Drugs of the Future 2003, 28(3): 229-236

CCC: 0377-8282/2003

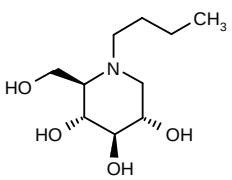
Miglustat

Prop INN

Treatment of Gaucher's Disease
Ceramide Glucosyltransferase Inhibitor
α-Glucosidase Inhibitor

N-Butyldeoxynojirimycin
OGT-918
SC-48334
Vevesca®
Zavesca®

1,5-(Butylimino)-1,5-dideoxy-D-glucitol
(2*R*,3*R*,4*R*,5*S*)-1-Butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol
N-Butylmoranoline



$C_{10}H_{21}NO_4$
Mol wt: 219.2789
CAS: 072599-27-0
EN: 155014

Abstract

Glucosphingolipid (GSL) storage diseases are a family of inherited, metabolic, progressive, lysosomal storage disorders in which fatty glycosylated sphingolipids accumulate in cells of the spleen, lungs, bone marrow and brain. Treatment options for GSL storage disorders are limited and for most patients there is no effective therapy available. Conventional drug-based treatment involving inhibition of GSL synthesis leading to a reduced rate of storage of GSLs represents a viable option for the treatment of GSL storage diseases. Iminosugars inhibit hydrolytic enzymes such as endoplasmic reticulum α-glucosidases I and II involved in the biosynthesis of glycoproteins. Modification of these compounds can result in inhibitory activity for other enzymes such as ceramide-specific glucosyltransferase (CerGlcT) which catalyzes the transfer of glucose to ceramide in the first step of the GSL biosynthesis pathway. The iminosugar inhibitor miglustat (first developed as an antiviral agent) exhibited potent CerGlcT inhibitory activity and was chosen for further development as a treatment for type 1 Gaucher's disease.

Synthesis

Miglustat (*N*-butyldeoxynojirimycin) can be obtained by several different ways:

1) The reductive ring opening of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (I) with $LiAlH_4$ in THF gives the diol (II), which is oxidized by means of DMSO, trifluoroacetic anhydride and triethylamine in dichloromethane to yield the unstable ketoaldehyde (III), which, without isolation, is submitted to a reductocyclization with butylamine and $NaBH_3CN$ in methanol to afford the protected iminosugar (IV). Finally, this compound is debenzylated by means of Li and NH_3 in THF (1, 2). Scheme 1.

2) The oxidation of 1,2-*O*-isopropylidene-5-oxo-α-D-glucofuranose (V) by means of Bu_2SnO and Br_2 in refluxing methanol provides the 5-oxoglucofuranose derivative (VI), which is hydrolyzed with Dowex 50W-X8 in water to yield 5-oxo-D-glucose (VII). Finally, this compound is submitted to a reductocyclization with butylamine and $NaBH_3CN$ in methanol (3, 4). Scheme 1.

3) The reductocondensation of D-glucose (VIII) and butylamine by means of H_2 over Pd/C in ethanol gives *N*-butylglucamine (IX), which is submitted to a biochemical oxidation by means of *Gluconobacter oxidans* in water to yield 6-(butylamino)-6-deoxy-α-L-sorbofuranose (X). Finally, this compound is submitted to a reductive cyclization with H_2 over Pd/C in ethanol/water (5-7). Scheme 2.

4) The selective hydrolysis of 1,2:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XI) (together with some of its 1,3:4,6-isomer) by means of H_2SO_4 in methanol gives 1,2-*O*-isopropylidene-α-L-sorbofuranose (XII), which is treated with tosyl chloride, triethylamine and pyridine to yield the monotosylated sugar (XIII). Reaction of the

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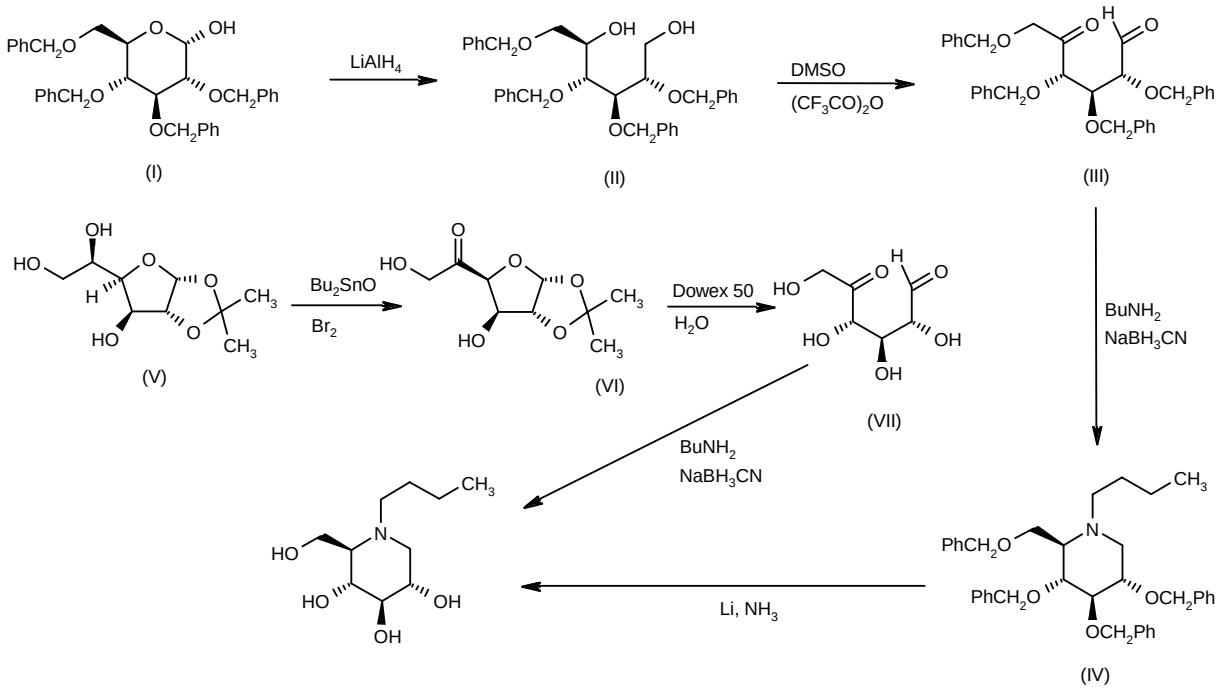
Scheme 1: Synthesis of Miglustat



