

2) Study 918-001X

Table 182: 918-001X Other Disease Assessments (Patients with follow-up exams only)

Patient	Assessment	Results (all follow-up occurred at Month 24)
201	MRI (L-spine, pelvis/femurs) QSCI (L-spine)	no change from 0.23 (Baseline) to 0.25 (Month 12) to 0.30-0.31 (Month 24)*
202	MRI (L-spine, pelvis/femurs) QSCI (L-spine)	no change from 0.16 (Baseline) to 0.2 (Month 12) to 0.25-0.26 (Month 24)*
403	Echo	T1 from 24 mmHg (Baseline) to 26 mmHg (Month 12) to 24 mmHg (Month 24)
	DEXA	No change
404	Echo	T1 from 33 mmHg (Baseline) to 27 mmHg (Month 12) to 25 mmHg (Month 24)
	DEXA	No change
405	Echo	T1 from 19 mmHg (Baseline) to 21 mmHg (Month 12) to 23 mmHg (Month 24)
	DEXA	No change
407	DEXA	No change
409	DEXA (L-spine) Echo	no change T1 from 31 mmHg (Baseline) to 29 mmHg (Month 12) to 25 mmHg (Month 24)
411	Echo	T1 from 23 mmHg (Baseline) to 27 mmHg (Month 12) to 25 mmHg (Month 24)
	DEXA	Decrease in z-score in femoral neck from -1.87 (Baseline) to -2.64 (Month 24)
412	DEXA (femoral neck, L-spine) Echo	L-spine: no change, femoral neck: change in z-score from 1.24 (Baseline, AVN noted) to -1.96 (Month 12) to -2.60 (Month 24) T1 from 28 mmHg (Baseline) to 20 mmHg (Month 12) to 22 mmHg (Month 24)
413	Echo DEXA	T1 from 20 mmHg (Baseline) to 25 mmHg, mild AI (Month 24) No change
414	Echo	T1 from 22 mmHg (Baseline) to 24 mmHg (Month 12) to 25 mmHg (Month 24)
	DEXA	Mild increases in z-scores in femoral neck and L-spine
415	Echo	T1 from 13 mmHg (Baseline) to 18 mmHg (Month 12) to 20 mmHg (Month 24)
	DEXA	No change
416	Echo	T1 from 22 mmHg (Baseline) to 26 mmHg (Month 24)
	DEXA	No change

\*Per Rosenthal et al<sup>17</sup>, normal range for healthy adults 23-35%. In Gaucher study with ERT mean QCSI prior to treatment 7.3%  $\pm$  6.7%, and after 42-months of treatment 22.9%  $\pm$  6.6%

<sup>17</sup> Rosenthal DI, Doppelt SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusick KA, Rosen BR, Baker J, Niklason LT, Hill SC, Miller SPF, Brady RO, Barton NW, and Collaborators. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. *Pediatrics* 1995;96(4):629-637.

### 3) Study 918-003

**Table 183: 918-003 Other Disease Assessments (Patients with follow-up exams only)**

Patient	Assessment	Results (all follow-up occurred on Day 169)
201	Echo	TI from 42 mmHg (Baseline) to 26 mmHg (Month 6)
206	Echo	TI from 30 mmHg (Baseline) to 26 mmHg (Month 6)
208	Echo	TI from 13 mmHg (Baseline) to 11 mmHg (Month 6)

### 4) Study 918-003X

**Table 184: 918-003X Other Disease Assessments (Patients with follow-up exams only)**

Patient	Assessment	Results (all follow-up occurred at Month 12)
201	Echo	TI from 42 mmHg (Baseline) to 26 mmHg (Month 6)
	DEXA	Decreased z-score from -0.41 (Baseline) to -0.54 (Month 12)
203	Echo	TI from 43 mmHg (Baseline) to 33 mmHg (Month 12)
	DEXA	Decreased z-score from -1.27 (Baseline) to -1.58 (Month 12)
205	DEXA	Decreased z-score from -0.17 (Baseline) to -0.43 (Month 12)
206	Echo	TI from 30 mmHg (Baseline) to 26 mmHg (Month 6) to 27 mmHg (Month 12)
	DEXA	Decreased z-score from -0.34 (Baseline) to -0.57 (Month 12)
208	Echo	TI from 13 mmHg (Baseline) to 11 mmHg (Month 6)

### 5) Study 918-004

**Table 185: 918-004 Other Disease Assessments (Patients with follow-up exams only)**

Patient	Treatment	Assessment	Results (all follow-up occurred at Month 6)
102	OGT 918	DEXA	Decreased z-score from -0.68 (Baseline) to -0.88 (Month 6)
		Echo	TI from 19 mmHg (Baseline) to 18 mmHg (Month 6)
103	OGT 918	DEXA	Increased z-score from -1.20 (Baseline) to -1.10 (Month 6)
		Echo	TI from 18 mmHg (Baseline) to 16 mmHg (Month 6)
111	OGT 918	DEXA	Increased z-score from 1.98 (Baseline) to 2.48 (Month 6)
120	OGT 918	DEXA	Increased z-score from 3.51 (Baseline) to 4.08 (Month 6)
		Echo	TI from 30 mmHg (Baseline) to 26 mmHg (Month 6)
121	OGT 918	DEXA	Increased z-score from 0.45 (Baseline) to 0.72 (Month 6)
		Echo	TI from 15 mmHg (Baseline) to 18 mmHg (Month 6)
126	OGT 918	DEXA	Increased z-score from -1.80 (Baseline) to -1.68 (Month 6)
		Echo	TI from 17 mmHg (Baseline) to 16 mmHg (Month 6)
129	OGT 918	DEXA	Increased z-score from -1.38 (Baseline) to -0.88 (Month 6)
		Echo	TI from 25 mmHg (Baseline) to 17 mmHg (Month 6)
130	OGT 918	DEXA	Decreased z-score from -0.96 (Baseline) to -2.15 (Month 6)
		Echo	TI from 25 mmHg (Baseline) to 17 mmHg (Month 6)
133	OGT 918	Echo	TI from 20 mmHg (Baseline) to 21 mmHg (Month 6)
136	OGT 918	DEXA	z-score ND, t-score decreased
101	Cerezyme	DEXA	Decreased z-score from -2.88 (Baseline) to -3.08 (Month 6)
		Echo	TI from 25 mmHg (Baseline) to 20 mmHg (Month 6)
107	Cerezyme	DEXA	Increased z-score from -2.01 (Baseline) to -1.78 (Month 6)
		Echo	TI from 25 mmHg (Baseline) to 25 mmHg (Month 6)
112	Cerezyme	DEXA	Decreased z-score from -2.31 (Baseline) to -2.97 (Month 6)
		Echo	TI from 22 mmHg (Baseline) to 26 mmHg (Month 6)
113	Cerezyme	DEXA	Increased z-score from -1.28 (Baseline) to -1.15 (Month 6)

115	Cerezyme	DEXA	Increased z-score from -1.74 (Baseline) to -1.44 (Month 6)
116	Cerezyme	DEXA	Increased z-score from -1.65 (Baseline) to -1.57 (Month 6)
		Echo	TI from 30 mmHg (Baseline) to 28 mmHg (Month 6)
117	Cerezyme	DEXA	Decreased z-score from -0.08 (Baseline) to -0.14 (Month 6)
		Echo	TI from 28 mmHg (Baseline) to 26 mmHg (Month 6)
127	Cerezyme	DEXA	z-score ND, t-score no change
		Echo	TI from 20 mmHg (Baseline) to 24 mmHg (Month 6)
132	Cerezyme	DEXA	Increased z-score from -1.08 (Baseline) to -0.96 (Month 6)
		Echo	TI from 25 mmHg (Baseline) to 27 mmHg (Month 6)
137	Cerezyme	DEXA	Decreased z-score from -1.86 (Baseline) to -1.89 (Month 6)
104	Combination	DEXA	Increased z-score from -0.73 (Baseline) to -0.57 (Month 6)
		Echo	TI from 25 mmHg (Baseline) to 15 mmHg (Month 6)
105	Combination	DEXA	Increased z-score from -0.72 (Baseline) to -0.35 (Month 6)
		Echo	TI from 20 mmHg (Baseline) to 27 mmHg (Month 6)
108	Combination	DEXA	Increased z-score from 1.27 (Baseline) to 1.76 (Month 6)
109	Combination	DEXA	Decreased z-score from -2.09 (Baseline) to -2.20 (Month 6)
		Echo	TI from 20 mmHg (Baseline) to 19 mmHg (Month 6)
114	Combination	DEXA	Increased z-score from -2.27 (Baseline) to -2.22 (Month 6)
119	Combination	DEXA	No change in z-score from -2.33 (Baseline) to -2.33 (Month 6)
		Echo	TI from 26 mmHg (Baseline) to 17 mmHg (Month 6)
124	Combination	DEXA	Increased z-score from 0.23 (Baseline) to 0.40 (Month 6)
		Echo	TI from 13 mmHg (Baseline) to 16 mmHg (Month 6)
125	Combination	DEXA	Decreased z-score from -2.24 (Baseline) to -2.23 (Month 6)
		Echo	TI from 22 mmHg (Baseline) to 25 mmHg (Month 6)
131	Combination	DEXA	Decreased z-score from -0.68 (Baseline) to -0.75 (Month 6)
134	Combination	DEXA	Decreased z-score from -1.63 (Baseline) to -1.67 (Month 6)
135	Combination	DEXA	Increased z-score from 1.04 (Baseline) to 1.52 (Month 6)
		Echo	TI from 14 mmHg (Baseline) to 13 mmHg (Month 6)

## 6) Study 918-004X

Table 186: 918-004X Other Disease Assessments (Patients with follow-up exams only)

Patient	Treatment	Assessment	Results (all follow-up occurred at Month 6)
102	OGT 918	DEXA	Decreased z-score from -0.68 (Baseline) to -0.88 (Month 6) to -1.16 (Month 12)
		Echo	TI from 19 mmHg (Baseline) to 18 mmHg (Month 6) to 16 mmHg (Month 12)
103	OGT 918	DEXA	Increased z-score from -1.20 (Baseline) to -1.10 (Month 6) to -1.02 (Month 12)
		Echo	TI from 18 mmHg (Baseline) to 16 mmHg (Month 6) to 17 mmHg (Month 12)
120	OGT 918	DEXA	Decreased z-score from 3.51 (Baseline) to 4.08 (Month 6) to 3.24 (Month 12)
		Echo	TI from 30 mmHg (Baseline) to 26 mmHg (Month 6) to 23 mmHg (Month 12)
121	OGT 918	DEXA	Increased z-score from 0.45 (Baseline) to 0.72 (Month 6) to 0.44 (Month 12)
		Echo	TI from 15 mmHg (Baseline) to 18 mmHg (Month 6) to 18 mmHg (Month 12)
126	OGT 918	DEXA	Increased z-score from -1.80 (Baseline) to -1.68 (Month 6) to -1.79 (Month 12)
		Echo	TI from 17 mmHg (Baseline) to 16 mmHg (Month 6) to 15 mmHg (Month 12)
129	OGT 918	DEXA	Increased z-score from -1.38 (Baseline) to -0.88 (Month 6) to -0.81 (Month 12)
		Echo	TI from 17 mmHg (Baseline) to 17 mmHg (Month 12)
130	OGT 918	DEXA	Decreased z-score from -0.96 (Baseline) to -2.15 (Month 6) to -1.85 (Month 12)
		Echo	TI from 25 mmHg (Baseline) to 17 mmHg (Month 6) to 21 mmHg (Month 12)
136	OGT 918	Echo	TI from 25 mmHg (Baseline) to 20 mmHg (Month 12)
101	Cerezyme	DEXA	Increased z-score from -2.88 (Baseline) to -3.08 (Month 6) to -2.29 (Month 12)
		Echo	TI from 25 mmHg (Baseline) to 20 mmHg (Month 6) to 22 mmHg (Month 12)
107	Cerezyme	DEXA	Increased z-score from -2.01 (Baseline) to -1.78 (Month 6) to -0.33 (Month 12)
		Echo	TI from 25 mmHg (Baseline) to 25 mmHg (Month 6) to 24 mmHg (Month 12)

