the following table.

Variable	Changes from baseline after 12 months treatment in each of the 3 treatment groups		
	6 month Zavesca/ 6 month Zavesca	6 month Cerezyme/ 6 month Zavesca	6 month Combination/ 6 month Zavesca
Liver volume (%)	-0.8%	-0.7%	-4.0%
Spleen volume (%)	-6.1%	1.5%	-4.8%
Haemoglobin (g/dl)	-0.128	-0.48	-0.133
Platelet count ($\times 10^9/L$)	-27.389	-3.750	-12.222
Chitotriosidase activity (nmol/ml.h) (%)	2634.2 (84.5%)	1980.7 (11.7%)	557.0 (28.6%)

Overall, the difference between the results at 6 and 12 months for the primary variables was marginal. The mean percentage changes in organ volumes were small and none were statistically significant. No clear deterioration in haemoglobin response was observed after switching to Zavesca but there were mean reductions in platelet count from baseline to Month 12 for all three treatment groups. This decrease was greater for the Zavesca/Zavesca group and approached statistical significance (p=0.062). For the Cerezyme/Zavesca and Combination/Zavesca groups, switching to Zavesca monotherapy resulted in statistically significant mean decreases in platelet count from Month 6 to Month 12

($p=0.014$ and $p=0.024$, respectively). For the Zavesca/Zavesca group, there was a much smaller mean decrease in platelet count from Month 6 to Month 12, which was not statistically significant.

For all three-treatment groups, there were mean increases in chitotriosidase from baseline to 12 months after switching to Zavesca monotherapy. The mean percentage increase in chitotriosidase for the Zavesca/Zavesca group was statistically significant (84.5% increase, $p=0.011$). The mean increase in chitotriosidase was statistically significant for the Zavesca/Zavesca and Cerezyme/Zavesca groups ($p=0.008$ and $p=0.042$, respectively) and approached statistical significance for the Combination/Zavesca group ($p=0.064$). The increases after switching to Zavesca monotherapy were statistically significant for the ERT and combination treatment groups.

In summary, the limited follow-up data suggest that miglustat monotherapy may not be sufficient to maintain the same control of disease activity in all patients.

Clinical studies in special populations

None has been performed.

Discussion on clinical efficacy

The pharmacokinetic information in humans is limited. The elimination of miglustat has been poorly studied and the applicant has committed to perform appropriate studies to elucidate the elimination of miglustat in humans. As supportive data from preclinical studies, human studies with the prodrug (OGT 924) and data in Fabry patients strongly suggest renal elimination mainly unchanged, it was considered sufficient to address the issue during the post-marketing phase. The SPC includes recommendations in severe renal impairment. In addition, a statement is included in the SPC on the lack of pharmacokinetic data in patients with liver impairment, in children or adolescents (<18 years) and in elderly (>70 years).

The pharmacodynamic information of miglustat in man is limited and no dose finding studies have been performed.

36 to 42 months of non-comparative data are available on treatment naïve patients with mild to moderate type 1 Gaucher disease. Fifty percent of the original cohort has remained on treatment in excess of 3 years. The chosen endpoints are relevant for clinical care as well as for monitoring. Modest, sustained reductions in organomegaly, increases in haemoglobin concentration and platelet counts, as well as reductions in chitotriosidase activities were seen. At 24 months, 8 of the 12 evaluable patients had $\geq 10\%$ reduction in liver volume and the mean response was 14.5%. All of the 10 evaluable patients had $\geq 10\%$ reduction in spleen volume and the mean reduction was 26.4%. 8 out of 13 evaluable patients had a ≥ 0.5 g/dl increase in haemoglobin concentration but only two of these had a response ≥ 1.5 g/dl. A platelet response of between $15-30 \times 10^9/l$ was observed in 6 of the 13 evaluable patients, but none of these had a response above $30 \times 10^9/l$. The mean reduction in chitotriosidase activities in the 14 evaluable subjects was 21.9%. Other biochemical markers such as hexosaminidase showed similar though lesser changes.

