CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

ADMINISTRATIVE DOCUMENTS

Item 13 PATENT INFORMATION

Patent Information as required by 21 CFR § 314.53				
Patent No.	Expiration Date	Type of Patent	Patent Owner	OGS' US Agent
5,472,969	13-May-2013	Method of use	Monsanto Company*	Mr Bruce R Manning President New England Biomedical Research, Inc. 96 West Main Street PO Box 809 Northborough, MA 01532
5,525,616	11-Jun-2013	Method of use	Monsanto Company*	Mr Bruce R Manning President New England Biomedical Research, Inc. 96 West Main Street PO Box 809 Northborough, MA 01532
*Licensed exclusively to Oxford GlycoSciences (UK) Ltd; assignment not yet recorded				

In accordance with 21 CFR § 314.53, the undersigned hereby declares that U.S. Patent Nos. 5,472,969 and 5,525,616 cover the method of use of ZAVESCA™, the subject of this application for which approval is being sought under section 505 of the Federal Food, Drug and Cosmetic Act.

Furthermore, in accordance with 21 CFR § 314.52, the undersigned further declares that it does not infringe any of the above-listed patents, as said patents are exclusively licensed from the owner(s).

17th May 2002

John Ilett
Oxford GlycoSciences (UK) Ltd, General Counsel and Company Secretary

Bruce R. Manning

Bruce Manning
President, New England Biomedical Research, Inc.
US Resident Agent for OGS

EXCLUSIVITY SUMMARY for NDA # 21-348 SUPPL #

Trade Name Zavesca Generic Name miglustat

Applicant Name Actelion Pharmaceuticals US, Inc HFD-510

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/XXX/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /XXX/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /XXX/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /**XXX**/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /**XXX**/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /**XXX**/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /**XXX**/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /**XXX**/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement

or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct

of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
8/4/03 03:20:42 PM
for Dr. Orloff

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-348 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: March 28, 2001 Action Date: July 31, 2003

HFD 510 Trade and generic names/dosage form: Zavesca (miglustat) 100 mg Tablets

Applicant: Actelion Pharmaceuticals US, Inc Therapeutic Class:

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):_____

Indication #1: treatment of adult patients with mild to moderate type I Gaucher disease for whom enzyme replacement therapy is not an option due to constraints such as allergy, hypersensitivity or poor venous access

Is there a full waiver for this indication (check one)?

XX Yes: Please proceed to Section A.

☐ No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
XX There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

udies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see achment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Patricia Madara
8/4/03 12:55:26 PM

Medical Team Leader Memo

NDA #:	21-348
Drug:	Zavesca (miglustat)
Sponsor:	Actelion (NDA formerly owned by Oxford Glycosciences, Ltd.)
Date of Submission:	February 7, 2003
Indication:	Treatment of Type 1 Gaucer Disease

BACKGROUND

Type 1 Gaucher disease is a lysosomal storage disease caused by a deficiency in the enzyme, β-glucocerebrosidase (β-glucosidase), which results in impaired hydrolysis of glucosylceramide, an intermediate substrate in the degradation pathway of glycosphingolipids (GSL). The accumulation of glucosylceramide in the macrophages found in the spleen, liver, and bone marrow results in the clinical findings of organomegaly, cytopenias, and bone disease. The clinical presentation is variable with mild forms going undiagnosed until late adulthood to the severe forms presenting in childhood with massive hepatosplenomegaly, anemia, thrombocytopenia and in some cases, fractures or painful "bone crises". Type 1 Gaucher disease is generally recognized as a non-neuronopathic disease, distinguishing itself from Types 2 and 3 Gaucher disease. In 1991, the placentally-derived, macrophage-directed form of the glucocerebrosidase enzyme was approved (Ceredase®) which demonstrated significant reductions in organ volume size and improvements in anemia and thrombocytopenia. The recombinant form of this enzyme was approved in 1994 (Cerezyme®). Enzyme replacement therapy (ERT), although a momentous scientific achievement that revolutionized the management of this disease and paved the way for therapies of other inborn errors of metabolism (e.g., Fabry's disease and α-mucopolysaccharidosis), is not readily available to all patients due to economic reasons and requirements of administration (dosed every 2 weeks as an infusion in a specialized center). In addition, approximately 15% of patients treated develop IgG antibodies to Cerezyme. Half of these patients may develop hypersensitivity reactions which may be managed with anti-histamines and steroids pre-dosing and a reduction in infusion rate. Anaphylaxis-like reactions have been reported in < 1% of the patient population.