112	Cerezyme	DEXA	Decreased z-score from -2.31 (Baseline) to -2.97 (Month 6) to -2.98 (Month 12)
		Echo	TI from 22 mmHg (Baseline) to 26 mmHg (Month 6) to 24 mmHg (Month 12)
113	Cerezyme	DEXA	Increased z-score from -1.28 (Baseline) to -1.15 (Month 6) to -1.10 (Month 12)
		Echo	TI from 19 mmHg (Baseline) to 18 mmHg (Month 12)
116	Cerezyme	Echo	TI from 30 mmHg (Baseline) to 28 mmHg (Month 6) to 27 mmHg (Month 12)
117	Cerezyme	DEXA	Decreased z-score from -0.08 (Baseline) to -0.14 (Month 6) to 0.50 (Month 12)
		Echo	TI from 28 mmHg (Baseline) to 26 mmHg (Month 6) to 20 mmHg (Month 12)
118	Cerezyme	DEXA	Increased z-score from -1.58 (Baseline) to -0.79 (Month 12)
		Echo	TI from 18 mmHg (Baseline) to 22 mmHg (Month 12)
122	Cerezyme	DEXA	Increased z-score from -0.73 (Baseline) to 0.37 (Month 12)
127	Cerezyme	DEXA	z-score ND, t-score no change, increased T-score at Month 12
		Echo	TI from 20 mmHg (Baseline) to 24 mmHg (Month 6) to 23 mmHg (Month 12)
132	Cerezyme	DEXA	Increased z-score from -1.08 (Baseline) to -0.96 (Month 6) to -0.82 (Month 12)
		Echo	TI from 25 mmHg (Baseline) to 27 mmHg (Month 6) to 26 mmHg (Month 12)
105	Combination	DEXA	Increased z-score from -0.72 (Baseline) to -0.35 (Month 6) to -0.62 (Month 12)
		Echo	TI from 20 mmHg (Baseline) to 27 mmHg (Month 6) to 25 mmHg (Month 12)
108	Combination	DEXA	Increased z-score from 1.27 (Baseline) to 1.76 (Month 6) to 1.71 (Month 12)
		Echo	TI from 17 mmHg (Baseline) to 15 mmHg (Month 12)
109	Combination	DEXA	Increased z-score from -2.09 (Baseline) to -2.20 (Month 6) to -1.31 (Month 12)
		Echo	TI from 20 mmHg (Baseline) to 19 mmHg (Month 6) to 14 mmHg (Month 12)
114	Combination	DEXA	Increased z-score from -2.27 (Baseline) to -2.22 (Month 6) to -1.62 (Month 12)
		Echo	TI from gradient undetectable (Baseline) to gradient undetectable (Month 12)
119	Combination	Echo	TI from 26 mmHg (Baseline) to 17 mmHg (Month 6) to 24 mmHg (Month 12)
124	Combination	DEXA	Increased z-score from 0.23 (Baseline) to 0.40 (Month 6) to 1.11 (Month 12)
		Echo	TI from 13 mmHg (Baseline) to 16 mmHg (Month 6) to 24 mmHg (Month 12)
125	Combination	DEXA	Increased z-score from -2.24 (Baseline) to -2.23 (Month 6) to -1.55 (Month 12)
		Echo	TI from 22 mmHg (Baseline) to 25 mmHg (Month 6) 23 mmHg (Month 12)
131	Combination	DEXA	Increased z-score from -0.68 (Baseline) to -0.75 (Month 6) to 0.36 (Month 12)
		Echo	TI from 19 mmHg (Month 6) 16 mmHg (Month 12)
135	Combination	DEXA	z-score from 1.04 (Baseline) to 1.52 (Month 6) to ND (Month 12)
		Echo	TI from 14 mmHg (Baseline) to 13 mmHg (Month 6) to 14 mmHg (Month 12)

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/s/

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Anne Pariser  
5/2/02 02:32:23 PM  
MEDICAL OFFICER

Mary Parks  
5/2/02 03:51:38 PM  
MEDICAL OFFICER

**MEMORANDUM :**

Public Health Service

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Food and Drug Administration**

**Division of Neuropharmacological Drug Products (HFD-120)  
Center for Drug Evaluation and Research**

**Date:** May 13, 2002

**From:** Russell Katz, MD, Director  
Division of Neuropharmacological Drug Products, HFD-120

**Subject:** Consult Request on Zavesca (OGT 918) for Gaucher Disease

**To:** David G. Orloff, MD, Director, Division of Metabolic and Endocrine Drug  
Products, HFD-510

The attached review by Dr. Tremblay and the appended memorandum by Neurology Team Leader John Feeney, MD, dated April 15, 2002 and May 10, 2002, respectively, represent the division's response to your consult received March 4, 2002.

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**Consultative Review and Evaluation of Clinical Data**

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Subject	Neurological Safety Review for Paresthesias & Tremors
NDA Number	21-348
Drug	Zavesca (miglustat, OGT 918)
Proposed Indication	Type I Gaucher Disease
Sponsor	Oxford GlycoSciences, Ltd.
Consultation From	Division Metabolic & Endocrine Drug Products, HFD-510
Material Received	ISS (10 vol); Ann. Report; Safety Update; Cons. Request
Date Received	March 4, 2002
Date Reviewed	April 5, 2002
Reviewer	Gerald Tremblay, MD, CDER, DNDP, HFD-120

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**QUESTIONS**

29

**MEMORANDUM BY NEUROLOGY TEAM LEADER, JOHN FEENEY, MD**

37

**Summary:** This consultation evaluates tremor, paresthesias, and abnormal electrodiagnostic testing in 3 small, open-label clinical trials of OGT 918 for adult Gaucher disease. OGT 918 inhibits the production of glycosphingolipids (GSLs) that accumulate in the liver, spleen and bones of patients with adult-type Gaucher disease. These individuals lack a degradative enzyme that is needed to eliminate spent GSLs. They have no difficulty *synthesizing* any GSLs, which are complex molecules required for normal cellular (especially neural) function. The usual treatment of Gaucher disease is to replace the missing degradative enzyme—enzyme replacement therapy (ERT). The present approach of decreasing the *synthesis* of substrate GSLs with OGT 918 is being evaluated. In the clinical studies, 29% of patients developed tremor on the drug, which stops with drug withdrawal. The sponsor admits that the drug causes an apparently benign, reversible tremor in some patients. There were also 18.8% patients who complained of paresthesias or numbness on the drug, and a larger number (mostly asymptomatic) who were also discovered to have abnormal electrodiagnostic testing. Sponsor argues that these patients had alternative explanations for the neuropathic signs or symptoms, but given a safety database of only 80 patients and without baseline or adequate comparative data, it is difficult to state conclusively whether OGT 918 played a causal role or not. Nevertheless, 5 troublesome neuropathy cases, preclinical evidence of neurotoxicity, and the fact that the drug depletes GSLs that are necessary for nerve function suggest OGT 918 may be neurotoxic in humans. Recommendations for further study, safety monitoring, and labeling are made. Pediatric use is not recommended

**Introduction and Background**

The neurological issues we are asked to address in this consultation are tremor, paresthesias, and abnormal electrodiagnostic testing (EMG/NCV) results observed during the clinical trials of OGT 918 (Zavesca®, Oxford GlycoSciences) in adult Gaucher disease. The specific questions that accompanied the Consultation Request are located at the end of this document with their answers.

Type I (adult type) Gaucher disease is a lysosomal storage disorder in which abnormal amounts of a glycosphingolipid (GSL) is stored in macrophages. It is manifested by hematologic abnormalities with hypersplenism, bone lesions, skin pigmentation, and brown spots of Gaucher cells at comeoscleral limbus. The disorder is particularly frequent in Ashkenazi Jews. All forms of the disease result from storage of glucosylceramide. Type 1 Gaucher may be diagnosed in infancy or in old age, and the genetics is autosomal recessive in most cases. The deficiency in the enzyme glucocerebrosidase was demonstrated by Brady and others in the mid-1960s<sup>2</sup>.

Important to the issue of peripheral neuropathy is the complication of monoclonal gammopathy. Long-term accumulation of glucocerebroside in Gaucher disease apparently stimulates lymphocyte clones to produce immunoglobulins, and multiple myeloma is not uncommon among Gaucher patients<sup>3</sup>. As will be pointed out below when discussing *peripheral neuropathies*, monoclonal gammopathies are one of many causes of them.

Glucocerebrosidase activity is not completely absent in adult type Gaucher patients, but is about 15% of normal. (In the neurological forms of Gaucher, types 2 and 3, the enzyme activity levels are only about 2% of normal.). The actual amount of enzyme may be normal in individual Gaucher patients (of any type), but because it exists in a mutated form, its activity is reduced or absent. The location of the gene mutation—over 30 are known—determines how much enzyme activity the mutated enzyme will have. Among type 1 (adult) Gaucher patients, there is a very mild form, a severe form and a moderate form, which itself can present in a variety of ways<sup>4</sup>.

It is important to keep in mind that the *synthesis* of glycosphingolipids (GSLs) is *normal* in Gaucher disease. I will devote several pages below to what may seem to be an unnecessary biochemical digression. The point is that OGT 918 inhibits the synthesis of GSLs. It decreases the amount of glucosylceramide that the patient's residual degradative enzyme has to cope with, but in doing so it also decreases all GSLs that have glucosylceramide as the parent molecule. Decreasing GSLs may have undesirable effects, as will be discussed toward the end of this consultation.

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<sup>1</sup> See the Online Mendelian Inheritance in Man (OMIM) web site for a complete discussion of these and all other lysosomal storage diseases. The link to Gaucher disease is <http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?230800>

<sup>2</sup> Brady, R. O.; Kanfer, J. N.; Shapiro, D. Metabolism of glucocerebrosides. II. Evidence of an enzymatic deficiency in Gaucher's disease. *Biochem. Biophys. Res. Commun.* 18: 221-225, 1965.

<sup>3</sup> Garfinkel, D.; Sidi, Y.; Ben-Bassat, M.; Salomon, F.; Hazaz, B.; Pinkhas, J. Coexistence of Gaucher's disease and multiple myeloma. *Arch. Intern. Med.* 142: 2229-2230, 1982.

<sup>4</sup> Zlotogora, J.; Zaizov, R.; Klibansky, C.; Matoth, Y.; Bach, G.; Cohen, T. Genetic heterogeneity in Gaucher disease. *J. Med. Genet.* 23: 319-322, 1986

The majority of patients with type 1 Gaucher disease need splenectomy to control the thrombocytopenia and anemia. Orthopedic complications vary from mild to severe with pathological fractures, vertebral compression (with nerve root entrapment), avascular necrosis of the femoral head, and frequent attacks of bone pain.

Treatment of the underlying disease has included gene therapy, enzyme replacement therapy, and bone marrow transplantation. Enzyme replacement therapy (ERT) was successfully tried on Gaucher patients using human placenta-derived glucocerebrosidase in the early 1990s. Modifications to the enzyme were later made so that it targeted the macrophages, (which is the what a so-called Gaucher cell is). This treatment is generally well-tolerated and causes a reduction in liver volume, increases in platelet counts, increased hemoglobin, and bone improvements. This modified enzyme was marketed as alglucerase (Ceredase®, Genzyme). Using the recommended dose of 60 units per kilogram of body weight every 2 weeks, the cost of annual treatment for a 70-kg patient is about \_\_\_\_\_ It was later demonstrated that more frequent administration might be more efficient. They showed that a dose of 2.3 units per kilogram 3 times weekly yielded satisfactory results with major financial benefits, reducing the cost to about \_\_\_\_\_ per year. Ceredase was approved by the FDA in 1991. In mid-1994, the FDA approved a recombinant alternative to Ceredase called Cerezyme. Cerezyme is also produced by Genzyme. It may have the advantage over Ceredase of stimulating a lower rate of antibodies.

In 1995 bone marrow transplantation (BMT) was reported in Gaucher patients from HLA-identical and partial matches was reported, with excellent results in several cases. BMT may be a definitive treatment for selected patients, provided a suitable donor is available<sup>5</sup>.

There may be 20,000 or more people with Gaucher disease in the United States.<sup>6</sup> Over two-thirds are Ashkenazi Jews, among whom Gaucher disease is one of the most frequent genetic disorders, with a heterozygote frequency of about 1 in 13. By examination of glucocerebrosidase activity in leukocytes of a series of blood donors, the estimated the frequency of carriers among Ashkenazi Jews in Israel as 4.6%, which agrees with the carrier rate of 4% estimated from the number of known cases of Gaucher disease in Israel<sup>7</sup> Although there are about 30 known mutations capable of causing Gaucher disease, only 4 mutations collectively account for 96% of the cases in Ashkenazi Jewish populations.<sup>8</sup>

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<sup>5</sup> Ringden, O.; Groth, C. G.; Erikson, A.; Granqvist, E. S.; Mansson, J.-E.; Sparrelid, E.. Ten years' experience of bone marrow transplantation for Gaucher disease. *Transplantation* 59: 864-870, 1995.

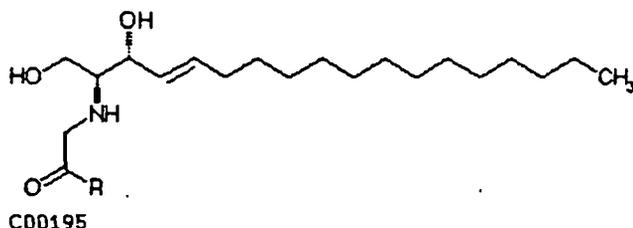
<sup>6</sup> OMIM, op cit.

<sup>7</sup> Id.

<sup>8</sup> Id.

Glycosphingolipids (GSLs) are derived from ceramide, in which a molecule of a fatty acid is attached to the amino-alcohol, sphingosine. (R is a 17-carbon chain):

Ceramide—The fatty acid portion is on right, from the point the top -OH group is attached



Ceramide is a parent molecule from which all other GSLs are synthesized by the attachment of various sugars or acidic groups to the sphingosine end. This results in a molecule that, because of its long fatty tail, is soluble in the lipid bilayer of cell membranes. The head of the molecule, however, projects out of the membrane surface and has many possible functions. They project out of the cellular membrane so that they can interact with the extracellular environment. GSL's in general are highly antigenic, and in fact, the blood group antigens, embryonic cell-cell recognition antigens, cholera and diphtheria receptors and some viral receptors are GSLs. Cell transformation (neoplasia) can be defined in terms of dramatic changes in the GSL composition of the cellular membranes. All membranes in the body contain GSLs, but they are especially abundant in nervous tissue. The very names of these molecules describe the place they were found in greatest abundance: cerebroside, ganglioside, sphingomyelin, psychosine, etc.

Ceramide, a parent molecule to all the other vital GSLs, is currently the subject of much research, because it can trigger apoptosis (programmed cell death), and its concentration also plays a regulatory role (as a "second messenger"). This may be relevant to disorders of GSL degradations, such as Farber disease, in which affected — cannot degrade ceramide. In one form of Farber disease, most of the affected — have a peripheral neuropathy, and it has been postulated that the pathogenic mechanism in Farber disease, aside from the obvious storage of lipid material typical of most lysosomal storage diseases (described below), may be due to the neurotoxicity of ceramide. In the present NDA, the drug OGT 918 blocks the attachment of glucose to ceramide. Although analogues of OGT 918 were known to be cytotoxic owing in part to the accumulation of free ceramide<sup>9</sup>, OGT 918 allegedly does not cause toxic levels of ceramide to accumulate.