A volume response was evident within one year while the haematological response rate was lower and became noticeable after 18 to 24 months of treatment. It was reassuring that there was no obvious deterioration among the non-responders. The size of the effect of miglustat is difficult to estimate because of the heterogeneity of the disease, the small number of evaluable patients and the lack of a placebo controlled arm for comparison.

The results from the pivotal study OGT 918-001 and its extension show that Zavesca has a modest sustained effect on patients with mild to moderate type 1 Gaucher disease. As the pivotal trial was an open uncontrolled trial, there were methodological limitations to the radiological assessment, and the overall interpretation of the results could have been affected by the withdrawals of non-responding patients. An intention to treat (ITT) analysis with last observation carry forward (LOCF) imputation provided during the review gives some reassurance.

The effect of Zavesca as a maintenance treatment is even less well studied. The results showed small mean percentage decreases in organ volumes but also a fall in platelet count and a rise in chitotriosidase upon switching from ERT to Zavesca. There was no statistically significant deterioration in haemoglobin response. These results suggest that miglustat monotherapy is less effective than ERT in suppressing disease activity.

In summary, defining an indication for Zavesca is difficult because of the limited trial data. The study in treatment naive patients included only those with mild to moderate type 1 Gaucher disease AND who are unsuitable or unwilling to receive ERT. Therefore the potential target population is already limited. Enzyme replacement therapy is the current treatment of choice in treatment-naive patients with type 1 Gaucher disease. Despite a lack of direct comparative studies, it appears that Zavesca does not offer any efficacy advantage over ERT. It is unknown if Zavesca can achieve the same effect as ERT. The role of Zavesca as a maintenance treatment is even less defined. In fact the trial results suggest that miglustat is less effective in suppressing disease activity in patients stabilised on ERT. Efficacy and safety of Zavesca has not been evaluated in patients with severe Gaucher disease, defined as a haemoglobin concentration below 9 g/dl or a platelet count below $50 \times 10^9/l$ or active bone disease is also discussed. There is no experience with the use of Zavesca in patients under the age of 18 and over the age of 70.

The effect of Zavesca on bone disease and painful infarctive bone crises was not an endpoint in the Gaucher studies. DEXA data was collected for future analysis only. The data on bone disease and Zavesca treatment are therefore still incomplete and further data are needed since little is known on the response of skeletal disease to enzyme replacement therapy despite the relatively more rapid improvement in organ volumes and haematological parameters. The bone data from the pivotal study (OGT 918-001) will be made available by the applicant within a predefined timeframe.

Clinical safety

Patient exposure

The safety data are primarily based on 12 to 24-month data from the three completed studies in 80 subjects with type 1 Gaucher disease. In addition, safety data on 16 Fabry subjects and 224 HIV patients in three phase II studies utilising either miglustat or the pro-drug have also been considered. The dosages used in these studies varied

Adverse events and serious adverse event/deaths

Gaucher patients

There were no deaths reported in the three Gaucher studies or their extended treatment periods. There were a total of 13 withdrawals and 9 were considered Zavesca-related in the Gaucher studies. The Zavesca-related withdrawals included two cases of at least moderately severe peripheral neuropathy that were confirmed by electrodiagnostic testing (EMG/nerve conduction studies), three cases of diarrhoea, two cases of gastrointestinal adverse events, one case of gastrointestinal adverse events and tremor, one withdrawal due to tremor (and to have a family). The withdrawals assessed to be unrelated to Zavesca were one each of partial thrombosis of the portal vein complicating undiagnosed hepatocellular carcinoma, concerns about pre-existing pulmonary hypertension, progressive weight loss and unacceptable disease progression caused by undiagnosed intra-abdominal sepsis and B-cell lymphoma, and EBV infection.