Zavesca (miglustat) is an inhibitor of glucosylceramide synthase, an enzyme that mediates the initial reaction in a series of steps involved in the production of GSLs. In August 2001, Oxford Glycosciences (previous holder of NDA 21-348) submitted an NDA to use Zavesca in the treatment of Type 1 Gaucher disease. Unlike ERT, Zavesca does not replace the deficient enzyme activity. Rather, this drug reduces the amount of glycosphingolipid substrate delivered to and processed by β-glucocerebrosidase, allowing residual enzyme activity to function effectively in the breakdown of GSLs. This mechanism is referred to as substrate-depletion therapy.

The sponsor submitted data from 3 clinical trials in the original NDA: 2 uncontrolled, monotherapy studies and 1 active-controlled study. The efficacy and safety results of these 3 studies were examined in Dr. Pariser's primary review dated May 2, 2002. All patients in these 3 studies were adults (18 years or older). Two studies were conducted in treatment-naïve patients or in patients who had discontinued ERT for at least 6 months prior to study enrollment. One study evaluated the effects of Zavesca added to

stable ERT (minimum 2 years duration) or switching from stable ERT to Zavesca therapy. Table 1 summarizes these studies.

Table 1. Studies Conducted in Support of NDA 21-348

Study No.	N	Treatment and Duration*	Extension	N	Treatment and Duration
918-001	28	OGT 918 100 mg tid x 12 mos	918-001X	18	OGT 918 100 mg tid x 12 mos
918-003	18	OGT 918 50 mg tid x 6 mos	918-003X	16	OGT 50 mg tid x 6 mos
918-004	12	OGT 918 x 6 mos	918-004X	10	OGT 918 → OGT 918 x 6 mos
	12	Cerezyme x 6 mos		10	Cerezyme → OGT 918 x 6 mos
	12	OGT 918 + Cerezyme x 6 mos		9	OGT 918 + Cerezyme → OGT 918 x 6 mos

The review of the original NDA showed reductions in liver and spleen volume and marginal improvements in hematological parameters in primarily treatment-naïve patients receiving Zavesca as monotherapy. In this same application, it was determined that the addition of Zavesca to patients whose disease was adequately controlled with ERT or the switching from ERT to Zavesca resulted in clinical deterioration of the hematologic indices.

The clinical efficacy was offset by poor tolerability secondary to diarrhea, weight loss, other gastrointestinal complaints and safety findings involving the nervous system including tremors, paresthesias, abnormal electrodiagnostic studies, and one case of memory loss. The tremors appeared self-limited or responsive to dose-reduction or drug cessation. Inadequate study designs, sample size, and safety assessments (no baseline neurologic evaluations) precluded any conclusion that peripheral neuropathy and paresthesias were unrelated to drug. Furthermore, the pharmacologic action of Zavesca on inhibiting GSLs, which are essential for normal nerve cell function, supported a plausible explanation for direct drug toxicity. As a result, the Agency issued a non-approval (NA) letter on June 20, 2002.

CLINICAL RESPONSES TO NON-APPROVAL LETTER

In response to the NA letter, the sponsor met with the Division in September 2002 to discuss a resubmission plan. The sponsor had proposed a more narrow indication for Zavesca. This indication would target only those adult Type 1 Gaucher patients who cannot take ERT for medical reasons. Furthermore, Zavesca would be available to patients through a limited distribution plan that would ensure physician awareness of the drug label and the indicated patient population. The resubmission would be comprised of primarily labeling changes, although efficacy and safety data from extension periods of previously reviewed clinical trials and new, ongoing studies would also be submitted.

Efficacy Update

Data from patients initially enrolled in the open-label, monotherapy study of Zavesca initiated at 100 mg tid (Protocol 918-001) provided additional efficacy data in a limited number of patients beyond 24 months of therapy. Of the 28 patients in the original cohort, a substantial percentage discontinued therapy due to side-effects of therapy, adverse events, and personal reasons. Only 14 patients received therapy beyond 91 weeks and 7 beyond 156 weeks (see Table 1 in Dr. Pariser's review of resubmission).

The following table summarizes the mean % change in organ volume size from baseline during the different periods of observation.

Table 2 Efficacy of Zavesca on Organ Volume at Months 12, 24, and 36 in Evaluable Patient Population (adapted from Tables 2 and 3 of Dr. Pariser's review)

	Liver Volume		Spleen Volume	
	n	Mean	n	Mean
Baseline sample size and organ volume size	27	2.381 L	20	1.658 L
Month 12 sample size and % chg from baseline	21	-12.11%*	10	-18.98%*
Month 24 sample size and % chg from baseline	12	-14.46%*	10	-26.4%*
Month 36 sample size and % chg from baseline	12	-17.51%*	10	-29.64%*

*all changes were statistically significant from baseline defined as Month 0 ($p<0.001$)

Dr. Pariser's review points out that a LOCF analysis, which included data from discontinued patients, did not reveal much difference in organ volume change between the Month 24 and 36 timepoints. The analysis of the evaluable patient population, however, suggests that for those patients who can tolerate therapy and continue on treatment, there is a persistence of effect on organ volume reduction.