<sup>9</sup> Platt FM, Butters TD. Substrate Deprivation: A new therapeutic approach for the glycosphingolipid lysosomal storage diseases. Expert Reviews in Molecular Medicine, 1 Feb 2000, <http://www-ermm.cbcu.cam.ac.uk>

### Synthetic Pathways of GSLs – The Inhibitory Effect of OGT 918

It is important to keep in mind that the synthetic routes to GSLs are distinct from the degradative pathways by which old GSLs are hydrolyzed. They occur in different parts of the cell, via different enzymes, and the drugs used in Gaucher disease, OGT 918 and Cerezyme, affect the synthetic and degradative pathways, respectively. GSLs are synthesized in the endoplasmic reticulum and packaged in the Golgi apparatus of the cell, whence they are transported in vesicles to the cell membrane. Senescent membrane is later taken back into the cell by endocytosis of the outer cell membrane. These vesicles fuse with the lysosomes, where sequential, irreversible hydrolysis of their glycosidic bonds takes place.

The synthesis of new GSLs begins with 'activated' fat in the form of palmitoyl-CoA and the amino acid serine which are to form precursors to sphingosine, which in turn is finally attached to a fatty acid to make ceramide.

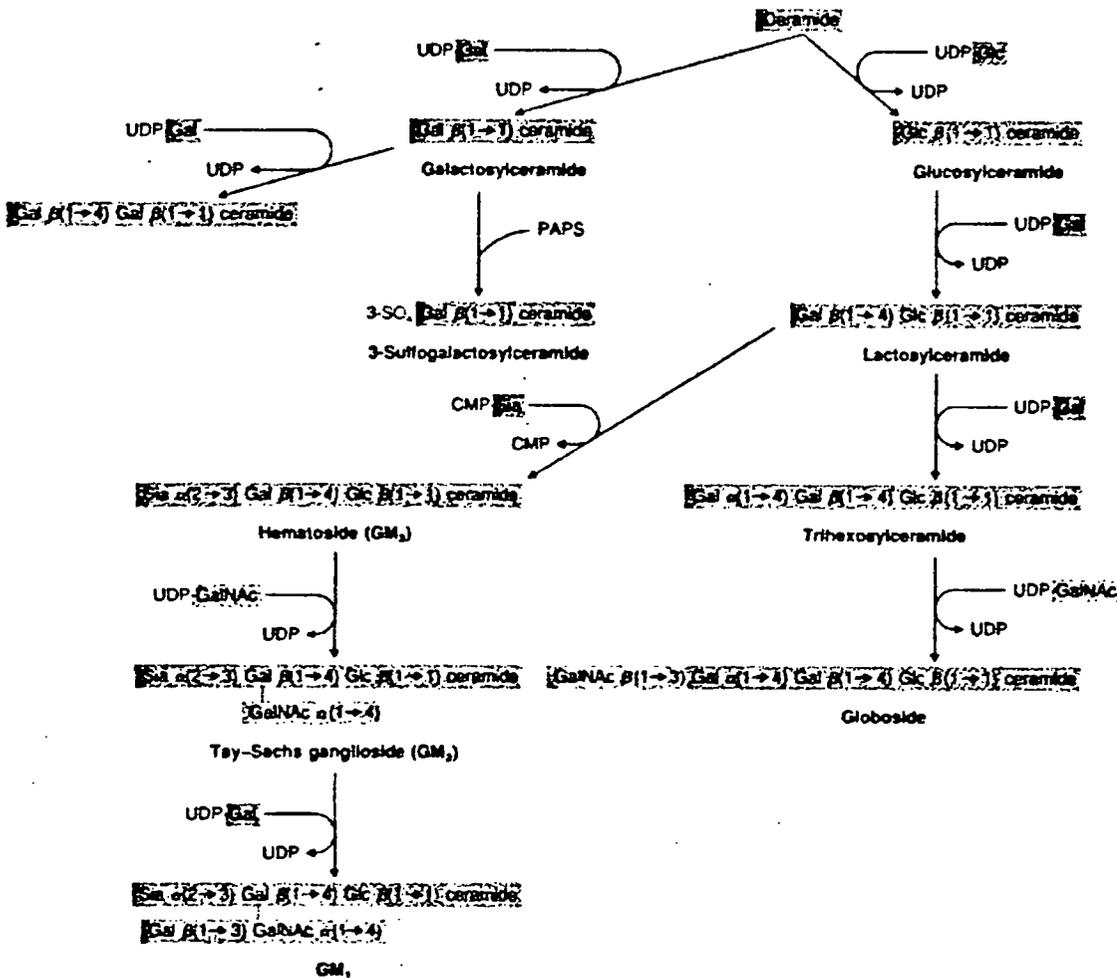
To create "neutral" GSLs, a glucose or galactose is attached to the sphingosine end. The glucose has to be "activated," so it is carried to the enzyme, ceramide glucosyltransferase by UDP-glucose. It is this reaction that OGT 918 primarily blocks. (It also interferes with enzymes that split disaccharides into monosaccharides, such as sucrose. This may explain why it causes osmotic diarrhea and flatulence in most patients.)

$\text{Ceramide} + \text{UDP-Glucose} \rightarrow \text{Glucosylceramide}^* + \text{UDP}$  [reaction blocked by OGT 918]

There are two points to keep in mind about GSL synthesis that may be pertinent to OGT 918's potential as a neurotoxin: First, by inhibiting the formation of GSLs from ceramide, there is at least a theoretical possibility that GSLs required for normal nerve membrane function may be reduced in absolute or relative amounts. Secondly, by inhibiting glucosylceramide production, there is the theoretical possibility that excessive amounts of free ceramide may accumulate, a phenomenon that was known to occur with earlier versions of this class of drugs. Excessive amounts of free ceramide trigger apoptosis.

**Synthesis of GSLs**

(right branch below ceramide are GSLs diminished by OGT 918)



**Degradation of GSLs, Genetic Defects, and Enzyme Replacement Therapy**

When ready for recycling, the cellular membrane is engulfed through the mechanism of endocytosis. The vacuoles containing old GSLs then fuse with the cell's engine of destruction, the lysosome, which contains enzymes capable of degrading GSLs, mucopolysaccharides, and other large, complex molecules. If one of these degradative enzymes is missing, the result is called a lysosomal storage disorder, because the material tends to be "stored" in ever-enlarging lysosomal bodies within the cells. The GSL family of lysosomal storage disorders includes Tay-Sachs, Gaucher, Metachromatic Leukodystrophy, Krabbe, Fabry,

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Farber, GM1 Gangliosidosis, Sandhoff, and Niemann-Pick. Except for the adult type of Gaucher and Fabry diseases, most individuals with the other GSL storage disorders die in infancy. A few individuals with Farber and GM1 may live into adulthood. The adult type Gaucher disease is by far the most common lysosomal storage disease. The following illustrates GSL degradative pathways:

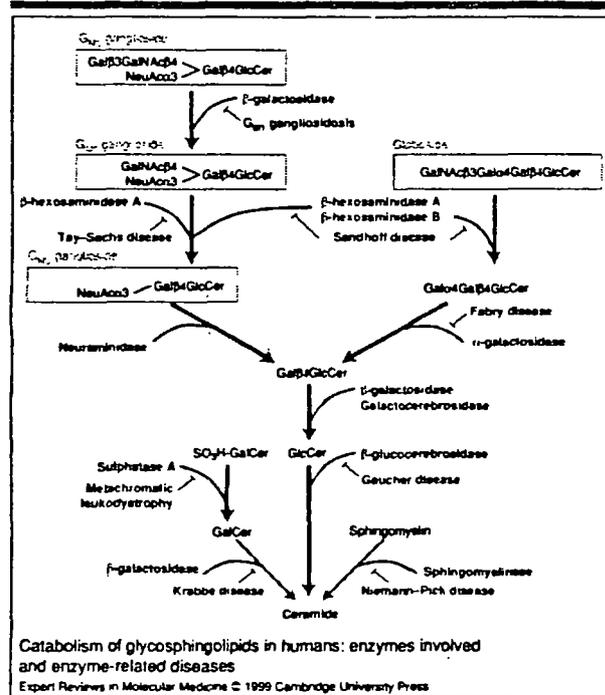


Figure 2 Catabolism of glycosphingolipids (GSLs) in humans: enzymes involved and enzyme-related diseases. This figure shows the disease states that arise due to mutations in the genes encoding the enzymes involved in the GSL catabolic pathway. Abbreviations used: Cer = ceramide, Gal = galactose, GalCer = galactosylceramide, GalNAc = N-acetylgalactosamine, Glc = glucose, GlcCer = glucosylceramide, NeuAc = N-acetylneuramic acid (sialic acid) (fig002tp).

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Table 1. Enzyme defects, affected genes and glycosphingolipids stored in human glycosphingolipid lysosomal storage diseases (tab001fpo)		
Disease*	Enzyme defect	Glycosphingolipid stored
Gaucher types 1, 2* and 3*	β-glucocerebrosidase	Glucosylceramide
Fabry	α-galactosidase	Ceramide trihexoside
Tay-Sachs*	Hexosaminidase A	G <sub>M2</sub> ganglioside
Sandhoff†	Hexosaminidase A and B	G <sub>M2</sub> ganglioside/igloboside
G <sub>M1</sub> gangliosidosis*	β-galactosidase	G <sub>M1</sub> ganglioside
Krabbe†	β-galactocerebrosidase	Galactosylceramide
Metachromatic leukodystrophy†	Arylsulphatase A	Galactosylceramide sulphate

\* The disease is characterized by neurological involvement.

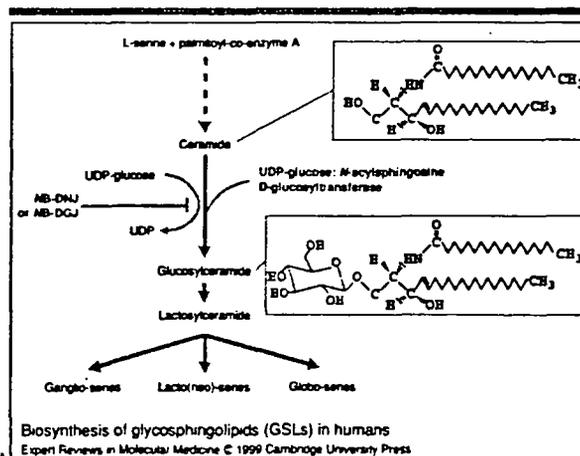
CNS involvement in the lysosomal storage diseases is common, but there is no primary CNS or peripheral nervous system involvement in adult type Gaucher disease. In Fabry disease, storage of the lipid material in blood vessels causes cerebral infarctions. In neuronopathic (infantile) Gaucher, the CNS involvement is

not due to storage of GSLs, but is caused by a poorly-understood toxicity or effect on brain development. Peripheral nerve involvement is seen in Metachromatic Leukodystrophy, Fabry, and Farber diseases. In Fabry there is storage of lipid material in arterial walls and there is excruciating paresthesias, but it is not clear whether these are due to ischemia of vessels, nerves, or some poorly-understood neurotoxic effect of a GSL. In Farber, peripheral neuropathy occurs in 75% of one variant; as stated above, this may be due to the toxicity of ceramide, which Farber patients cannot degrade, and which some suggest may be at the heart of the pathogenic mechanisms in Farber disease.

Inhibition of GSL Synthesis as Treatment for Gaucher Disease: "Substrate Deprivation" by Imino Sugars (e.g., OGT 918)

Whereas bone marrow transplant and enzyme replacement therapy (ERT) aim at replacing the missing or defective lysosomal enzyme in Gaucher disease, and thereby enabling the patient to degrade the accumulating GSLs, "substrate deprivation" takes the opposite tack. In the latter strategy, the idea is to inhibit the synthetic enzymes which make GSLs, thereby reducing "the biosynthesis of GSLs to a level such that the residual [degradative] enzyme activity can catabolize the GSLs that enter the lysosomes. The ultimate objective is to equalize the rates of synthesis and degradation. However, even if this cannot be fully achieved, as long as the rate of accumulation is slowed sufficiently to prevent the toxic threshold of GSL storage being reached, the patient should avoid symptomatic disease, or exhibit a greatly slowed rate of disease progression."<sup>10</sup>

The target enzyme for this "substrate deprivation" strategy has been the one that converts ceramide to glucosylceramide. (Please also refer to the synthetic pathways, above, and note that this reaction is the first step in the synthesis of 7 of the 10 GSLs depicted.) The enzyme inhibited by this group of drugs is called ceramide-specific glucosyltransferase<sup>11</sup>.



<sup>10</sup> Platt and Butters, op cit. (italics added)

<sup>11</sup> Also known as glucosylceramide synthase or glucosyltransferase)

Figure 1. Biosynthesis of glycosphingolipids (GSLs) in humans. In this figure, emphasis has been placed on the first step in the GSL biosynthetic pathway, the transfer of glucose (in the form of uridine diphosphate glucose [UDP-glucose]) to ceramide (N-acylsphingosine). This step is catalysed by the enzyme ceramide-specific glucosyltransferase which is inhibited by the imino sugars N-butyldeoxynojirimycin (NB-DNJ) and N-butyldeoxygalactosylmycin (NB-DGJ) (fig0017p).

Among the ceramide-specific glucosyltransferase inhibitors are those that are a class consisting of imino sugars, which are N-alkylated derivatives of deoxynojirimycin (DNJ) and deoxygalactonojirimycin (NGJ). The N-butyl derivative of DNJ (*N*-butyldeoxygalactonojirimycin or NB-DNJ) has mainly been used as the inhibitor of GSL synthesis. It is not entirely specific in its inhibitory activity, because it also inhibits  $\alpha$ -glucosidases, which are needed to hydrolyse disaccharides to monosaccharides. OGT 918 is NB-DNJ.