protected sugar (XIII) with butylamine in hot pyridine/triethylamine affords 6-(butylamino)-6-deoxy-1,2-*O*-isopropylidene-α-L-sorbofuranose (XIV), which is finally submitted to a reductive cyclization by means of H_2 over Pd/C in water (8). Scheme 2.

5) Directly by reductocondensation of 1-deoxynojirimycin (XV) with butyraldehyde (XVI) by means of H_2 over Pd/C in methanol (9, 10) or with $NaBH_3CN$ in methanol/HCl (11). Scheme 2.

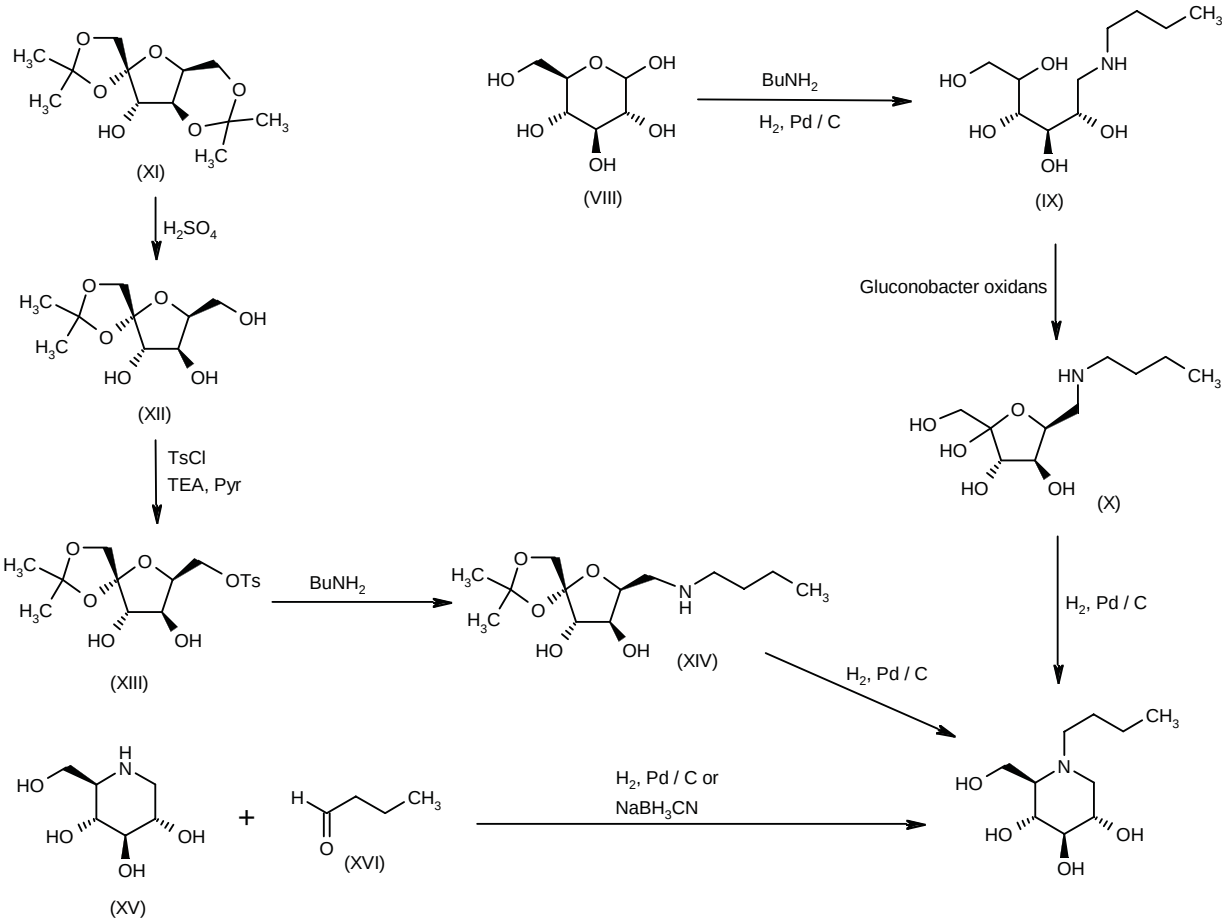
Introduction

Glucosphingolipid (GSL) storage diseases are a family of inherited, metabolic, progressive, lysosomal storage disorders in which harmful quantities of fatty glycosylated sphingolipids accumulate in cells of the spleen, lungs, bone marrow and brain. Glycosylated sphingolipids are composed of the GSL and galactosphingolipid families. GSLs in particular are located on plasma membranes on mammalian cells. They are required during embryonic development and differentiation and are the targets of several types of bacterial viruses. The population of GSL is strictly balanced by precise control of GSL biosynthesis. In GSL storage diseases, disruption of GSL degradation leads to GSL accumulation and subsequent cellular dysfunction and death. GSL storage diseases, including types 1, 2 and 3 Gaucher's, Fabry's Tay-Sachs, Sandoff's, GM2 gangliosidosis and Pompe's (or glycogenosis), are caused by mutations in genes that encode acid glycosidases or their protein cofactors which are involved in the removal of monosaccharide units from GSLs in the lysosome. While Fabry's disease is X-linked, other GSL storage diseases are autosomal recessive. The mutations responsible for the diseases alter the residual activity of the specific encoded enzyme thus determining the severity of the condition. For example, low or undetectable enzyme activity is evident with infantile-onset disease variants, low but detectable residual enzyme activity is seen with juvenile-onset variants and moderate residual activity is associated with adult-onset variants (12-15).

The pathology of GSL storage diseases involves accumulation of GSLs in the brain with the exception of type 1 Gaucher's disease, in which disruption of GSL storage in the nervous system presents only in rare cases. In severe cases, accumulation of GSL in the brain leads to progressive neurodegeneration which is fatal in early infancy. GSL disorders occur in 1 of every 18,000 live births and are the most common neurodegenerative diseases affecting infants and children (12-16).

Treatment options for GSL storage disorders are limited and, for most patients, there is no effective therapy available. This is partly due to the difficulties in therapeutically accessing the central nervous system. Direct enzyme replacement therapy, bone marrow

Scheme 2: Synthesis of Miglustat