There were a total of 8 serious adverse events (SAE) in the Gaucher studies of which 2 cases of neuropathy were considered to be treatment-related. There were 6 SAEs considered unrelated to Zavesca and they were 1 bone crisis, 1 partial thrombosis of the portal vein (undiagnosed hepatocellular carcinoma at entry), 2 orthopaedic surgeries, 1 hospitalisation for elective respiratory tests and 1 elective tonsillectomy.

Nearly all subjects experienced at least one event that was considered related to study medication. The adverse events were mild or moderate in intensity for the majority of subjects. Diarrhoea has been reported by 86% of subjects in the Gaucher study, followed by weight loss (64%), flatulence (43%)

and abdominal pain (40%). The incidence of diarrhoea decreased during therapy, but reports of flatulence and abdominal pain did not decrease to the same extent. Tremor, headache, nausea and dizziness were reported by 10 to 20% of subjects.

Fabry patients

In the Fabry studies the most common adverse events were those of the gastrointestinal system, affecting all 16 subjects. The most frequent event was diarrhoea, reported by 15 (94%) subjects. The time course of this event suggests that it was study treatment-related despite the fact that gastrointestinal disturbances are common manifestations of Fabry disease. Tremor was reported by 13 (81%) subjects and weight decrease was reported by 11 (69%) subjects. In the Fabry study, there were 2 withdrawals due to tremor, one diarrhoea, and one withdrawal due to tremor, diarrhoea and weight loss.

HIV patients

The safety data clearly showed a comparatively higher incidence of gastrointestinal adverse events complicating miglustat treatment. 92% of patients who received miglustat reported diarrhoea compared with 36% in the placebo group. A mean weight loss was noted in the miglustat arm compared with 1 kg weight gain in the placebo arm. Granulocytopenia was also twice as often in the miglustat arm in this study.

Neurological Adverse events

Neurological adverse events were common and at least 35 Gaucher subjects reported tremor, leg cramps, or symptoms of peripheral neuropathy. There were 8 reports of paraesthesia and 23 reports of tremor, with an onset of symptoms before, during or after the study. Such symptoms and signs are not generally recognised as part of the natural course of type 1 Gaucher disease. Among the 16 Fabry patients, 11 developed a tremor during the study period and 2 had an exacerbation of existing tremor, 2 complained of treatment emergent paraesthesia and there was 1 report of sexual dysfunction and are difficult to interpret in this patient population. In phase II HIV studies using OGT 918 or its prodrug 924, there were higher incidences of paraesthesia, neurologic dysfunction, peripheral neuropathy, tremor and ataxia in the miglustat/AZT arm compared to the placebo/AZT arm. Although relatively more HIV patients who received miglustat/AZT than those who received placebo/AZT reported neurological adverse events, it should be taken into account that these patients were at risk of other co-existing illnesses. In general, a relatively lower percentage of HIV patients reported a neurological event but the exposure was only 6 months. Ataxia was only observed in this patient group for whom much higher doses of Zavesca were used. No definitive conclusion can be drawn based on the data provided but possible Zavesca-related ataxia cannot be excluded.

There was clearly a temporal relationship between miglustat therapy and tremor, either in the onset or as an exacerbating factor. There were also two withdrawals each in the Gaucher and Fabry studies due to tremor. In contrast with the HIV studies, tremor was common among the Fabry and Gaucher patients despite the use of a lower dose of miglustat.

The applicant has suggested that the development of peripheral neuropathy is related to the presence of co-morbidities associated with peripheral neuropathy, including monoclonal gammopathy, vitamin B₁₂ deficiency, diabetes mellitus and congenital abnormalities. Although co-morbidities such as B₁₂ deficiency and monoclonal gammopathy were thoroughly investigated as alternative causes, Zavesca as a probable cause cannot be excluded in all of the cases of treatment emergent neuropathy. Three patients with tremor underwent assessment and no central nervous component to the tremor was observed during treatment with the drug. The exact mechanism of the tremor remains unknown.