Molecular structure of OGT 918 (NB-DNJ, lower right) and related inhibitors of glucosylceramide synthesis:

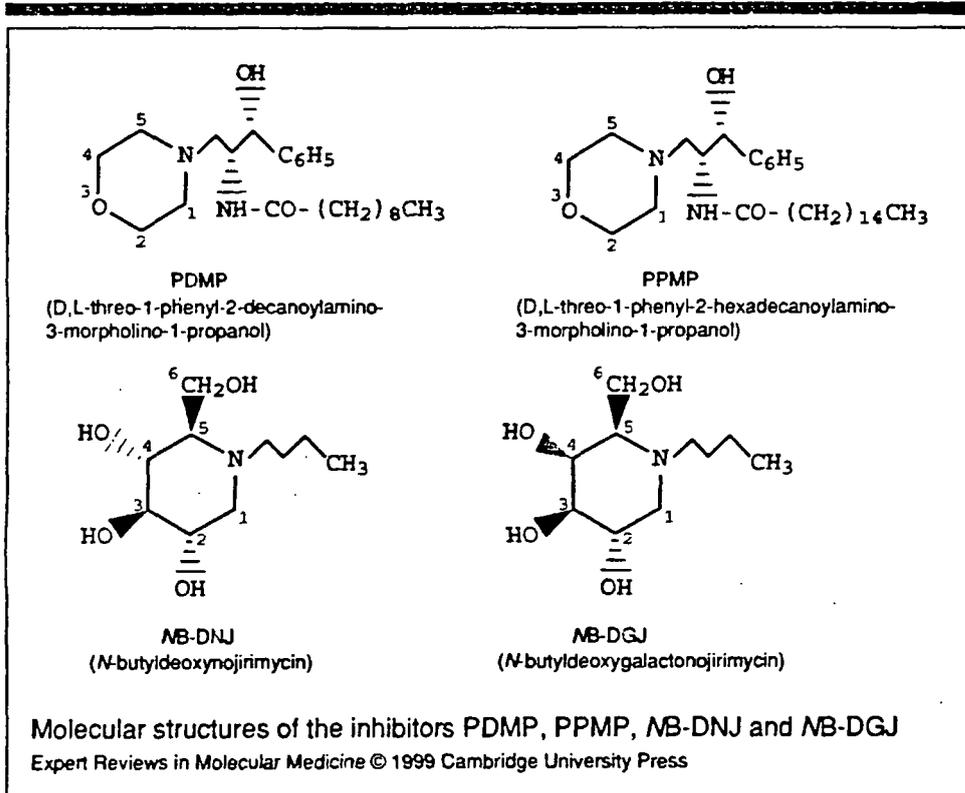


Figure 3. Molecular structures of the Inhibitors PDMP, PPMP, NB-DNJ and NB-DGJ (fig003fpo).

The two drugs shown at the top of the above illustration, PDMD and PPMP, also inhibit ceramide-specific glucosyltransferases, but they "are not available for oral administration, are relatively cytotoxic, owing to their hydrophobicity and accumulation of free ceramide, and are metabolized in vivo."<sup>12</sup> The newer generation of inhibitors represented by NB-DNJ (OGT 918), allegedly does not lead to the accumulation of free ceramide, but I do not know if it has been measured in a patient taking the drug.<sup>13</sup>

Some of the effects of NB-DNJ (OGT 918) may not be via enzyme inhibition, but may be as mimics of ceramide.<sup>14</sup>

NB-DNJ does not inhibit *galactosyltransferase*, so GalCer and sulphatide, important constituents of myelin, won't be affected. Only GSLs that are derived from glucosylceramide are inhibited by NB-DNJ (OGT 918). For this reason, the drug will not be useful in \_\_\_\_\_ both of which involve a failure to degrade GSLs based on the galactosylceramide parent molecule. The drug may be useful in Tay Sachs, Sandhoff disease, GM1 gangliosidosis, and other types of Gaucher disease, however, because each of these involves storage (degradation failure) of a glucosylceramide-based GSL.

NB-DNJ (OGT 918) crosses the blood-brain barrier.

#### Overview of the OGT 918 Clinical Trials

The following table taken from Dr. Pariser's consultation request summarizes the OGT 918 clinical trials. I will refer to the trials as 001, 003, 004, or to their extensions as 001x, 003x, etc. Note that there are no placebo-controls in any of the trials; trial 004 did, however, include an active control group on ERT (Cerezyme only). The primary endpoints were reduction in liver size and platelet counts. In the table, ERT refers to enzyme replacement therapy.

Although the efficacy of OGT 918 is not an issue in this consultation, modest but statistically significant reductions in organ volumes and increases in hemoglobin and platelets were observed. The trials have therefore shown the drug to be effective in adult Gaucher disease.

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<sup>12</sup> Platt and Butters, op cit, p. 8.

<sup>13</sup> Id.

<sup>14</sup> Op cit p.7

**Table 1: OGT 918 Clinical Studies**

<b>Study</b>	<b>Description</b>
918-001	Phase I/II non-comparative, open-label study in 28 adults with type 1 Gaucher disease who were either unable or unwilling to receive ERT. All patients received OGT at a starting dose of 100 mg TID, and could be increased to a maximum of 300 mg TID. Treatment was for 12 months. 22 patients completed the study.
918-001X	12-month extension to 918-001. 18 patients were rolled over (entered) after completion of 918-001. 14 patients completed a total of 24 months of study drug treatment.
918-003	Phase I/II non-comparative, open-label study in 18 adults with type 1 Gaucher disease who were either unable or unwilling to receive ERT. All patients received OGT 918 at a starting dose of 50 mg TID for a 6-month treatment period. This study was undertaken to allow comparison of safety and efficacy outcomes at the lower and higher doses of OGT 918. 17 patients completed the study.
918-003X	6-month extension to 918-003. 16 patients were rolled over after completion of 918-003. 13 patients completed a total of 12 months of study drug treatment.
918-004	Phase II open-label, active-comparator, randomized study in 36 adults with type 1 Gaucher disease who had received ERT for a minimum of 2 years. Patients were randomized to one of 3 treatment groups: 1) OGT 918 alone; 2) Cerezyme alone; 3) OGT 918 + Cerezyme The starting dose of OGT 918 was 100 mg TID, and treatment was for 6 months. The study was designed to investigate whether OGT 918 could safely be coadministered with ERT. 33 patients completed the study.
918-004X	6-month extension to 918-004. After completion of 918-004, patients were given the option to receive OGT 918 alone or in combination with Cerezyme for an unlimited period of time (minimum 6 months) regardless of their randomized treatment in the original study. 29 patients entered the study and all 29 patients elected to receive OGT 918 alone. The starting dose was OGT 918 100 mg TID. 28 patients completed 6 months of the extension study.

## Tremor

A general overview of tremor is presented in the Appendix.

Tremor occurred in 29% of patients exposed to the drug in clinical trials. The tremor may respond to a lowering of the dose, the tremor stops when the drug is stopped, and the Sponsor agrees that the drug is probably the cause:

*Five patients in Study OGT 918-001, eight patients in Study OGT 918-003 and 12 patients in Study OGT 918-004 complained of tremor. Tremor was mild in 21 patients and moderate in 4 patients. No patient required treatment for tremor although tremor was the cause, or a contributory factor in the withdrawal of at least two patients. The tremor was usually described as a fine bilateral tremor of the hands, similar to physiological tremor with a frequency of about 8 hz. In a few cases the tremor was asymmetrical and in one case tremor affected the neck. Tremor usually began within the first month and in many cases resolved between 1 to 3 months while treatment continued. Several patients had pre-existing tremor and this seemed to be exacerbated by Zavesca [OGT 918]. The severity of the tremor was also affected by changes in dose. Follow up is available on all patients except one, who withdrew when complaining of tremor, and in all these cases the tremor disappeared. Usually tremor resolved within days of withdrawal of drug.*

*Thus tremor appears to have a clear association with the use of the drug, but is usually mild, often self-limited and responds to a reduction in dose or withdrawal of drug.<sup>15</sup>*

Because the tremor did not normally interfere with functioning, appeared after the drug was started, and resolved when the drug was stopped, we agree with the Sponsor that it is an AE that is most likely caused by OGT 918. *What we do not know is whether the tremor will continue to be reversible after longer exposures to the drug.*

Tremor is not described as being a manifestation of type 1 Gaucher disease, but because a state of hypermetabolism may occur,<sup>16</sup> it is possible that some Gaucher disease patients may already have a tremor or may be predisposed to develop one with the drug. Usually it was described as "mild," meaning presumably that it did not usually interfere with function. We note that one Gaucher patient<sup>17</sup>, however, described herself as a \_\_\_\_\_ and that the "tremor disappeared with withdrawal of OGT 918." Clearly, some will be more tolerant of so-called "mild" tremor than other, depending on the degree and whether or not it affects their daily activities.

#### Relationship Between Paresthesias and Tremor

There does not seem to be an association between the paresthesias and the tremor. Although several of the patients had both (e.g. 103 and 105), the patient who was most affected with a well-documented neuropathy (101) never apparently complained of tremor. Likewise, patient 107 complained of cramps and paresthesias, but never complained of tremors. Patient 208 (study 003) had moderate (most patients had only mild tremor), but she never had paresthesias. She had normal EDX testing. Since 29% of exposed patients complained of tremor, and only 8% complained of paresthesias, it was usual to have one symptom without the other. We will therefore treat tremor as a neurological symptom that is separate from paresthesia in the rest of this consultation.

In summary, OGT 918, is associated with mild tremor in a significant number of patients. The effect appears to be reversible, at least after short-term exposure. Apart from listing tremor as a common AE in labeling, we do not think more needs to be done except to see if the tremor remains reversible after patients have been using OGT 918 longer than in the clinical trials.

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<sup>15</sup> Neurological Safety Update, Oxford GlycoSciences, February 2002, page 10 of 17.

<sup>16</sup> Beutler E, Grabowki GA, Gaucher Disease, in The Metabolic and Molecular Basis of Inherited Disease, 8<sup>th</sup> Ed., Wonsiewicz, et al, eds., vol. 3, p. 361, 2001.

<sup>17</sup> Neurological Safety Update, page 318 (patient 106).

### Paresthesias and Abnormal Electrodiagnostic Testing (EDX)

In the clinical trials of OGT 918 for Gaucher disease, 6 patients (8%) complained of paresthesias. If the adverse event is defined as "paresthesias or numbness," 15 patients (18.8%) complained of these symptoms during the clinical studies.<sup>18</sup> Because of the paresthesias that were noted in the first Gaucher trial, electrophysiological testing (EMG/NCV) was started after the patients were already taking OGT 918. No pre-treatment, baseline electrodiagnostic data exists, but 8 patients underwent electrodiagnostic testing in trial 004 while on Cerezyme only. Although the electrodiagnostic testing was not done in any standardized way, and was done by different examiners at different study centers, 60 patients underwent testing. Twenty of the 60 patients tested had abnormal electrodiagnostic results, and 19 were "consistent with a peripheral neuropathy." I will present these cases in more detail below.

Since submission of the NDA, one patient<sup>19</sup>, a 48 year-old woman with Gaucher disease, who originally had documented normal electrodiagnostic testing results, subsequently developed paresthesias. This is the only patient the Sponsor agrees has a peripheral neuropathy that was possibly caused by OGT 918:

*"The progress of this patient is being followed and information sought as to investigations carried out to determine the cause of her neuropathy. There is no record of her having any objective neurological signs. As she developed symptoms while on Zavesca [OGT 918] and following an increase in dose, Zavesca is a possible cause of her neuropathy."<sup>20</sup>*

In all other cases the Sponsor posits an alternative explanation, i.e., that some condition other than OGT 918 caused the paresthesias and/or the EDX abnormalities.

### Differential Diagnosis of Peripheral Neuropathy

A general overview of the peripheral neuropathy is presented in the Appendix. Briefly, the peripheral neuropathies are a large, diverse group of non-mechanical disorders that affect the nerves in a widespread and fairly symmetrical way. The symptoms are predominantly distal, beginning in the feet, with a loss of vibratory sense and ankle jerks initially. Motor loss may occur late. Paresthesias (described as pain, burning, tingling, etc.) and loss of sensation (numbness) are common symptoms. For the acquired causes of peripheral sensorimotor

<sup>18</sup> As of December 14, 2001.

<sup>19</sup> Patient 207, study 003. Her first EDX, May 11<sup>th</sup>, 2000, was normal. At the end of February, 2001, she began complaining of numbness in her hands and feet while on OGT 918. She started taking Cerezyme (enzyme replacement therapy) on March 26<sup>th</sup>, 2001, and her symptoms improved. On May 13<sup>th</sup>, 2001, her EDX was abnormal, and her followup on August 29, 2001, also shows changes consistent with sensorimotor peripheral neuropathy.

<sup>20</sup> Neurological Safety Update, February 2002, p. 8 of 17.

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neuropathy, a partial listing of the differential diagnosis is provided in the following table:

Acquired Syndromes of Sensorimotor Polyneuropathy <sup>21</sup>		
Time Course	Cause	Examples, Comment
Acute & Subacute	Deficiency States	alcoholism (beriberi), pellagra, B <sub>12</sub> deficiency, chronic gastrointestinal disease
	Poisonings with heavy metals and solvents	arsenic, lead, mercury, thallium, n-hexane, etc.
	Drug Toxicity	isoniazid, vincristine, cisplatin, paclitaxel, phenytoin, adulterated L-tryptophan, etc.
	Uremic polyneuropathy	
	Subacute inflammatory polyneuropathy	
Chronic	Paraneoplastic	lymphoma, myeloma, other malignancies
	Chronic inflammatory demyelinating polyneuropathy	
	Paraproteinemias	
	Uremia	occasionally subacute
	Beriberi	usually subacute
	Diabetes	also cause other types of neuropathy
	Connective Tissue Disease	
	Amyloidosis	
	Hypothyroidism	
Benign sensory form in the elderly		

### Paresthesias/Numbness & Abnormal Electrophysiology Results in the Gaucher OGT 918 Trials

As of December 14<sup>th</sup>, 2001, the combined dataset included 80 patients exposed to OGT 918; 6 of them (8%) complained of new-onset paresthesias while on the OGT 918. When the event is defined as "paresthesia or numbness" 15 patients (18.8%) while on the drug. As stated, there are no baseline, pre-exposure electrodiagnostic data on any patients, but eight patients in the Cerezyme group in trial 004 underwent electrodiagnostic testing before being exposed to OGT 918 (in the extension phase).