transplantation and gene therapy have been a main focus of research attempts to find an effective method to increase enzymatic activity in the lysosome enabling GSL degradation. However, to date, several disadvantages are evident with these approaches. Direct enzyme replacement therapy was established for type 1 Gaucher's disease although progress has also been made in Fabry's and Pompe's disease. However, it is invasive because the patient is infused i.v. with the fully functional enzyme form and enzyme uptake across the blood-brain barrier is inefficient; efficacy of this method is generally only seen for nonneuropathic GSL storage disorders although systemic manifestations of other neuropathic variants do improve. Bone marrow transplantation which replaces wild-type cells with wild-type cells secreting the wild-type enzyme, is clinically limited due to the low level of brain reconstitution seen with bone-derived microglial cells (*i.e.*, low level of functional enzyme available to brain cells), the high mortality rates associated with the procedure and the need for HLA-matched donors. Gene therapy, although theoretically an excellent therapeutic option, still involves major technical difficulties and its efficacy and safety remain clinical concerns (14, 15, 17-21).

An alternative option would be conventional drug-based treatment involving inhibition of GSL synthesis leading to a reduced rate of storage of GSLs. The goal of this method would be to balance synthesis of the substrate with the impaired rate of degradation due to the inherited enzyme deficiency. Through use of oral CNS penetrating agents and targeting an early step in the GSL biosynthetic pathway, this therapeutic method – known as substrate reduction therapy (also referred to as substrate deprivation, substrate inhibition or substrate balance) – could result in complete balance of GSL synthesis and storage in individuals with sufficient residual enzyme activity. Moreover, progression of severe disease could be slowed in cases where residual enzyme activity was low or undetectable (22, 23).

Iminosugars are monosaccharide mimics that act as charge transition-state analogues. Some members of this

family of compounds occur naturally in plants and microorganisms and at submicromolar conceentrations, they inhibit hydrolytic enzymes such as endoplasmic reticulum α-glucosidases I and II involved in the biosynthesis of glycoproteins. According to Prous Science Integrity®, 266 iminosugars have been studied to date as potential antiviral or antidiabetic agents. Modification of the nitrogen atom and simple alkylation of iminosugars with glucose and galactose stereochemistries can result in inhibitory activity for other enzymes such as ceramide-specific glucosyltransferase (CerGlcT; also known as UDP-glucose-*N*-acylsphingosine D-glucosyltransferase; EC 2.4.1.80). CerGlcT catalyzes the transfer of glucose to ceramide in the first committed step of the biosynthesis of GSLs to yield glucosylceramide, the precursor for all GSLs (24-26).