Seventy-two of the 80 patients exposed to Zavesca had EDX testing performed. The same operator performed the tests at each centre and all were subject to central review by a single expert. The results of both local and central assessment were provided. Abnormal electrodiagnostic findings were found in 6 of the 8 patients who reported paraesthesia following commencement of miglustat. These abnormal findings were consistent with peripheral neuropathy or changes suggestive of demyelination on EMG/nerve conduction studies. There were also at least 8 subjects who had not complained of paraesthesia but were found to have abnormal EDX results. To complicate the analysis, abnormal

EDX findings were found in 2 of 8 Gaucher patients who had never received miglustat but had received Cerezyme, although one of these patients had also received non-neurotoxic chemotherapy for multiple myeloma previously.

Five patients developed complaints of memory loss during or following participation in the Zavesca clinical trial program in Gaucher type 1 disease. Cognitive impairment was found in two of the five patients. The diagnosis of B12 deficiency has been proposed as the aetiology of cognitive dysfunction in one patient but Zavesca as a possible cause could not be excluded. The aetiology of cognitive impairment in the other patient was unclear.

Based on the observed adverse neurological events, the current standing of the importance of glycosphingolipids as structural and functional molecules, and the incomplete understanding on the actions of miglustat on glycosphingolipids pathway, neurotoxicity of miglustat cannot be excluded.

Laboratory findings

The majority of mean changes from baseline in haematology and biochemistry parameters were less than 10%. Apart from the changes in haemoglobin and platelets, greater than 10% mean percentage increases or decreases in the following parameters were reported in one of more of the studies: basophils, eosinophils, lymphocytes, white cell count, ALP, LDH, and creatinine. Greater than 10% increases were seen for ACE, AST, ALT, bilirubin and acid phosphatase.

Weight loss was consistently observed in the clinical trial program. The mean loss in weight during OGT 918-001 was 4.5 kg and the mean weight at baseline was 67.9 kg, representing a 7% weight loss over 12 months. Apart from a few subjects, most subjects had less than 10% decrease in weight from screening to endpoint.

Safety in special populations

No specific studies have been performed and this has been appropriately reflected in the SPC.

Discussion on clinical safety

The number of adverse neurological events including peripheral neuropathy, cognitive dysfunction and tremor is of great concern considering the limited number of subjects treated and the duration of treatment. In the study population, treatment emergent neurological adverse events were frequent and affected over 30% of the patients. Tremor was usually mild and transient, responded to dose reduction and only few patients had to withdraw due to tremor. Of those patients who withdrew from the trials, Zavesca-related tremor also subsequently subsided. There seems to be a clear association between the use of miglustat and development of tremor. The underlying mechanism for tremor is, however, unknown, although it could not be distinguished from an exaggerated physiological tremor. This contrasts with peripheral neuropathy, as that has not been shown to be reversible in all of the affected patients. Although co-morbidities such as B₁₂ deficiency and monoclonal gammopathy were thoroughly investigated as alternative causes, Zavesca as a probable cause cannot be excluded in all of the cases of treatment emergent neuropathy. Therefore, all patients should undergo baseline and repeat neurological evaluation. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of risk-benefit and may require cessation of treatment.

Overall, five of the Gaucher patients complained of memory loss during the study and two were subsequently found to have developed cognitive impairment, including one case with reduced functional capability. The possibility of drug-related neurotoxicity could not be totally excluded in these two patients. The need for baseline and periodic assessment of cognitive functions is recommended in all patients on Zavesca treatment.

It is difficult to discuss causality and biological plausibility given the small number of patients studied, and with the limited knowledge on the effects of Zavesca on glycosphingolipids metabolism. Taking together the development of tremor, unexplained peripheral neuropathy and cognitive impairment affecting about one-third of the study patients in the Gaucher program, it is impossible to dismiss that

there are signals of Zavesca-related neurotoxicity. The information from the HIV trials is limited but useful. Even if an alternative cause could be established for peripheral neuropathy, Zavesca is likely to have an effect on the central nervous system. Preclinical studies have also shown that Zavesca can penetrate into the brain. The long-term safety implications of Zavesca treatment are unknown and there is therefore clearly a need to prospectively assess and follow up patients on Zavesca treatment longitudinally.