There was no baseline electrodiagnostic testing because, during trial 001 several patients complained of paresthesias, cramps, or tremors, and 2 were demonstrated to have peripheral neuropathies. The investigators then decided to start doing electrodiagnostic (EDX) studies on as many patients as possible in the Gaucher OGT 918 trials, regardless of symptoms. Unfortunately, not all

<sup>21</sup> Table adapted from Table 46-1, Principles of Neurology, op. cit.

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patients underwent the testing, there were no pre-treatment baseline electrodiagnostic data available on any patients, and the testing methods were not standardized. So far, 80 patients have received OGT 918 in trials for Gaucher disease and electrodiagnostic studies were done on 60 patients while they receiving OGT 918 and on 8 patients who were only receiving Cerezyme.

In reviewing the data below, one should keep in mind that trials 001 and 004 were high dose trials (100 mg TID), and trial 003 was a low dose trial (50 mg TID). Trial 004 had a group that received both OGT 918 *and* Cerezyme and it had a group that received *only* Cerezyme. Therefore, despite the lack of baseline data and confounding factors, there is the potential for recognizing a dose-response trend for OGT 918, an interaction trend between the OGT 918 and Cerezyme combination, and for a comparison between the OGT 918 groups and the Cerezyme controls. In the tabular presentations of these groupings that will follow, I hope to make these points clearer.

#### Trial OGT 918-001 and its 12-month extension, 001X

28 patients participated in Trial 001 and 18 of them continued for another 12 months in the extension phase. Most patients received 100 mg OGT 918 TID. Electrodiagnostic testing was done on 15 of 28 patients, and 7 results were abnormal. Eight patients had paresthesias, cramps, or numbness. The following tables are adapted from the Sponsor's Integrated Summary of Safety, p. 303:

#### Summary of Electrodiagnostic Findings & Symptoms in Trial 001 & 001X (High Dose—100 mg TID, up to 24 month exposure).

Patient ID 001-	Visit (Mo.)	EDX Normal (N) or Abnormal	Comments
-101	24	Abnormal	Most severely affected patient; 64 y.o. woman; paresthesias began approx 1 yr after OGT 918; not improved after stopping; 25% wt. loss; IgA monoclonal gammopathy; chronic sensorimotor peripheral neuropathy; (also has ulnar and C8/T1 neuropathies);
-103	9	Abnormal	Paresthesias, tremors on drug, but resolved while on drug. 9 mo. after stopping drug, EDX shows mild, gen. sensorimotor peripheral neuropathy. Tremors recurred after drug stopped.
-105	15	Abnormal	Tremor and foot cramps 1 mo. after OGT 918, then foot numbness about 3 weeks after drug stopped; decreased sural sensory responses <sup>22</sup> ; prolonged sural latencies
-106	19	N	Intermittent tremor began 10 mo. after starting OGT 918
-107	15	N	Paresthesias before starting OGT 918; incomplete EDX (NCV only)
-201	27	Abnormal	Patient known to have pre-existing B <sub>12</sub> deficiency, vasculitis, & cryoglobulinemia; low sural sensory nerve action potentials; no neurological symptoms
-202	27	N	No neurological symptoms
-301	21	N	No neurological symptoms
-404	24	Abnormal	Pre-existing B <sub>12</sub> deficiency; borderline low sural sensory nerve action potential consistent with peripheral neuropathy; no neurological symptoms

<sup>22</sup> Sural nerve action potentials (SNAPs) are sensitive to axonal loss

-405	24	N	No neurological symptoms
-407	24	Abnormal	Muscle cramps; low/absent sural sensory nerve action potential;
-411	24	N	No neurological symptoms
-412	24	N	No neurological symptoms
-414	24	Abnormal	Low sural and medial sensory nerve action potentials consistent with peripheral neuropathy; no neurological symptoms
-416	24	N	Transient cramps at 8 months, fine tremor began at 10 months

Rather than elaborate further on the individual patients in the above table, I will present the EDX findings from the lower dose (50 mg TID), shorter duration trial (003) next.

Trial OGT 918-003 and its 6-month extension, 003x

Eighteen patients participated in this open-label trial in which they received 50 mg OGT 918 tid for 6 months. Seventeen patients completed the trial, and 16 entered the 6-month extension (003x). Twelve completed 12 months of exposure.

Summary of Electrodiagnostic Findings & Symptoms in Trial 003 & 003x  
(Low Dose, 50 mg TID, up to 12 month exposure)

Patient ID 003-	Visit (Mo.)	EDX Normal (N) or Abnormal	Comments
101	9	N	Tremor and paresthesias reported
102	9	N*	Leg cramps; * L5-S1 radiculopathy but no generalized peripheral neuropathy
103	9	N**	Tremor and paresthesias reported; **chronic C8-T1 radiculopathy bilaterally, but no generalized periph. neuropathy
104	9	N	Tremor reported
105	9	N	Tremor reported
106	9	N	Leg cramps, paresthesias, numbness reported
107	9	N	No neurological symptoms
110	9	N	Tremor and leg cramps reported
111	9	Abnormal	Tremor, leg cramps, paresthesias. Repeat EDX 2 months after stopping OGT 918 remained abnormal; examiner felt she may have Charcot-Marie-Tooth, despite lack of peroneal n. involvement and no history of a gait disorder
112	6	N	Tremor reported
201	12	N	No neurological symptoms
203	12	Abnormal	No neurological symptoms; small sural sensory nerve action potentials; history of low B12 levels
204	9	N	No neurological symptoms
205	12	N	No neurological symptoms
207	12	N, Abnormal***	No neurological symptoms initially; ***initial electrodx testing normal; later developed numbness and 2 subsequent electrodx test results consistent with sensorimotor peripheral neuropathy
208	9	N	Tremor reported

Superficially at least, there appear to be fewer neurological adverse events (paresthesias, tremors, cramps, abnormal EDX) in the low dose, shorter duration

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trial (003) than were seen in the high dose, longer duration trial (001). The causation in some of the individual cases, however, has alternatives besides OGT 918.

Rather than discuss the individual cases in the above tables in greater detail (I will return to them later after this overview), I will present one last summary table that presents the EDX and neurological symptom data from the OGT 918 Gaucher trial, 004.

#### Trial OGT 918-004 and its 6-month extension, 004x

Trial OGT 918-004 was an open-label, active control trial for patients with a prior history of at least 2 years of ERT. Thirty-six enrolled and 33 completed 6 months. All who entered the extension phase (004x) elected to go to OGT 918. Twenty-nine enrolled and 28 completed the 6 month extension.

Trial OGT 918-004 had three groups of patients:

- 100 mg TID OGT 918
- Cerezyme (enzyme replacement therapy) only
- 100 mg TID OGT 918 + Cerezyme

Patient ID	EDX Normal (N) or Abnormal	Comment
<b><u>OGT 918 100 mg TID</u></b>		
102	Abnormal	Pre-existing diabetes; borderline low sural sensory nerve action potential c/w mild peripheral neuropathy
103	N	Tremor after starting drug
106	N	Tremor after starting drug
110	N	Leg cramps, diminished tactile sensitivity
111	N	No neurological symptoms
120	Abnormal	Pre-existing tremor; borderline low sural n. action potential
121	N	No neurological symptoms
126	N	No neurological symptoms
130	Abnormal	Tremor; pre-existing wrist deformity
133	N	Possible worsening of pre-existing tremor
136	N	No neurological symptoms
<b><u>CEREZYME</u></b>		
101	N	No neurological symptoms
107	N	No neurological symptoms
112	N	No neurological symptoms
113	N	Tremor after starting OGT 918 during extension phase
116	Abnormal	Tremor before starting Cerezyme; pre-existing diabetes; small bilateral sural nerve action potentials
117	Abnormal	No neurological symptoms; multiple myeloma on Mephegan; small sural sensory nerve potentials and chronic neuropathic changes on EMG consistent with

		n. action potentials and chronic neurogenic changes on EMG consistent with peripheral neuropathy
127	N	Tremor after starting OGT 918 during extension phase, resolved without dose reduction
132	N	No neurological symptoms
<b><u>OGT 918 100 mg TID plus CERZYME</u></b>		
104	Abnormal	Hand tremor, weakness in hands and legs; absent sural n. action potential on one side; may have been due to technical difficulties
105	N	Transient (1 day) tremor resolved without dose change
108	N	No neurological symptoms
109	Abnormal	Leg cramps; history of epilepsy; patient taking carbamazepine
114	N	No neurological symptoms (has B12 deficiency however)
123	Abnormal	No neurological symptoms; low sural sensory nerve action potential, slight slowing of nerve conduction
124	N	Tremor resolved within a month
125	Abnormal	Tremor; low sural sensory nerve action potential
131	N	No neurological symptoms
135	Abnormal	Transient leg/calf pain & hand/finger numbness; mild peripheral neuropathy

Summary of Abnormal Electrodiagnostic Results

**Electrodiagnostic Results Summarized**

Trial	No. pts. enrolled	No. pts. who got electrodiagnostic testing	No. pts. with abnormal electrodiagnostic results (% of those tested)
001 (100 mg OGT 918 x 12 mo.)*	28	15	7 (47)
003 (50 mg OGT 918 x 6 mo.)**	18	16	3 (19)
004 (all 3 subgroups)**	36	29	10 (34)
004 subgroup: OGT 100 mg tid	12	11	3 (27)
004 subgroup: Cerezyme	12	8	2 (25)
004 subgroup: OGT 100 mg tid plus Cerezyme	12	10	5 (50)

\*with option of 12-month extension

\*\* with option of 6-month extension

Pre-existing risk factors for neuropathy in the patients with abnormal electrodiagnostic results

As stated, there are no baseline, pre-treatment EDX results in any patients except for the 8 Cerezyme patients, 2 of whom had abnormal EDX results. The following table suggests some alternative or predisposing risk factors for neuropathy in some patients. (Note that some patients, like patients 201 and 101 (Trial 001) are listed several times in the table below because of multiple alternative causes.):

Alternative Causes for Abnormal Electrodiagnostics & Paresthesias	Trial Number & Patient ID
Severe weight loss, nutritional factors	Trial 001: 101,
B <sub>12</sub> Deficiency	Trial 001: 201, 404
Diabetes mellitus	Trial 004: 102, 116,
Monoclonal Gammopathy (IgA), cryoglobulinemia, etc.	Trial 001: 201, 101,
Other Drug (sotalol, etidronate, carbamazepine)	Trial 001: 101. Trial 004: 109
Connective Tissue Disease (vasculitis)	Trial 001: 201
Alcoholism suspected	Trial 001: 103
Multifactorial (i.e. combination of above factors in unknown proportions)	Trial 001: 101, 201

### Discussion of Alternative Causes & Sponsor's Consultant Report

\_\_\_\_\_ a neurologist consulted by the Sponsor, evaluated data from the 3 Gaucher trials discussed above (001, 003, and 004).<sup>23</sup> She described the facts of the trials, the patients' symptoms, and the EDX results as I have done above. She confusingly describes 8 patients as "controls," and seems to distinguish them from the Cerezyme (active control) group. I am unable to determine who these control patients are, however.

In performing her analysis, \_\_\_\_\_ looked at the Gaucher patients who had had electrodiagnostic testing during OGT 918 trials (001, 003, and 004) and eliminated those with alternative explanations such as diabetes, B<sub>12</sub> deficiency, monoclonal gammopathy, extreme weight loss, etc. and other conditions that could cause a peripheral neuropathy. In this manner, she concluded that the rate of electrodiagnostic abnormalities in the high dose (trials 001 and 004) groups was approximately the same as for her "control" group. She concedes that the high dose group (001) appears to have a higher rate of electrodiagnostic abnormalities than the low dose (003) group, and that the combination of Cerezyme and OGT 918 has a higher incidence of electrodiagnostic abnormalities than other groups.

### Conclusions

\_\_\_\_\_ Concluded, on p. 48 of her report:

<sup>23</sup> She also looked at the data from trial OGT 918-002 in Fabry disease. Fabry disease is another lysosomal storage disorder due to an degradative enzyme deficiency upstream from the one that causes Gaucher disease. The Fabry patients also experience tremor when exposed to OGT 918, and tremor is not normally a symptom of their disease. (Because tremor has been dealt with in another part of this consultative review, and because the Sponsor agrees that OGT 918 causes tremor, I will not discuss what \_\_\_\_\_ had to say about tremor here. Briefly, she agreed that OGT 918 appears to cause tremor in a reversible, dose-related manner. I will confine my discussion to her evaluation of the paresthesias, cramps, numbness, and especially the abnormal EDX data.)

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"Of control patients with Gaucher disease who had EDX studies done, 25% (two of eight subjects) had abnormal EDX studies consistent with peripheral neuropathy. Both patients had also been receiving Cerezyme, although one had not received Cerezyme for over a year preceding the EDX studies. This subject also had multiple myeloma and had been on chemotherapy, although this drug is not known to cause a peripheral neuropathy. The control patients were not taking Cerezyme, and had normal EDX studies...."

"In Summary, 25% of control patients with Gaucher disease who had EDX studies done had electrophysiologic evidence consistent with peripheral neuropathy. (These two patients had also been on Cerezyme therapy either currently or at some time in the past). This is in comparison to 29% of patients receiving OGT 918 alone who had EDX studies done, 25% receiving Cerezyme alone who had EDX studies done, and 50% of patients receiving OGT 918 in combination with Cerezyme who had EDX studies done...."

"If one excludes those patients with co-existent conditions that might cause a peripheral neuropathy, such as vitamin B12 deficiency or diabetes, the numbers then change. The control patients remain at 25%, those receiving OGT 918 alone are 21%, those receiving Cerezyme alone are 14%, and those receiving a combination of OGT 918 and Cerezyme who had EDX studies done are 44%, quite elevated in comparison to the control group, as well as the other groups...."