The prototypic iminosugar inhibitor is miglustat (OGT-918; *N*-butyldeoxynorjirimycin [NB-DNJ]; SC-48334; Vevesca®; Zavesca®) which was first developed as an antiviral agent. Orally active miglustat inhibits CerGlcT in addition to α-glucosidases I and II in the endoplasmic reticulum. However, the agent showed poor efficacy as a treatment of HIV infection (27, 28) possibly due to difficulties in reaching the endoplasmic reticulum. This, however, proved to be an advantage for GSL storage diseases in which the inhibition of other cellular enzymes such as glucosidases must be avoided. Furthermore, CerGlcT is the enzyme more accessible to miglustat because of its location on an early Golgi compartment with a cytoplasmic catalytic domain (29). Miglustat has displayed potent activity *in vitro* and *in vivo* and was selected for further development as a treatment for type 1 Gaucher's disease.

Pharmacological Actions

The effects of miglustat (0.5 mM) on glycolipid biosynthesis were examined *in vitro* in HL-60 cells labeled with [^{14}C]-palmitic acid. Although the major cellular phospholipid species were unaffected by treatment, neutral glycolipids and gangliosides were absent from cultures. Further examination showed that treatment with the agent inhibited synthesis of glycolipid species by 90%. Experiments using rat brain homogenate found that miglustat (0.45 and 4.5 mM) inhibited transfer of glucose from radiolabeled CerGlcT. Inhibition of glycolipid synthesis was further confirmed in *in vitro* experiments in which cholera toxin (a probe for the GM1 ganglioside) binding was decreased by about 90% in miglustat-treated lymphoid (MOLT-4 and H9) and myeloid (HL-60 and K-562) cells. These results suggest that treatment with the agent caused a decrease in GM1 from the cell surface, further demonstrating that miglustat inhibited biosynthesis of all glucosylceramide-based GSLs (26).

Miglustat was shown to be effective in inhibiting GSL accumulation in 2 *in vitro* models of Gaucher's disease. Experiments using a murine macrophage cell line (WEHI-3B) cultured in the presence of an irreversible glucocerebrosidase inhibitor (conduritol-B-epoxide [CBE]) to increase intracellular glucosylceramide levels, showed that miglustat treatment (50 or 500 μM) prevented accumulation of glucosylceramide (26). Similarly, in murine neuroblastoma x rat glioma cells (NG108-15) incubated with CBE, treatment with miglustat inhibited the elevation in intracellular ceramide levels and did not induce cell death in contrast to the glucosylceramide synthase inhibitor, D,L-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D,L-*threo*-PDMP) (30).

Miglustat was safe, tolerable and effective *in vivo*. Long-term administration of miglustat (600 mg/kg/day for 50 days followed by 1200 mg/kg/day for 50 more days and 1800 mg/kg/day for 20 days or 2400 mg/kg/day p.o. for 14 days) to young (6-week old) mice resulted in significant reductions in liver and splenocyte GSL levels of 50-79%. No overt toxicity was observed in treated animals through the 118 days of the experiment. Growth rates of miglustat-treated animals were 15% lower as compared to untreated controls at 118 days. Serum concentrations of the agent were dose-dependent with 18 μM observed after dosing with 600 mg/kg/day and 57 μM observed with 2400 mg/kg/day. In treated animals, lymphoid tissues (spleen and thymus) were 50% acellular as compared to nonlymphoid tissue (liver and brain). These results suggest that miglustat may have additional effects, possibly on the immune system (28).

Similar results were obtained in another *in vivo* study. GSL depletion (GM2) was observed in the liver of miglustat-treated (300-4800 mg/kg/day p.o. for 10 days or 2400 mg/kg/day for 5 weeks) 6-week old mice; a reduction in GM2 of 35 ± 4% was observed after long-term treatment with 2400 mg/kg. Serum and liver concentrations of miglustat following treatment with 2400 mg/kg for 5 weeks, were 51 ± 13.3 and 103 ± 21.2 μM, respectively. However, treated animals displayed a decrease in body weight (25% less than controls) and a shrinkage of the thymus (61 ± 2%) and spleen (62 ± 3%); the decrease in lymphoid organs was not responsible for the weight loss. Miglustat treatment was also found to inhibit glycogen catabolism in the liver (after 12 h of starvation) which could be partially responsible for the weight loss observed in treated animals. *In vitro* enzyme experiments revealed that the agent also potently inhibited porcine sucrase (K_i = 0.26 μM) and maltase (K_i = 0.37 μM) but not lactase (31).

Miglustat was shown to be effective in 2 *in vivo* mouse models of a GSL storage disease with CNS pathology. Miglustat (4800 mg/kg/day p.o. starting at 4 weeks postpartum) showed marked efficacy in the brain in a mouse model of Tay-Sachs disease, in which targeted disruption of the Hexa gene results in a deficiency in hexosaminidase A and consequent GM2 ganglioside accumulation. Serum concentrations of miglustat after dosing were about 50 μM. Treatment was well tolerated with no toxicity observed. Alterations in lymphoid tissue (spleen and thymus) were observed with treatment so that they were 50% acellular. A decrease in brain GM2 accumulation was observed in mice after 4 weeks of treatment as

compared to untreated controls. Significant reductions in brain GM2 of approximately 50% were observed at 12 weeks of treatment (32).