Diarrhoea occurred in 86% of all patients and weight loss in about 70%. The diarrhoea, flatulence and abdominal pain are probably due to inhibition of disaccharidases in the small intestine. The symptoms are mild and the diarrhoea decreases in prevalence over time, probably due to up-regulation of intestinal enzymes and modifications in diet. Some patients do find these symptoms intolerable and gastrointestinal symptoms were a prominent cause of withdrawal. However, these symptoms disappeared promptly on cessation of treatment.

Studies in the rat have shown that miglustat adversely affects spermatogenesis, sperm parameters and reduces fertility (see pre-clinical discussion). Until further information is available, it is further advised that before seeking to conceive, male patients should cease Zavesca and maintain reliable contraceptive methods for 3 months thereafter.

The clinical trial program has not involved any children. The neurological adverse events would raise questions on the use of miglustat in children and women of childbearing age. There are no studies planned to investigate the use of Zavesca in either of those groups.

There are no data from the use of miglustat in pregnant women. Studies in animals, however, have shown effects on reproduction, including dystocia (see pre-clinical discussion). Miglustat crosses the placenta. Zavesca should therefore not be used during pregnancy and women of childbearing potential should use contraceptive measures.

Since it is not known if miglustat is secreted in breast milk, Zavesca should not be used during breast-feeding.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way and the product is formulated, manufactured and controlled. The specifications and batch analytical results indicate a consistent product with a uniform clinical performance from batch to batch. There are no outstanding quality issues, which have a negative impact on the benefit/risk balance.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic and pharmacokinetic studies provided adequate evidence relating to miglustat in the indication, which is the scope of this application. The preclinical pharmacological documentation is somewhat limited. *In vitro* activity of miglustat against an enzyme in a pathway relevant for Gaucher disease has been shown. There are no animal models of Gaucher disease but efficacy *in vivo* animal models has been shown in related models of lysosomal storage diseases.

The main effects common to all species were weight loss and diarrhoea, and, at higher doses, damage to the gastrointestinal mucosa (erosions and ulceration). Further, effects seen in animals at doses that result in exposure levels moderately higher than the clinical exposure level were: changes in lymphoid organs in all species tested, transaminase changes, vacuolation of thyroid and pancreas, cataracts, nephropathy and myocardial changes in rats. These findings were considered to be secondary to debilitation.

Repeated dose toxicity studies in rats showed effects on the seminiferous epithelium of the testes. Other studies revealed changes in sperm parameters (motility and morphology) consistent with an observed reduction in fertility. These effects occurred at exposure levels similar to those in patients but showed reversibility. Miglustat affected embryo/foetal survival in rats and rabbits; dystocia was reported; postimplantation losses were increased and an increased incidence of vascular anomalies occurred in rabbits. These effects may be partly related to maternal toxicity. Changes in lactation were observed in female rats in a 1-year study. The mechanism for this effect is unknown.

Miglustat did not show any potential for mutagenic or clastogenic effects in the standard battery of genotoxicity tests. Long-term studies on the carcinogenic potential have not been conducted but the applicant has made appropriate commitments to undertake further studies. Overall, the pre-clinical findings have been adequately reflected in the SPC based on currently available data.

Efficacy

For treatment naïve type 1 Gaucher patients with mild or moderate disease, the 36-month non-comparative data available indicate that miglustat conferred a modest sustained benefit relative to baseline. Although no direct comparisons with Enzyme Replacement Therapy (ERT) have been performed in treatment naïve patients, it appears that it would take longer to achieve an effect with Zavesca and Zavesca does not offer any efficacy advantage over ERT. It is yet unknown if treatment with Zavesca would achieve the same effect obtainable with ERT, the current standard of care for patients who require treatment for type 1 Gaucher disease. The efficacy and safety of Zavesca has not been evaluated in patients with severe Gaucher disease, defined as a haemoglobin concentration below 9 g/dl or a platelet count below $50 \times 10^9/l$ or active bone disease.