*"Based on this information, OGT 918, used alone does not appear to carry a significant risk for developing peripheral neuropathy, above the control population, based on EDX studies. However, there is a tendency for an increased incidence for abnormal EDX findings associated with peripheral neuropathy in patients starting at the higher dose of OGT 918, compared with those starting at the lower dose, although the incidence in those starting at the higher dose is comparable to the control patients, although it should be noted that the two control patients with abnormal EDX studies had received Cerezyme therapy. The combination of OGT 918 and Cerezyme appears to carry an elevated risk for peripheral neuropathy based on EDX criteria."* [italics in original]

### Sponsor's Neurological Summary (Feb 2002)

The Sponsor argues that "it would be premature to classify Zavesca [OGT 918] as definite cause of peripheral neuropathy."<sup>24</sup> In support of their view, the Sponsor cites a reference listing the criteria that should be met to establish a causal link between a potential neurotoxin and neuropathy.<sup>25</sup> The criteria include:

- a temporal relationship between drug and symptoms, which may include a latency of up to several months;
- subjective and objective (abnormal electrodiagnostic) manifestations;
- the possible existence of susceptibility factors "such as pre-existing neuropathy, simultaneous use of neurotoxic drugs, or metabolic dysfunction interfering with drug metabolism" that may increase the risk of developing a toxic neuropathy;
- and improvement (possibly after an initial worsening) following drug cessation.

<sup>24</sup> Neurological Safety Update, February 2002, p. 9.

<sup>25</sup> Id., p. 5.

Definite proof of causation is not required to raise safety concerns or require a warning label.<sup>26</sup> The 3<sup>rd</sup> bulleted criterion above emphasizes that risk factors for neuropathy may exist, implying that "causation" in this context includes drugs that may not be the exclusive cause, but also drugs that may *contribute* to the neuropathy in a susceptible person.

The real question is not whether there is sufficient proof that OGT 918 is the sole cause of these patients' neuropathic signs and symptoms; the question is whether, given the uncertainties of the data, there is reasonable evidence of an association. Sponsor assumes the former standard and attempts to argue why each patient has an alternative explanation for his or her neuropathic signs and symptoms.

Rather than argue each case and adopt the Sponsor's high standard of proof and exclusive causation, I will argue below that there is sufficient evidence of a neuropathic signal in these data for the Agency to describe the signs and symptoms of it in labeling (in a Precautions section) and to require further investigations. Before presenting those arguments, I would like to discuss 4 cases in detail and describe a plausible mechanism for OGT 918's effects on nerves: GSL depletion.

Five Cases Discussed in Detail: 101, 103, 105, 111, and 207

There were five patients with definite sensorimotor peripheral neuropathy that merit closer discussion, because the Sponsor and their expert have argued for excluding four of them from the safety analysis. They agree that the fifth one has a peripheral neuropathy that may be caused by OGT 918.

Patient 101 (of trial 001) had been taking OGT 918 in a dose of 100 mg tid for about a year when she began complaining of numbness in her soles, burning in her shins, and paresthesias in the fingers of both hands. She was taken off the drug. Several electrodiagnostic evaluations confirmed a chronic sensorimotor peripheral neuropathy. She also had either a left ulnar or a C8/T1 radiculopathy. Over the following year her hand symptoms improved, but her soles remained numb and dysesthetic. The electrodiagnostic testing remained abnormal about 5 months after the drug was stopped.

Sponsor and the consultant, \_\_\_\_\_ argue that OGT 918 cannot be said to have caused Patient 101's peripheral neuropathy because she had an underlying IgA monoclonal gammopathy, was taking etidronate and sotalolol, and had marked weight loss on the drug (she lost more than 25% of her weight at trial entry). The IgA gammopathy, however, had been present for 6 years, and there is no

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<sup>26</sup> "The label shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with the drug; a causal relationship need not have been proved." (italics added). 21 CFR 201.57(e)

documentation that she was malnourished or vitamin deficient as a result of her weight loss.

Patient 103 (of trial 001) had been taking OGT 918 only about a week when he began complaining of intermittent paresthesias of his hands and feet. These reportedly resolved before the drug was stopped. Four to six months after stopping the drug, he began complaining of burning feet. Electrodiagnostic testing performed 9 months after stopping the drug showed evidence of a mild chronic peripheral neuropathy. Sural nerve action potential were low bilaterally, with a prolonged latency on one side. He had stopped taking the drug after 12 months of exposure.

The electrodiagnostic results were interpreted as showing a mild generalized sensorimotor peripheral neuropathy. The main reason his case was excluded from consideration is the improvement in the paresthesias on drug and their return several months after the drug was stopped. The Sponsor states there "is a questionable history of excessive alcohol consumption..." but there is no documentation that vitamin levels were low or that nutrition was poor.

Patient 105 (of trial 001) was taking OGT 918, 100 tid, for about a year when he began to complain of numbness in his feet and hands. Electrodiagnostic testing done 3 months after the drug was stopped was consistent with a mild, generalized demyelinating sensory peripheral neuropathy. Sural nerve amplitudes were markedly reduced. When the testing was repeated about 1 year later, the sural sensory responses could not be detected. This finding was interpreted as showing progression of the neuropathy off of the drug, so Sponsor and the consultant eliminated him as a possible example of OGT 918-induced neuropathy.

Patient 111 (of trial 003) complained of paresthesias and had a peripheral neuropathy on electrodiagnostic testing. Her symptoms included sensations of tingling, "needle-like pains in sole of feet," "tingling in toes," and these began about 5-6 months after starting OGT 918. The local neurologist who did the electrodiagnostic testing found slightly prolonged sensory latencies and speculated she may have Charcot-Marie-Tooth. However, she had no history of a gait disorder, no family history of CMT, and no peroneal motor involvement (a key feature of CMT) at all. A repeat electrodiagnostic study done 2 months after she had stopped the drug showed the same results.

Patient 207 (trial 003) was initially asymptomatic. She took OGT 918 for 6 months in a dose of 50 mg TID. After 6 months, her dose was increased to 100 mg BID. She had electrodiagnostic testing 10 months after starting the drug (11/2000), and the results were normal. At month 9 her dose was increased to 150 mg BID. A few months later she began complaining of numbness in both hands and feet with muscle pain in both legs. The drug was stopped. Electrodiagnostic testing performed twice (5/01 and 8/01) after the drug was

stopped are consistent with a sensorimotor peripheral neuropathy. Sponsor concedes that, in this patient, OGT 918 is a "possible cause of her neuropathy."<sup>27</sup>

#### Toxicological Evidence that GSL depletion by OGT 918 may cause neuropathy

The neuropathy concerns and their relationship to GSL depletion has been discussed by Lachman and Platt, two investigators at Oxford University who have closely involved with the development of OGT 918.<sup>28</sup> The authors point out that a lack of one type of GSL (GM1 ganglioside) derived from glucosylceramide is associated with axonal degeneration and demyelination in both the central and the peripheral nervous systems in transgenic animals, and that antibodies to other GSLs are also associated with peripheral neuropathy. Certain GSLs are vital for cell-cell signaling between myelin-producing cells in the central and peripheral nervous systems and axons. The authors state, "It is therefore possible that the cases of peripheral neuropathy seen in patients treated with NB-DNJ [OGT 918] are directly related to glycolipid depletion in the nervous system..."<sup>29</sup>

In the clinical trials, no systematic attempt was made to measure the effect of OGT 918 on GSL synthesis except for in 7 patients who had their leukocyte GM1 (a ganglioside type of GSL) measured at baseline in trial 918-001. The decline in GSL apparently takes time to occur, because at month 6 the decline from baseline was not yet significant ( $p = 0.072$ ). By 12-months, however, the GSL levels had decreased about 39% ( $p = 0.006$ ).<sup>30</sup> This demonstrates that the drug can have a substantial impact on at least one GSL (and there is no reason not to believe that all glucosylceramide-derived GSLs would not have a similar decline, as OGT 918 affect the key, rate-limiting step in their biosynthesis.) The most clinically significant peripheral neuropathies<sup>31</sup> did not occur until patients had been treated for at least one year, a time course consistent with the observation that significant declines in GM1 GSL were not present at 6 months, but were documented at 1 year of treatment.

We did not review and were not provided preclinical data, but have been informed that chronic primate exposure in the preclinical studies included a 1-year monkey study in doses that were 4-6.5 times the human dose (in mg/kg). Neuropathological changes were documented in the brains of males; these included vascular mineralization and mineralization and necrosis of the white matter. There were no clinical signs of toxicity, however.<sup>32</sup>

<sup>27</sup> Neurological Safety Update, February 2002, p. 8

<sup>28</sup> Lachmann RH, Platt FM. Substrate reduction therapy for glycosphingolipid storage disorders. *Exp Opin Invest Drugs* 10:455-466, 2001.

<sup>29</sup> *Id.* p. 463.

<sup>30</sup> A. Pariser, MD, NDA review, "GM1 Analysis"

<sup>31</sup> e.g., patients 101, 103, 105, and 207

<sup>32</sup> A. Pariser, personal communication (and possibly misquoting her).

Our Interpretation of the Paresthesia, Numbness, and Abnormal EDX Results

Despite the small safety database and inadequate controls, we are struck by what seems to be a high incidence of paresthesias, numbness, and abnormal electrodiagnostic test results in this group of patients. The interpretation of asymptomatic electrodiagnostic testing results is difficult, and the incidence of abnormal electrodiagnostic test results in asymptomatic adults with Gaucher disease is unknown. Paresthesias and numbness are not listed among the manifestations of the disease, however, and there is no obvious direct mechanism by which the disease should cause a diffuse peripheral neuropathy. It is true that Gaucher patients may have a number of associated conditions or disease complications that may *secondarily* affect the nerves. These include a high rate of multiple myeloma and plasma cell dyscrasias, which may cause monoclonal gammopathies. These are known to cause peripheral neuropathy in some patients. Likewise, Gaucher patients may have diabetes, vertebral collapse with root compression, B12 deficiency, and other factors that may cause neuropathy. Without baseline or adequate control data, it is difficult to draw confident conclusions from this small safety database alone.

We disagree with Sponsor's post-hoc approach of eliminating patients from consideration because they supposedly had alternative causes for their neuropathic signs and/or symptoms. OGT 918 may have *contributed* to neuropathy in any or all of the affected patients; it need not have been the *exclusive* cause. In practice, Gaucher patients will likely have the same risk factors as the patients in the clinical trials had, and an evaluation of safety has to consider the features of the population that is likely to take the drug.

Even if we agreed that it makes sense to exclude some patients, both the Sponsor and their consultant, \_\_\_\_\_ were very liberal in excluding patients from the OGT 918 groups<sup>33</sup>, yet they strove to include the two patients with abnormal electrodiagnostic testing results in the so-called control group, even though one of them had multiple myeloma and was on chemotherapy. The other patient with abnormal results in the Cerezyme group had diabetes.

The Sponsor and \_\_\_\_\_ excluded patients 101, 103, and 105 (discussed above). Patient 101 may have been at risk for neuropathy because of her gammopathy, etc., but the question remains whether she would have developed the symptoms and signs without OGT 918. We believe OGT 918 probably contributed to her neuropathy, because her risk factors existed already when she was asymptomatic; she only became symptomatic when OGT 918 was added. "Causation" can mean "contributes to," and in this sense OGT 918 is a possible cause of neuropathy, even though the patient had pre-existing susceptibilities. Sponsor's own criteria for identifying a neurotoxin, cited above, allow for susceptibility factors, and exclusive causation is not required.

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<sup>33</sup> e.g., blaming the neuropathy on undocumented alcoholism, Tegretol, minor asymmetries in presentation, latent period after stopping the drug, etc

With respect to Patient 103, the Sponsor seeks to exclude him because his symptoms appeared after the drug was stopped. Sponsor's criteria for a neurotoxic drug, cited above, allow for a latent period, however. This latency is typical of the neuropathy associated with antineoplastic drugs, such as cisplatin.

We would also not have eliminated Patient 105, because he seemed to have a worsening in his electrodiagnostic test results off the drug. This may occur, for the reasons given in the last paragraph. Also, we find it unpersuasive that alcoholism is assumed to be the cause in this patient without documentation of malnutrition. Some authorities believe that well-nourished alcoholics do not develop peripheral neuropathy<sup>34</sup>, which is felt to be due to B vitamin deficiencies (e.g., beriberi). Absent documentation of malnutrition, we would not accept the facile explanation of alcoholism as the cause of this man's peripheral neuropathy.

We would not have ascribed Patient 111's peripheral neuropathy to Charcot-Marie-Tooth (CMT) because she had no history of a gait disorder, no motor involvement, no peroneal nerve motor abnormalities on electrodiagnostic testing, and no family history of CMT. After she had been on the drug for 6 months she started complaining of tingling and a needle-like sensation in her feet, similar to what other affected patients complained of. She is atypical in that her neuropathy was interpreted as demyelinating whereas the others were axonal.

Lastly, the Sponsor accepts that for Patient 207, who had no symptoms and a normal electrodiagnostic evaluation, only to be followed by symptoms and two results consistent with a sensorimotor peripheral neuropathy, OGT 918 is the most likely cause.

Rather than attempt statistical analysis with the paresthesia and electrophysiology data, it may be more reasonable to accept the fact that the data are confused to begin with, because there are no baseline electrophysiology results, the testing was not done in any standardized way, and not all patients were tested. Given that the data are poor, it does not improve the strength of inference to—post-hoc—try to guess who had some other reason for their neuropathic signs or symptoms.

A simpler approach is to accept the data's deficiencies, accept that Gaucher patients may have some risk factors for neuropathy, and recognize the obvious: a lot of patients complained of paresthesias and numbness, and many more had abnormal electrodiagnostic test results. This could be a signal of toxicity.

We also note the fact that OGT 918, by design, decreases GSL synthesis, yet GSLs are required for normal nerve function. Without documenting that the GSLs

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<sup>34</sup> "Our own observations support Strauss's contention that alcoholic polyneuropathy is essentially a nutritional disease." p1212, Adam's and Victor's Principles of Neurology, 7<sup>th</sup> ed., 2001.

levels were not critically reduced, it is difficult for sponsor to argue that OGT 918 does not adversely affect GSL levels.