Another *in vivo* study used a mouse model of Sandhoff disease consisting of mice with targeted disruption of the Hexb gene resulting in a lack of hexosaminidase A and B isozymes and a consequential increase in GM2 and GA2 gangliosides. Miglustat (2400 or 4800 mg/kg p.o. starting from 3 or 6 weeks of age)-treated mice had significantly delayed symptom onset (about 30 days), decreased GM2 and GA2 storage in the brain (41% and 35%, respectively), decreased GM2 storage in the liver (41%) and an increased life expectancy (about 40%) as compared to untreated mice. Serum concentrations of the agent were approximately 50 μM (33).

Pharmacokinetics

The pharmacokinetics of miglustat (100 mg p.o. t.i.d.) were reported for 5 patients with nonneuropathic Gaucher's disease participating in an open-label, 1-year study. The parameters obtained appeared to be dose-linear and time-dependent. T_{max}, C_{max} and $t_{1/2}$ values were 2.5 h, 0.86 μg/ml and 6.3 h, respectively. Steady-state plasma levels of the agent were reached after 4-6 weeks of treatment (34).

The pharmacokinetics of miglustat (50 mg p.o. t.i.d.) were assessed in 6 patients with type 1 Gaucher's disease involved in a 6-month, open-label, phase I/II trial. T_{max}, C_{max} and $t_{1/2}$ values were 2.5 h, 800 ng/ml and 5-6 h, respectively. Steady state was reached within the first month of treatment and was sustained throughout the 6-month study period (35).

Further information on the pharmacokinetics and toxicity of miglustat can be found in the Product Fact Sheet from Oxford GlycoSciences (36).

Clinical Studies

Results from a 1-year, open-label study involving 28 adults with nonneuropathic Gaucher's disease (who were unable or unwilling to received enzyme replacement therapy) demonstrated the efficacy in improving clinical disease features and the safety of miglustat (100 mg p.o. t.i.d.). Treatment was well tolerated. Two patients each withdrew for gastrointestinal complaints, personal reasons and severe preexisting disease. The most common adverse event was diarrhea (79%). Analysis of leukocytes from 5 patients revealed that treatment reduced the rate of glycolipid synthesis (*i.e.*, decrease in cell surface GM1 expression). At 12 months, significant reductions of 12% and 19% were observed in liver and spleen volumes, respectively, which were increased at baseline (1.1-2.7 and 5.1-24.8 times, respectively) as compared to normal subjects. Treatment was also associated with a slight improvement in hemoglobin concentrations (0.5 g/dl increase at 12 months) and platelet counts (more than 15 x 10^9/l increase). Blood counts and mean organ volumes increased progressively from 6 until 12 months of treatment. A significant reduction in chitotriosidase levels of 16.4% was also seen (34) (Table I).

The efficacy and safety of low-dose miglustat (50 mg p.o. t.i.d.) were examined in an open-label, 6-month, phase I/II study with an optional extension-use phase (100 mg p.o. t.i.d.). The study involved 18 patients with type 1 Gaucher's disease who were unable or unwilling to receive enzyme replacement therapy; 17 patients completed the 6-month phase. Of the 16 patients who entered the extension phase, 13 were evaluable at 12 months; 4 patients discontinued this phase due to disease progression, concurrent illness and weight loss (1 patient), gastrointestinal complaints (1 patient) and at the investigator's request (2 patients). Treatment was well tolerated with no serious adverse events observed with treatment. The most common adverse events were diarrhea (94%) and weight loss (66.7%). Other adverse events seen during the first 6-month phase were abdominal pain, flatulence and headache (50%), fine tremor (39%) and flu-like symptoms (33%). Two patients developed neurological symptoms or abnormal electrodiagnostic findings after 12 months. Significant reductions in liver and spleen volume (5.9% and 4.5%, respectively) and chitotriosidase levels (4.6%) were observed at 6 months, although the reductions were lower than those observed in the study described above (35) in which patients received 100 mg miglustat. No changes in hemoglobin or platelet counts were observed. At 12 months during the extension study and administration of 100 mg miglustat, significant reduc-

Table I: Clinical studies of miglustat in Gaucher's disease (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Gaucher disease	Open multicenter	Miglustat, 100 mg p.o. b.i.d. x 1 y Miglustat, 200 mg p.o. t.i.d. x 1 y	28	Miglustat was well tolerated and may be effective in patients with type 1 Gaucher disease	34
Gaucher disease	Open, multicenter	Miglustat, 50 mg p.o. t.i.d. x 6 mo → [extension period] 50-150 mg b.i.d. [dose adjusted according to investigator]	18	Miglustat was well tolerated and induced significant liver and spleen reductions as well as improvements in hemoglobin concentrations and platelet counts in patients with Gaucher disease	35

tions in liver and spleen volume (6.2% and 10.1%, respectively) and chitotriosidase (15.3%) and hexosaminidase (13.1%) levels were observed; slight changes in platelet counts and hemoglobin concentrations were also noted. It was concluded that miglustat dose-dependently improved symptoms of type 1 Gaucher's disease. However, the lower 50 mg miglustat dose did not result in any improvement over the 100 mg t.i.d. dose in improving the rate of hematological response or reducing adverse events. Thus, the 100 mg t.i.d. dose was recommended as the starting regimen for patients with symptomatic type 1 Gaucher's disease (35) (Table I).