Among patients with disease stabilised on enzyme replacement therapy, a reduction in platelet count and a rise in chitotriosidase activity after switching to miglustat from ERT were consistently observed and that would suggest that miglustat could not maintain the previously achieved disease stabilisation in all patients. Further data are needed to clarify the clinical relevance of the small effects in the three potential target groups, namely in treatment naïve patients, combination treatment with ERT, or as maintenance treatment in patients with stable disease following response to a minimum of 2 years of ERT.

There is no experience with the use of Zavesca in patients under the age of 18 and over the age of 70.

Safety

The gastrointestinal adverse events are not unexpected and can be managed while the aetiology of the neurological adverse events has not been clarified.

Diarrhoea occurred in 86% of all patients and weight loss in about 70%. The diarrhoea, flatulence and abdominal pain are probably due to inhibition of disaccharidases in the small intestine. The symptoms are mild and the diarrhoea decreases in prevalence over time.

The number of reports of peripheral neuropathy and tremor is of concern considering the limited number of subjects treated and duration of treatment. There seems to be a clear association between the use of miglustat and development of tremor. Cases of peripheral neuropathy have been reported in patients treated with Zavesca with or without concurrent conditions such as vitamin B₁₂ deficiency and monoclonal gammopathy. In view of the number of adverse neurological events in the trial population and the incidence of B₁₂ deficiency among Gaucher patients in general, there is a need for regular monitoring of vitamin B₁₂ and all patients should also undergo baseline and repeat neurological evaluation. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of risk-benefit and may require cessation of treatment. An effect of Zavesca on higher cerebral functions cannot be excluded based on the reports of cerebral dysfunction. There is a need to conduct baseline and periodic neurological assessment as well as re-evaluation of the risk-benefit of treatment should adverse neurological events develop.

Benefit/risk assessment

Following the assessment of the documentation that did not show any efficacy or safety advantage over standard ERT in treatment naive patients and even less defined benefit as a maintenance treatment, it was concluded that additional input was required from external experts to define the role of Zavesca treatment. The Company was also invited to clarify a number of efficacy and safety issues, as previously defined by the CPMP, at the CPMP ad hoc Expert meeting as well as at an oral explanation before the CPMP.

The conclusions from the Experts were:

“With reference to the use of Zavesca in treatment naive patients, Zavesca has an effect on the study endpoints and that effect may be clinically relevant. The results may be difficult to generalise, however, because the majority of the study population has a predilection for milder disease. There is no agreement on the effect size of Zavesca as compared with ERT. One view is that the effect size is about 30 % of that achievable with ERT but the other is that a relatively smaller response is expected in treating patients with mild disease compared with more severe disease. Zavesca exerts sustained effect with continued treatment and it seems to take longer to achieve an effect compared with ERT. There is a place for oral treatment and Zavesca may be indicated because of patient inability/unwillingness to accept ERT or in the rare case of intolerance to ERT. The lack of data on bone disease is a clear deficiency. So far the only data available is increase in fat fraction suggestive of clearance of Gaucher cells, whether that can predict course of bone disease is unknown.

With reference to Zavesca as maintenance treatment, it was agreed that the results are less robust and elevation in chitotriosidase is a concern. Based on the currently available data it is not possible to identify those patients who might have sufficient disease control with Zavesca. Close monitoring is necessary because of probable need to restart ERT. It is agreed that further studies need to be conducted and there is insufficient data to support an indication for Zavesca as a maintenance treatment of Gaucher disease.

Regarding combination treatment, only 6 months of data on a small number of patients are available. It is agreed that the data are inconclusive. There may be a need for combination treatment if there is severe poorly responsive disease but this should be studied further.