### Conclusion with Respect to Neuropathic Symptoms (Paresthesias, Numbness, and Abnormal Electrodiagnostic Testing)

Although there were no baseline electrodiagnostic test results and a safety database that was too small, we believe there is sufficient basis to conclude there is a signal of neurotoxicity in these data. Our background level of concern was raised by what we were told of the preclinical neuropathology. Next, the mechanism whereby OGT 918 lowers GSLs, and the fact that two of the drug's developers have expressed concerns that excessive depletion of some GSLs may adversely affect nerves further raised concerns. Finally, we note there are 5 cases with similar symptoms and abnormal electrodiagnostic findings (Patients 101, 103, 105, 111, and 207). There are other cases with paresthesias or asymptomatic abnormal electrodiagnostic testing, but we believe these 5 cases represent cases with significant symptoms, supportive electrodiagnostics, and few convincing alternative explanations for their neuropathies besides OGT 918.

Patient 207 is especially troublesome, because she had no symptoms and initially had normal electrodiagnostic testing. Later she developed numbness and had two subsequent abnormal electrodiagnostic test results consistent with a peripheral sensorimotor neuropathy. Unlike the other 4 patients, Patient 207 appears to have been free of other risk factors or alternative explanations for her neuropathy.

We think it will not be productive to argue the merits of specific cases with the Sponsor. We would point out that proof of causation is not required for the Agency to warn of suspicious adverse events, that causation does not mean exclusive causation, and that, unless they seek to limit the use of the drug to only those patients with no risk factors for neuropathy, then doing it as a post-hoc justification to explain away a high rate of AEs is not justified.

### Questions

- 1) *Please evaluate the incidence of tremor and paresthesias in OGT 918 treated patients vs control group, and compared to baseline. Do these appear to be valid given the potential Investigator bias after tremor (in particular) was first noted in the 918-001 study, and the lack of a control group in 5/6 studies?*

#### **Reply:**

We believe the figures are "valid" in the sense that they reflect the true frequency of tremor and paresthesias at the time the evaluations were done. We would not interpret close scrutiny as bias. Since there are no data before treatment and the control (Cerezyme) group only had 8 patients, we cannot say what the frequency of these two AEs would be in a group of Gaucher patients not taking OGT 918.

The reported frequency for "essential" tremor, obtained by closely examining large groups of people irrespective of symptoms, is about 3%. Therefore the 29% figure for the treated Gaucher patients seems high compared to the general population. However, without pre-treatment data, we cannot say with confidence whether the 29% figure is elevated with respect to the population of Gaucher patients. Tremor is not listed as a symptom of Gaucher, but hypermetabolism is a feature, and that we speculate may cause tremor.

Similar comments can be made with regard to paresthesias. One patient in the control group complained of paresthesias (Table 52, Consult Request), but that group consisted of only 8 patients. We also do not know what the frequency of paresthesias is in an untreated group of Gaucher patients. They would seem to be at risk for paresthesias for the same reasons they are at risk for peripheral nerve disease (B12 deficiency, monoclonal gammopathies, nerve compression, etc.), but without adequate data on untreated patients, it requires speculation to say whether the reported frequency of paresthesias was higher with OGT 918 than it would be without it. Paresthesias are not listed as a feature of Gaucher disease in the standard references, however.

- 2) *Due to the unexpected finding of tremor and paresthesias, EMG and NCV were added to the safety monitoring as protocol amendments after the studies had been initiated. EMG/NCV were not obtained at baseline in any patient, nor were they performed in all exposed patients. In addition, the sponsor obtained a Neurology consult for interpretation of the EMG/NCV studies and neurologic Adverse Events after the trial was completed and the safety data was being evaluated. Please evaluate the EMG/NCV results and the Neurologist's conclusions.*

**Reply:** We agree with the Sponsor and with the expert, \_\_\_\_\_ that many cases of abnormal EMG/NCV results were confounded by alternative explanations. We also agree with your implication that the data are difficult to draw firm conclusions from because of the lack of knowledge about the incidence of abnormal EMG/NCV tests in Gaucher patients, the lack of baseline data in the patients, the small size of the safety database, and the incomplete and inconsistent manner in which the data were obtained.

We are also uncertain what to make of abnormal electrodiagnostic test results in the absence of any symptoms. The most common finding was diminished sural nerve action potentials (SNAPs), which can be an early sign of axonal neuropathy, but can also be seen in older individuals. The planned study of 14 patients with Gaucher disease is going to include baseline, pre-treatment EMG/NCV. These data may provide a better sense of what the frequency of abnormal electrodiagnostic test results is in Gaucher, but the small size of the group and lack of a control arm will still hamper our ability to make confident conclusions.

We disagree with the Sponsor and \_\_\_\_\_ that the EMG/NCV testing can be argued away in most cases. First, there is the problem of the large number of abnormal results, most of which represented one diagnosis: peripheral sensorimotor neuropathy. Secondly, there is the problem of finding an alternative explanation for the result in every patient. While some of their alternative explanations seem

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reasonable (e.g., monoclonal gammopathy, vasculitis, B12 deficiency), others are less convincing (e.g., Tegretol, undocumented alcoholism without malnutrition, etc.). Thirdly there is the fact that a significant number of patients complained of paresthesias or numbness, which are typical symptoms of peripheral neuropathy. Lastly, there is the possible mechanistic argument that OGT 918 might lower GSLs critical for normal nerve function.

We disagree with Sponsor's apparent position that OGT 918 must be shown to be the *exclusive* cause for it to be implicated as a "cause," because the word also means "contributes to." Many Gaucher disease patients are at risk for peripheral neuropathy because of reasons provided above, but *it seems reasonable to us, given the large number of abnormal test results, that OGT 918 might have contributed to the abnormal EMG/NCV results in this vulnerable population.* We derive no reassurance from the frequency of 25% abnormal (2 of 8) EMG/NCV in the control group (i.e., Cerezyme only in trial 004). One of the 2 abnormal had multiple myeloma, a known cause of monoclonal gammopathy, and the other patient also could arguably have been excluded as having alternative causes (eg. entrapment neuropathies, diabetes). Regardless, the group is too small to draw any secure conclusions from by itself.

The strongest arguments supporting a neurotoxic signal come from 5 cases that were discussed (101, 103, 105, 111, and 207), the preclinical data, and the mechanism by which OGT 918 depletes GSLs. We have discussed the 5 cases above because they developed paresthesias or numbness on OGT 918 and had abnormal electrodiagnostic studies consistent with peripheral neuropathy. We stated the reasons we did not think the alternative explanations for these patients' signs and symptoms argued by the Sponsor are persuasive. We were not provided preclinical data except what was summarized above, but that data suggests OGT 918 may be neurotoxic. Lastly, two developers of OGT 918, Lachman and Platt, have themselves expressed concern about the cases of peripheral neuropathy in the trials and have speculated that the mechanism may be GSL depletion. When measured in 7 trial participants, one GSL (GM1 ganglioside) was significantly decreased after one year of treatment, and a deficiency in this GSL (as Lachman and Platt point out) causes axonal neuropathy in an animal model.

- 3) *There are no reports of tremor or paresthesias in the Ceredase or Cerezyme (enzyme replacement therapy for Gaucher disease) clinical trials or in the Ceredase/Cerezyme labeling, and this Reviewer was unable to find references to tremors or paresthesias in type 1 (non-neuropathic) Gaucher disease in the medical literature. Please evaluate for the association of tremor and paresthesias with the underlying disease.*

Reply: We have alluded to these points in the answers to questions 2 and 3. The major problem in trying to interpret the tremor, paresthesias, and abnormal electrodiagnostic testing is the small safety database and small (8 patient) control group. We agree that these events (tremor, paresthesia, numbness—and we would add abnormal EMG/NCV) are not reported to be typical manifestations of Gaucher disease in the standard reference works. Hypermetabolism may occur, however, and that may manifest as tremor. Regardless, the Sponsor agrees that the evidence of causation with respect to tremor is clear.

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With respect to the other symptoms and signs of neuropathy, we believe these Gaucher patients had documented risk factors such as monoclonal gammopathies, diabetes, and B12 deficiency. We do not know what the rate of abnormal EMG/NCV is in an untreated group of Gaucher patients. A study of a large group of untreated Gaucher patients is needed to determine what the background frequency of neuropathy is in that population.

- 4) *Please evaluate for the association of tremor and paresthesia with contributing factors seen in these studies, including: diarrhea, weight loss, concomitant medication use, and, in some patients, other contributing illnesses such as diabetes, vitamin deficiencies, and gammopathies (noted by the Neurology Consultant as likely causes of the paresthesias in several patients).*

**Reply:** We agree that each of these factors might have contributed to an individual's risk for developing neuropathy, but cannot say how much. We disagree with the Sponsor and the Consultant about the meaning of "causation" in the context of a deciding whether a drug may be a neurotoxin. We also do not agree with their approach of post-hoc exclusion of individual patients who had risk factors or alternative causes for neuropathy. We believe that a drug can be considered neurotoxic if it *contributes* to a neuropathy; it need not be the *sole, exclusive* cause. This drug will be used in patients with Gaucher disease, many of whom have risk factors for neuropathy, all of whom will have diarrhea, many of whom will have significant weight loss, and some of whom may have nutritional deficiencies.

It is not an appropriate analysis of AEs to--after the fact--try to find some alternate reason why the patients developed symptoms or abnormal EMG/NCVs unrelated to the drug. Would they have developed these signs and symptoms without the drug? We doubt it, but cannot prove our suspicion for the same reason the Sponsor cannot prove theirs. The regulations do not require proof for safety labeling however; and, unlike the standards for efficacy, we only need to have evidence of a reasonable likelihood. There is a reasonable likelihood, that, notwithstanding the presence of risk factors in the Gaucher population, that OGT 918 may cause or contribute to the appearance of neuropathic signs and symptoms.

- 5) *Is there a subgroup of patients that can be identified that appears to be at particular risk, or is at lower risk, of neurologic complications during treatment with OGT 918?*

Except for tremor, we cannot state with confidence whether or not OGT 918 caused neurological complications because the safety database is too small, the control group was not adequate, and there was no pre-treatment baseline data. Subgroup analysis is therefore not possible, and we do not believe we can answer this question.

- 6) *Please make recommendations for:*

- *Adequacy of safety testing and validity of results*
- *Monitoring of patients receiving OGT 918, and recommendations for future evaluation and monitoring, 1*
- *Wording and precautions that should appear in OGT 918 labeling, specifically for neurologic findings.*

**Reply:** Before exposing a patient to OGT 918, we recommend a thorough, well-documented neurological examination by a neurologist. It should include careful documentation of the history and examination findings of tremor, paresthesias, numbness, and pain. The exam should include careful sensory testing, including vibratory sense, pain & temperature, and epicritic sensation, especially in the distal upper and lower extremities. If there are abnormalities found on examination, their underlying cause should be discovered. In selected patients this may require EMG/NCV, sural nerve biopsy, B12 and other vitamin levels, rheumatic serologies, serum electrophoresis, ESR, blood chemistry, LFTs, thyroid function, evaluation for diabetes, Schilling test, and imaging (for nerve/root compression due to vertebral collapse).

We recommend that the neurological examination and history document whether patients have tremor and any personal or family history of one. Tremor should be characterized by body part affected, approximate frequency of the oscillations, approximate amplitude (e.g., fine, coarse, gross), whether they are rhythmic or not, whether they are present at rest, in a static posture, or on attempted intentional movements; their diurnal fluctuations, if any; and their severity with respect to their impact on activities of daily living (e.g., writing, voice quality), and whether they disturb the patient or not (e.g., cause embarrassment). Thyroid function testing should be done in those with tremor.

Patients who developed tremor in the clinical trials experienced a resolution of the tremor when OGT 918 was stopped. Further observation will be needed to see if longer exposures to OGT 918 are also associated with a tremor that stops after drug withdrawal.

If further studies support the possibility that OGT 918 contributes to signs and symptoms of neuropathy in Gaucher patients, we speculate that a possible mechanism might be an induced deficiency in a GSL needed for nerve function or an excess amount of ceramide. If subsequent studies confirm that there is, in fact, a causal link between OGT 918 and neuropathy, and if the Sponsor can link the problem to GSL depletion or ceramide toxicity, then monitoring those substances might allow early recognition of a problem. But until there is greater confidence that OGT 918 is actually causing a problem and until there is evidence that it is due to GSL levels or ceramide, we cannot recommend routine monitoring of these substances.

OGT 918 crosses the blood-brain barrier and may inhibit synthesis of GSLs vital for normal brain development. OGT 918 has been shown to lower GM gangliosides, which are important for brain development and function. We would not recommend exposing children to OGT 918, without further evidence that lowering GSLs in the developing brain will not cause more harm than the underlying disease.

**Labeling:** With respect to the proposed labeling for tremor, we are generally satisfied with the existing language. ("...tremor or exacerbation of existing tremor [

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1   page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

### Tremor in General<sup>35</sup>

Tremor is the commonest of the involuntary movements. It is defined as a rhythmic, repetitive movement of a body segment due to alternating contraction of opposing muscle groups. In diagnosing the cause of tremor, it is helpful to describe the pattern, frequency, and provoking factors, because all of these elements are helpful in localizing the part of the nervous system that is involved.

Tremors are usefully categorized as 1) tremor-at-rest; 2) static (postural) tremor; and 3) kinetic (action or intention) tremor. Tremor-at-rest or with the part fully supported is usually a moderate amplitude, 5-6/sec tremor that may be most obvious in the hands. Parkinson disease presents a good example of this.