Miglustat (Zavesca®) was approved in the E.U. in November 2002 for the treatment of patients with mild to moderate type 1 Gaucher's disease who are unable to receive enzyme replacement therapy (36). Zavesca® is now available in the U.K. and launches in other countries are expected to begin in early March (37, 38).

Source

Oxford GlycoSciences Ltd. (GB); marketed by Actelion Ltd. (CH); licensed to Teva Pharmaceutical Industries Ltd. (IL) for Israel.

References

1. Matos, C.R.R., Lopes, R.S.C., Lopes, C.C. *Synthesis of 1-deoxynojirimycin and N-butyl-1-deoxynojirimycin.* Synthesis (Stuttgart) 1999: 571-3.

2. Lopes, C.C., Lopes, R.S.C., Matos, C.R.R. *A novel process for the synthesis of aza-sugars with biological activity.* BR 9902585.

3. Baxter, E.W., Reitz, A.B. *Expeditious synthesis of azasugars by the double reductive amination of dicarbonyl sugars.* J Org Chem 1994, 59: 3175-85.

4. Reitz, A., Baxter, E. (Ortho-McNeil Pharmaceutical, Inc.). *Process for producing polyhydroxylated piperidines and pyrrolidines and cpds. thereof.* WO 9205152.

5. Grabner, R.W., Landis, B.H., Wang, P.T., Prunier, M.L., Scaros, M.G. (Pharmacia Corp.). *Process for producing N-substd.-1-deoxynojirimycin.* EP 0477160.

6. Landis, B.H., McLaughlin, J.K., Heeren, R., Grabner, R.W., Wang, P.T. *Bioconversion of N-butylglucamine to 6-deoxy-6-butylamino sorbose by Gluconobacter oxydans.* Org Process Res Dev 2002, 6: 547-52.

7. Scaros, M.G., Prunier, M.L., Rutter, R.J., Yonan, P.K., Grabner, R., Landis, B. *A new and improved synthesis of N-butyl-1-deoxynojirimycin.* Chem Ind (New York) 1994, 53: 41-8.

8. Behling, J.R., Farid, P., Khanna, I., Medich, J.R., Prunier, M., Weier, R.M. (Pharmacia Corp.). *Process for preparation of 1,5-(alkylimino)-1,5-dideoxy-D-glucitol and derivs. thereof.* WO 9117145.

9. Partis, R.A., Koszyk, F.J., Mueller, R.A. (Pharmacia Corp.). *Antiviral cpds.* US 5310745.

10. Bryant, M.L., Koszyk, F.J., Mueller, R.A., Partis, R.A. (Pharmacia Corp.). *Use of 1-deoxynojirimycin and its derivs. for treating mammals infected with respiratory syncytial virus.* WO 9522975.

11. Junge, B., Krause, H.P., Müller, L., Puls, W. (Bayer AG). *New 3,4,5-trihydroxypiperidine derivs., process for their preparation and medicaments and fodder containing them.* DE 2758025, EP 0000947.

12. Walkley, S.U. *Cellular pathology of lysosomal storage disorders.* Brain Pathol 1998, 8: 175-93.

13. Yamashita, T., Wada, R., Sasaki, T., Deng, C., Bierfreund, U., Sandhoff, K., Proia, R.L. *A vital role for glycosphingolipid synthesis during development and differentiation.* Proc Natl Acad Sci USA 1999, 96: 9142-7.

14. Dwek, R.A., Butters, T.D., Platt, F.M., Zitzmann, N. *Targeting glycosylation as a therapeutic approach.* Nat Rev Drug Discov 2002, 1: 65-75.

15. Platt, F.M., Jeyakumar, M., Andersson, U. et al. *Inhibition of substrate synthesis as a strategy for glycolipid lysosomal storage disease therapy.* J Inherit Metab Dis 2001, 24: 275-90.

16. Meikle, P.J., Hopwood, J.J., Clague, A.E., Carey, W.F. *Prevalence of lysosomal storage disorders.* JAMA - J Am Med Assoc 1999, 281: 249-54.

17. Beutler, E., Grabowski, G. *Gaucher disease.* In: The Metabolic and Molecular Bases of Inherited Disease, 8th ed. C.R. Scriver, A.L. Beaudet, D. Valle, W.S. Sly (Eds.), McGraw Hill, New York, 2000, 3635-68.

18. Eng, C., Phelps, R., Kim, L. *Enzyme replacement therapy for Fabry disease.* J Inherit Metab Dis 2000, 23(Suppl. 1): 222.

19. Van den Hout, J.M., Reuser, A.J., de Klerk, J.B., Arts, W.F., Smeitink, J.A., Van der Ploeg, A.T. *Enzyme therapy for Pompe disease with recombinant human α-glucosidase from rabbit milk.* J Inherit Metab Dis 2001, 24: 266-74.

20. Erikson, A., Bembi, B., Schiffmann, R. *Neuronopathic forms of Gaucher's disease.* Baillière's Clin Haematol 1997, 10: 711-23.