With reference to Zavesca as rescue treatment, there is no known case of no-response to ERT but suboptimal response could be a matter of dose and dosing schedule.

There is a lack of systematic survey of neurological symptoms and signs in Gaucher disease, therefore no conclusion can be drawn. Different experiences were exchanged. One view is that neurological symptoms can occur in type 1 Gaucher disease but different from those of types 2 and 3. Another is that the extent of electrophysiological abnormalities reported in the Zavesca study is much larger than expected from previous experience. Regarding the data submitted by the company, there are either methodological deficiencies or lack of electrophysiological data that make it difficult to draw conclusions on the background prevalence of neurological events in type 1 Gaucher disease.

It was further agreed that miglustat cannot be excluded as a possible cause for peripheral neuropathy and vitamin B12 deficiency is unlikely to be the sole explanation.

With reference to cognitive dysfunction, there were again different views expressed. Two of the 5 cases of memory loss are still unresolved, of which one case is not typical of early Alzheimer's disease. The opposite view is that none of the cases can be attributed to Zavesca. It is agreed that baseline neuropsychological testing with follow-up should be undertaken.

With reference to possible future studies, the Experts agreed that the efficacy data primarily apply to treatment naive patients with mild to moderate disease, even though it is difficult to define mild to moderate disease. There is little or no efficacy data to support maintenance, combination or rescue treatment. There are unresolved safety concerns that need to be addressed. Therefore follow-up studies

should be considered. In view of the small number of patients, the preference for larger benefit achieved with ERT and the ‘open’ studies that will be conducted, any future studies would have difficulties in recruiting a sufficient number of patients.”

Following the review of the submitted documentation, the final revised SPC and the post-marketing commitments made by the applicant, and taking into account the advice from the expert meeting, the CPMP agreed that although ERT is the standard of care for patients with type 1 Gaucher disease, there is a population of patients, however few, for whom ERT is not suitable and where there is an unmet medical need. Zavesca has shown efficacy in such patients that may be clinically relevant and an acceptable benefit/risk ratio would apply only to those patients for whom ERT is deemed unsuitable by a physician knowledgeable in the management of these patients, provided diligent prospective monitoring is put in place to anticipate the adverse neurological events. The SPC has been revised to convey the limited role of Zavesca and give the treating physician a clearer overview of its anticipated clinical effects as well as the need for careful monitoring.

The CPMP, thus, concluded that a marketing authorisation for Zavesca would be granted under exceptional circumstances, subject to fulfilling the clinical and pre-clinical follow-up measures and clinical specific obligations undertaken by the applicant. The indication for which the medical product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the safety and efficacy of the medicinal product. In order to collect additional data, the applicant has committed to complete an extensive programme of clinical studies post-authorisation within pre-specified time frames, the results of which shall form the basis of an annual reassessment of the benefit/risk profile.

The applicant has committed to undertake the following post-marketing programme to address all open efficacy and safety issues:

- A randomised, open label, case-controlled study of the efficacy and safety of Zavesca versus Enzyme Replacement Therapy (ERT) in the Maintenance of Patients with type 1 Gaucher disease.
- A natural history observational studies of 200 patients with type 1 Gaucher disease, in conjunction with the European Working Group for Gaucher disease (EWGGD).
- A comprehensive Post-Marketing Surveillance Plan (PMSP) in the EU which will educate prescribers on the appropriate use of Zavesca and actively solicit safety information on as many patients as possible who receive Zavesca to supplement the PSURs.
- A capture protocol for all patients currently receiving Zavesca in the ongoing type 1 Gaucher disease clinical studies.
- Extension of the currently ongoing OGT 918-005 study in the USA from the current 12 months to 24 months. This study is an ongoing phase II monotherapy study of open-label Zavesca in adult patients with type 1 Gaucher disease.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of Zavesca in - the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1) - was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.