Static tremor is produced when the part is held in a posture, such as when the arms are extended. It may be proximal or distal, and the former is associated with cerebellar and brainstem lesions while the latter is more likely seen with midbrain lesions. The latter is also probably the most common tremor, and is seen in both case of "benign essential tremor" (probably a genetic trait), but also in toxic disorders, such as in alcoholism and in thyrotoxicosis. The amplitude is small and the frequency of the tremor is rapid at about 10/sec. The tremor may be confined to the hands, but can affect the voice (vocal tremor) and head. In severe cases, handwriting can be affected, and in this sense it is "benign" only insofar as it is not caused by a progressive, degenerative disease; it can impact a person's life in ways that are not benign. The tremor caused by drugs, such as valproic acid (Depokote), is of the static type. It is dose related, reversible with stopping the drug, and the occurrence and severity of the tremor varies among individuals.

The last type of tremor is the kinetic type, which is more commonly called "intention" tremor or "action" tremor. When the affected patient attempts to perform a task, such as the finger-nose test, the oscillations become ever larger as the target is approached. This is the hallmark of cerebellar disease.

Since this consultation deals with neuropathies, the association of tremor and neuropathy should be mentioned. This movement, like the one described in the last paragraph, is probably more of an ataxia than a tremor, because the movements are not rhythmic. The distinction may be difficult to make in practice, however, and patients who have preserved motor function with lost proprioceptive feedback may have jerky, flinging movements—a clumsiness that appears to be superimposed upon a tremor.<sup>36</sup>

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<sup>35</sup> Yahr, MB. Involuntary Movements, in Scientific Foundations of Neurology, M. Critchley, JL O'Leary, and B Jennett, eds. Heinemann, London, 1972, p. 83-88.

<sup>36</sup> Diseases of the Peripheral Nerves (Ch. 46, p. 1376), in Principles of Neurology, 7<sup>th</sup> ed., M. Victor and AH Ropper, McGraw-Hill, 2001.

## Appendix II

### Peripheral Neuropathy, Paresthesias, and EDX Testing in General

Peripheral neuropathies are a large group of diseases affecting a number of peripheral nerves that are caused by non-mechanical factors in a widespread, more-or-less symmetrical way. Usually they are slowly progressive and develop over weeks, months, or years. Clinical symptoms usually begin symmetrically and distally, beginning in the lower extremities in a stocking pattern, especially with a loss of vibratory sense distally or a loss of epicritic (fine discrimination) at the fingertips. Motor loss is less frequent, less disturbing, appears late in the course of the disease, tends to also be symmetric, and also begins first in the lower extremities, especially the feet dorsiflexors. Absent ankle tendon jerks are an essential early clue, followed by loss of knee jerks, then loss of upper extremity tendon reflexes. Trophic changes are normally seen, and these include muscle atrophy, diminished sweating, dry, smooth skin, and trophic ulcers.

One would think, given what appears to be the anatomical simplicity of peripheral nerve, that the diagnosis of peripheral neuropathies would also be correspondingly simple. Paradoxically, the disorders of peripheral nerve, their diagnosis, and treatment constitute a large and complex specialty, and much more is unknown about peripheral neuropathy than is known. The number of potential causes numbers easily in the hundreds, and in one series 24% of patients, despite extensive evaluations by recognized authorities, could not be diagnosed.<sup>37</sup>

The symptoms of peripheral nerve disease may include varying degrees of impaired motor function, impaired tendon reflexes, sensory loss, paresthesias, pain, dysesthesias, autonomic dysfunction, and sometimes other manifestations. Most peripheral neuropathies affect both motor and sensory functions, but one may be affected far more than the other. In toxic and metabolic neuropathies, the sensory symptoms usually exceed any weakness, and there may in some sensory neuropathies be no motor deficit at all.

The usually approach to the differential diagnosis of peripheral nerve disease is to classify the patients condition into where in the peripheral nerve the lesion is and the time course. For example, the causes of single nerve (mononeuropathy) or several individual nerves (mononeuropathy multiplex) will differ from the causes of a plexopathy as will the causes of a polyneuropathy. If one is dealing with a polyneuropathy (bilaterally symmetrical distal, usually feet greater than hands), then the time course becomes important. Acute and subacute onset polyneuropathies have a different differential diagnosis than chronic ones. Furthermore, those that are predominantly sensory have a different differential than those that are mainly motor.

Because the patients that in the OGT 918 trial complained of pain, paresthesias, numbness, and on EDX testing had, most commonly, abnormalities "consistent with a sensorimotor peripheral neuropathy," and because the time course was unknown, I provided a tabular listing for subacute and chronic causes of sensorimotor polyneuropathy. (A few patients had entrapment mononeuropathies (e.g. carpal tunnel), plexopathies (C8 root compression), one had possible inherited neuropathy (Charcot-Marie-Tooth, HMSN type I or II); and others may have had complications of diabetes which can cause mononeuritis multiplex). Although beriberi is listed, it should not be assumed that it is rare or necessarily associated with a diet of milled-rice, edema, and a cardiomyopathy. The condition refers to the deficiency of certain B vitamins and is more common than is generally recognized, even in the developed world.

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<sup>37</sup> Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. *Ann Neurol* 10:222, 1981.

Memorandum by Neurology Team Leader, John Feeney, MD

**NDA 21-348 Zavesca (miglustat)**

**FROM:** John Feeney, M.D.  
Neurology Team Leader

**SUBJECT:** Consult from DMEDP dated February 21, 2002

**DATE:** May 10, 2002

Dr. Tremblay has provided a detailed review for this consultation. I have tried to briefly summarize what I believe are the important points below. Please refer to his review for a detailed discussion of the issues.

We have been asked to comment on the occurrence of tremor and peripheral neuropathy during the clinical development of Zavesca (miglustat) for the treatment of Type I Gaucher Disease. Type I Gaucher Disease is an autosomal recessive disorder characterized by the accumulation of so-called foamy macrophages in numerous body organs to include bone marrow, liver, and spleen. As a result patients develop pathologic fractures, various degrees of abdominal distention, hypersplenism, thrombocytopenia, and anemia. The disorder is due to a deficiency of the enzyme glucocerebrosidase and the accumulation of glucocerebroside in cells. Type I Gaucher Disease is not characterized by central nervous system involvement, while Type II and III Gaucher disease are. The estimated prevalence for all types of Gaucher Disease in the U.S. is 20,000.

Peripheral nervous system disorders (not only peripheral neuropathy) occur in Type I Gaucher Disease, secondary to identifiable intermediary disorders. For instance, lymphocyte clones are sometimes stimulated to produce immunoglobulins in Gaucher Disease and monoclonal gammopathies can result. Monoclonal gammopathies have been associated with peripheral neuropathy. During Zavesca development, B12 deficiency was not unusual and the sponsor has submitted references suggesting a higher incidence of B12 deficiency in Gaucher Disease populations. Neuropathy can be associated with B12 deficiency. Local compression neuropathies and radiculopathies can result from pathologic fractures. I do not know the frequency of these intermediary disorders in Type I Gaucher Disease and I do not know the frequency of peripheral nerve disorders amongst the intermediary disorders. We are certainly not aware of any prospective studies in Gaucher Disease that incorporated electrophysiologic screening tests (nerve conduction studies or NCVs and electromyographic studies or EMGs).

To our knowledge, the occurrence of tremor is not increased in patients with Gaucher Disease. New onset tremor can suggest hyperthyroidism. Hyperthyroidism is not reported with increased frequency in Gaucher Disease. We are not aware if thyroid function studies were performed during trials with Zavesca. If they were not, they should be investigated in future patients with new onset tremor.

Enzyme replacement therapy and bone marrow transplantation are the currently available treatments for Type I Gaucher Disease. Zavesca inhibits the rate-limiting enzyme in the synthetic chain resulting in decreased formation of glucocerebroside (and all glycosphingolipids derived from glucocerebroside).

We do not have a complete summary of the preclinical pharm/tox. However, vascular mineralization and mineralization and necrosis of the white matter were apparently observed in

## Zavesca

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chronic 1-year monkey studies at doses that were 4-6.5 x the proposed human dose (in mg/kg). No associated clinical signs were observed and there may not have been a dose-response for this finding. Axonal degeneration and demyelination in both the central and peripheral nervous systems were observed in transgenic animal models that were deficient in some of the same downstream metabolic products of glucocerebroside that Zavesca will deplete.

In the first trial in Gaucher Disease, Study 001, tremor and paresthesia were both noted so that increased monitoring for these particular disorders was instituted during continuing development.

The only randomized, controlled experience with Zavesca comes from Study 004 in which patients were randomized to Zavesca, 100mg tid, enzyme replacement therapy, or the combination of the two. Treatment was open-label and continued for 6 month. There were only 12 patients per group.

Comparing the Zavesca alone group to ERT alone, tremor occurred in a third of the Zavesca patients and none of the ERT patients. Paresthesia occurred in no Zavesca patients and 1 (8%) ERT patient.

Study 001 and the extension allowed for 24 months of open-label treatment with Zavesca at 100mg tid. A total of 28 patients enrolled and 14 completed the full 2 years. During the first year, tremor occurred in 14% of patients; paresthesia occurred in 11 % of patients.

Study 003 and the extension allowed for 12 months of open-label treatment with Zavesca at 50mg tid. A total of 18 patients enrolled and 13 patients completed the full year. In the first 6 months, tremor occurred in 39 % of patients; paresthesia occurred in none of the patients.

The entire safety database consists of 80 patients with Gaucher disease. There are roughly another 200 patients treated in an HIV development project. Another 20 patients were treated with Fabry's Disease.

Apparently, access to the data on HIV studies is limited so, at this time, we do not know about the occurrence of tremor or paresthesias in those studies. One HIV study randomized 60 patients to placebo and 60 patients to active drug, so that experience could be very illuminating.

Because of heightened concerns about neuropathy, NCVs and EMGs were performed in a subset of the Gaucher patients. Eight of the "control" patients from the 004 study had this testing; 2/8 (25%) had evidence of a peripheral neuropathy by NCVs. Against this background, almost 50% of patients had abnormal electrodiagnostic testing in the 001 study. Given the small numbers of patients studied, *this difference may not be significant.*

In his review, Dr. Tremblay discusses 5 Zavesca-treated patients in some detail. These are patients 101, 103, 105, 111, and 207. The experience of these patients suggests a picture of a drug-induced or drug-aggravated peripheral neuropathy.

### Conclusions/Recommendations

Tremor is a common occurrence with Zavesca in Gaucher Disease. It occurred with higher frequency in Study 003 at 50mg tid than in Study 001 at 100mg tid, but the trials were so small that the estimates from any given trial cannot be very precise. Heightened awareness and reporting in the later trial may also be a factor in this apparent reverse dose-dependence. For labeling purposes, the sponsor's description of the tremor (in italics) on page 14 of Dr. Tremblay's review would be excellent with the modifications proposed by Dr. Tremblay.

There were clearly some cases of peripheral neuropathy that developed during the Gaucher trials. For some, the existence of diabetes, B12 deficiency, and monoclonal gammopathy suggest that the neuropathy may not be drug related. For some, the time course of the

Zavesca

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symptoms and the lack of other concomitant illness or concomitant drug associated with neuropathy, suggest drug relatedness. The clinical course of the 5 patients highlighted by Dr. Tremblay best characterizes the experience to date; this can be summarized in labeling. The overall small size of the safety database (n=80) and the limited controlled data make it impossible to determine the true frequency of peripheral neuropathy with Zavesca.

The mechanism of action of this drug must raise the level of concern about its safety, as discussed by Dr. Tremblay. Because of this, we believe a re-evaluation of the preclinical pharm/tox should be undertaken to better delineate the presence or absence of histological changes in the central and peripheral nervous system. If tissue is still available from those studies, special staining techniques may be helpful. If histological changes are present, further discussions about the safety of Zavesca and appropriate clinical monitoring will be necessary.

Histological changes would raise concerns both for Gaucher patients without and with prior central nervous system dysfunction. Prior to considering \_\_\_\_\_ we would strongly encourage preclinical developmental studies, careful review of a much larger adult safety database, and institution of careful monitoring of both central and peripheral nervous system function.

In his review, Dr. Tremblay has carefully outlined the biochemistry of glycosphingolipids (GSLs) and their importance in nervous system development and function. He is especially concerned that Zavesca will inhibit the formation of many of these different GSLs with unknown ramifications for both adult and \_\_\_\_\_ patients. Given a safety database of 80 patients, we have not excluded other potential adverse events, frequent or infrequent, with any certainty. Pertinent to this point, we have recently been made aware of a Zavesca-treated patient who seems to have developed a dementing process. While B12 deficiency may have confounded this case, it still raises concern and merits careful follow-up.

For further investigation, consideration should be given to measuring GSLs and ceramide levels from all patients exposed (including former patients if possible) and correlating these levels with adverse events of concern. Dr. Tremblay has outlined the need for baseline and follow-up neurologic exams to include electrodiagnostic studies in ongoing studies. It is also my understanding that the sponsor has begun screening for cognitive problems, using the MMSE. The MMSE is an insensitive measure for early cognitive changes and should be supplemented with a more sensitive neuropsych battery. Several commercial neuropsych batteries have been developed for the purpose of screening for mild cognitive deficits during drug development. Rather than recommend any one battery, we would recommend that the sponsor consult with experts in the field before choosing a more sensitive test battery.

The HIV database should be investigated for controlled-trial experience with adverse events to include tremor, paresthesias, and memory problems.

We will be happy to discuss this application and any further development of Zavesca with you.

Gerald Tremblay, MD  
Neurology Medical Officer, HFD-120

John Feeney, MD  
Neurology Team Leader, HFD-120

Russell Katz, MD  
Division Director, Division of Neuropharmacological Drug Products, HFD-120

cc: HFD-120



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This is a representation of an electronic record that was signed electronically and  
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/s/

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Gerald Tremblay  
5/13/02 02:49:13 PM  
MEDICAL OFFICER

John Feeney  
5/13/02 02:53:53 PM  
MEDICAL OFFICER  
Concur...my memo is attached as an appendix.

Russell Katz  
5/13/02 04:57:54 PM  
MEDICAL OFFICER