21. Krivit, W., Sung, J.H., Shapiro, E.G., Lockman, L.A. *Microglia: The effector cell for reconstitution of the central nervous system following bone marrow transplantation for lysosomal and peroxisomal storage diseases.* Cell Transplant 1995, 4: 385-92.

22. Vunnam, R.R., Radin, N.S. *Analogs of ceramide that inhibit glucocerebroside synthetase in mouse brain.* Chem Phys Lipids 1980, 26: 265-78.

23. Radin, N.S. *Treatment of Gaucher disease with an enzyme inhibitor.* Glycoconjugate J 1996, 13: 153-7.

24. Butters, T.D., Dwek, R.A., Platt, F.M. *Inhibition of glycosphingolipid biosynthesis: Application to lysosomal storage disorders.* Chem Rev 2000, 100: 4683-96.

25. Butters, T.D., van den Broek, L.A.G.M., Fleet, G.W.J., Krulle, T.M., Wormald, M.R., Dwek, R.A., Platt, F.M. *Molecular requirements of imino sugars for the selective control of N-linked glycosylation and glycosphingolipid biosynthesis.* Tetrahedron Asymmetry 2000, 11: 113-24.

26. Platt, F.M., Neises, G.R., Dwek, R.A., Butters, T.D. *N-Butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis.* J Biol Chem 1994, 269: 8362-5.

27. Fischl, M.A., Resnick, L., Coombs, R. et al. *The safety and efficacy of combination N-butyl-deoxynojirimycin (SC-48334) and zidovudine in patients with HIV-1 infection and 200-500 CD4 cells/mm^3.* J Acquir Immune Defic Syndr 1994, 7: 139-47.

28. Platt, F.M., Reinkensmeier, G., Dwek, R.A., Butters, T.D. *Extensive glycosphingolipid depletion in the liver and lymphoid organs of mice treated with N-butyldeoxynojirimycin.* J Biol Chem 1997, 272: 19365-72.

29. Platt, F.M., Butters, T.D. *Inhibitors of glycosphingolipid biosynthesis.* Trends Glycosci Glycotechnol 1995, 7: 495-511.

30. Bieberich, E., Freischutz, B., Suzuki, M., Yu, R.K. *Differential effects of glycolipid biosynthesis inhibitors on ceramide-induced cell death in neuroblastoma cells.* J Neurochem 1999, 72: 1040-9.

31. Andersson, U., Butters, T.D., Dwek, R.A., Platt, F.M. *N-Butyldeoxygalactonojirimycin: A more selective inhibitor of glycosphingolipid biosynthesis than N-butyldeoxynojirimycin, in vitro and in vivo.* Biochem Pharmacol 2000, 59: 821-9.

32. Platt, F.M., Neises, G.R., Reinkensmeier, G., Townsend, M.J., Perry, V.H., Proia, R.L., Winchester, B., Dwek, R.A., Butters, T.D. *Prevention of lysosomal storage in Tay-Sachs mice treated with N-butyldeoxynojirimycin.* Science 1997, 276: 428-31.

33. Jeyakumar, M.,. Butters, T.D., Cortina-Borja, M., Hunnam, V., Proia, R.L., Perry, V.H., Dwek, R.A., Platt, F.M. *Delayed symptom onset and increased life expectancy in Sandhoff disease mice treated with N-butyldeoxynojirimycin.* Proc Natl Acad Sci USA 1999, 96: 6388-93.

34. Cox, T., Lachmann, R., Hollak, C. et al. *Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis.* Lancet 2000, 355: 1481-5.

35. Heitner, R., Elstein, D., Aerts, J., Weely, S., Zimran, A. *Low-dose N-butyldeoxynojirimycin (OGT 918) for type I Gaucher disease*. Blood Cells Mol Dis 2002, 28: 127-33.

36. *Zavesca™ hard capsules (miglustat). Summary of product and characteristics*. Oxford GlycoSciences Product Fact Sheet November 20, 2002.

37. *Zavesca marketing approval sought in Israel.* DailyDrugNews.com (Daily Essentials) January 21, 2003.

38. *First launch announced for Zavesca.* DailyDrugNews.com (Daily Essentials) March 4, 2003.

Additional References

Johnson, V.A., Merrill, D.P., Chou, T.C., Hirsch, M.S. *Synergistic inhibition of HIV-1 replication by N-butyl-deoxynojirimycin (N-butyl-DNJ) and zidovudine (AZT).* 29th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Houston) 1989, Abst 504.

Pottage, J.C., Farrington, K., Spear, G., Benson, C.A., Landay, A., Kessler, H.A. *Comparative in vitro anti-HIV activity of four new aminosugar derivatives*. 29th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Houston) 1989, Abst 506.

Bryant, M., Mueller, R., Smidt, M., Tiemeier, D., Jacobs, G., Platt, F., Butters, T., Karlsson, N., Houseman, K., Marr, J. *Anti-HIV properties of α-glucosidase inhibitor SC-48334, the active component of prodrug SC-49483.* 9th Int Conf AIDS (June 6-11, Berlin) 1993, Abst WS-A17-6.

Fischl, M., Resnick, L., Coombs, R. et al. *The preliminary efficacy and safety of N-butyl-deoxynojirimycin (SC-48334), an alpha-glucosidase I inhibitor, in combination with zidovudine (ZDV).* 9th Int Conf AIDS (June 6-11, Berlin) 1993, Abst PO-B26-2039.

Tierney, M., Pottage, J., Kessler, H., Fischl, M., Richman, D., Merigan, T., Powderly, W., Pettinelli, C., Sherman, J., Hirsch, M. *The tolerability and pharmacokinetics of N butyl deoxynojirimycin in patients with advanced HIV disease (ACTG 100)*. 33rd Intersci Conf Antimicrob Agents Chemother (Oct 17-20, New Orleans) 1993, Abst 46.

Smith, M., Smith, S., Piergies, A., Kowalski, K., Wallemark, C., Sherman, J., Karim, A. *Single oral dose safety and pharmacokinetics of SC-49483 (N-butyl deoxynojirimycin [NB-DNJ] prodrug)*. 33rd Intersci Conf Antimicrob Agents Chemother (Oct 17-20, New Orleans) 1993, Abst 715.

Ratner, L., Vander Heyden, N. *Mechanism of action of N-butyl deoxynojirimycin in inhibiting HIV-1 infection and activity in combination with nucleoside analogs.* AIDS Res Hum Retroviruses 1993, 9: 291-7.

Block, T.M., Lu, X., Platt, F.M., Foster, G.R., Gerlich, W.H., Blumberg, B.S., Dwek, R.A. *Secretion of human hepatitis B virus is inhibited by the imino sugar N-butyldeoxynojirimycin.* Proc Natl Acad Sci USA 1994, 91: 2235-9.

Tierney, M., Pottage, J., Kessler, H. et al. *The tolerability and pharmacokinetics of N-butyl-deoxynojirimycin in patients with advanced HIV disease (ACTG 100).* J Acquir Immune Defic Syndr Hum Retrovirol 1995, 10: 549-53.

Asano, N., Kizu, H., Oseki, K., Tomioka, E., Matsui, K., Okamoto, M., Baba, M. *N-Alkylated nitrogen-in-the-ring sugars: Conformational basis of inhibition of glycosidases and HIV-1 replication.* J Med Chem 1995, 38: 2349-56.

Barranger, J.A. *Risks of Gaucher's treatment.* Lancet 2000, 356: 1353-4.

Mistry, P.K. *Treatment of Gaucher's disease with OGT 918.* Lancet 2000, 356: 676-7.

Ranes, M.K., Manfredi, M.G., El-Abbadi, M.M., Platt, F.M., Seyfried, T.N. *N-Butyldeoxynojirimycin reduces growth rate and ganglioside content in mouse barin tumors.* Proc Am Assoc Cancer Res 2000, 41: Abst 1640.

Jordan, R., Conyers, B., Wang, L. et al. *Inhibitors of host ER alpha-glucosidases as potential "resistant proof" therapies for hepatitis C virus infection.* Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-177.

Priestman, D.A., Platt, F.M., Dwek, R.A., Butters, T.D. *Imino sugar therapy for type 1 Gaucher disease.* Glycobiology 2000, 10: iv-vi.

Narita, K., Platt, F.M., Dwek, R.A., Ichikawa, S., Hirabayashi, Y., Butters, T.D. *Characterization of imino sugar compounds for inhibition of human ceramide-specific glucosyltransferase.* Glycoconjugate J 2000, 17: 92.

Lachmann, R.H., Hollak, C.E.M., Aerts, J.M.F.G. et al. *Substrate reduction using N-butyldeoxynojirimycin (OGT 918): Clinical trial of a novel oral therapy for Gaucher's disease.* J Inherit Metab Dis 2000, 23(Suppl. 1): 217.

van Weely, S., Maas, M., Aerts, J. *Long-term effects of oral treatment of Gaucher disease with N-butyldeoxynojirimycin (OGT 918) in The Netherlands*. Blood 2001, 98(11, Part 1): Abst 955.

Zimran, A., Hollak, C., Aerts, J., van Weely, S., Cox, T., Lachmann, R., Hrebicek, M., Elstein, D. *Efficacy and tolerability of N-butyldeoxynojirimycin (OGT 918) in adult patients with type 1 Gaucher disease: Long-term follow-up.* Blood 2001, 98(11, Part 2): Abst 3695.

Heitner, R., Elstein, D., Zimran, A. *A dose comparison of the efficacy and safety of oral N-butyldeoxynojirimycin (OGT 918) in clinical studies in Gaucher disease.* Blood 2001, 98(11, Part 2): Abst 3704.

van der Spoel, A.C., Jeyakumar, M., Butters, T.D., Charlton, H.M., Moore, H.D., Dwek, R.A., Platt, F.M. *Reversible infertility in male mice after oral administration of alkylated imino sugars: A nonhormonal approach to male contraception.* Proc Natl Acad Sci USA 2002, 99: 17173-8.

Ouzounov, S., Mehta, A., Dwek, R.A., Block, T.M., Jordan, R. *The combination of interferon α-2b and n-butyl deoxynojirimycin has a greater than additive antiviral effect upon production of infectious bovine viral diarrhea virus (BVDV) in vitro: Implications for hepatitis C virus (HCV) therapy.* Antiviral Res 2002, 55: 425-35.