The following table summarizes the changes in hematologic parameters obtained at different periods of observations.

Table 3. Efficacy of Zavesca on Hb and Plts at Months 12, 24, and 36 in Evaluable Patient Population (adapted from Tables 4 and 6 of Dr. Pariser's review)

	Hemoglobin		Platelets	
	N	Mean	N	Mean
Baseline sample size and hematologic measure	28	12.8 g/dL	28	88.1 x 10^9/L
Month 12 sample size and % chg from baseline	22	+2.6%	22	+16%
Month 24 sample size and % chg from baseline	13	+9.05%*	13	+26.1%*
Month 36 sample size and % chg from baseline	13	+9.23%*	13	+34.3%*

*$p<0.001$; change from baseline Month 0

Similar to the analyses of organ volume reduction, a persistence of drug effect on Hb and Plt levels was observed in those patients tolerating and continuing therapy out to 36 months.

Safety Update

From the initial safety review of this application, AEs affecting the Gastrointestinal body system predominated with diarrhea reported by 90% of the 80 subjects exposed to drug followed by flatulence and abdominal pain in approximately 45% of the cohort. These side-effects appear to be related to the disachharidase inhibitory effect of the drug in the gut resulting in an osmotic diarrhea. Although viewed primarily as a tolerability and compliance issue, weight loss was observed in 65% of patients and valid concerns on growth and development in the ——— patient population were raised by Dr. Pariser in her reviews. Of greater concern and less well-defined, were the findings of tremor, paresthesias, and neuropathy. The tremors appeared reversible with drug discontinuation.

In this resubmission the sponsor provided additional safety data from the extension period of Study 918-001. Drop-outs and discontinuations were substantial in this cohort of 28 patients. The number of patients available for safety assessment by time interval is summarized in Table 4 (see section B1 of Dr. Pariser's review of causes of discontinuation/drop-out).

Table 4. Study 001 Patient Disposition

Time Interval (Mos)	0-6	>6-12	>12-18	>18-24	>24-30	>30-36	>36-42	>42-48	>48-52
N	28	23	20	15	14	14	14	3	3

No deaths were reported and only one additional patient had an SAE reported that appeared unrelated to study drug (post-procedural wound infection in a patients s/p hip replacement). No meaningful conclusions can be derived from the Study 001 safety update given the significant number of study discontinuations.

In addition to the extension study, the sponsor submitted additional data asserting that peripheral neurologic symptoms are manifestations of type 1 Gaucher disease that have previously gone unrecognized. These data were derived from the following sources:

1. ——— Type 1 Gaucher Neurological Symptom Survey
2. ——— Type 1 Gaucher Natural History Study: Baseline Data
3. Compiled Electrodiagnostic Study (EDX) Results from Treated and "Control" Patients
4. Interim Data from Study 005
5. Follow-up Data Information on Tremor

The results from each of these data sources have been reviewed by Dr. Pariser. These studies were uncontrolled (Studies ——— and 005) or controlled but non-randomized (compiled EDX study). In two of the studies ———, a reported background incidence of peripheral neuropathy in Type 1 Gaucher patients was based on information garnered from questionnaires and surveys. These methods of data ascertainment have the potential to introduce recall bias as signs and symptoms of peripheral neuropathy are collected retrospectively. Overall, one cannot exclude the possibility that neurologic findings observed in the clinical trials are caused or exacerbated by Zavesca therapy based on these additional safety databases.

Conclusions on Efficacy and Safety

Zavesca therapy reduces liver and spleen volume in adult type 1 Gaucher patients who are either treatment-naïve or have not received ERT in the past 6 months. Zavesca therapy also resulted in increases in Hb concentration and Plt counts but significant changes from baseline were observed later than the organ volume reductions. Patient tolerability was poor and substantial drop-outs were seen in the open-label extension phases of the clinical studies. For those patients who could continue therapy beyond 24 months, the effect of Zavesca on volume size and hematologic parameters were sustained.

Enzyme replacement therapy remains the standard of care for patients requiring treatment for Type 1 Gaucher disease. From the original review of this application, the addition of Zavesca to ERT or switching from ERT to Zavesca in patients with adequately managed disease appears to worsen the hematologic indices while providing only marginal reductions in liver volume.

The sponsor has postulated that peripheral neuropathy is a manifestation of Type 1 Gaucher disease; however, the data submitted are inadequate to make any definitive conclusions on this finding. Despite the outstanding safety concerns observed with Zavesca therapy, the clinical findings of paresthesias and neuropathy appear monitorable. The proposal to market Zavesca therapy for only a limited patient population who cannot take ERT for medical reasons in addition to labeling and limited drug distribution will enable appropriate management of the benefits to risks of using this drug.

[redacted]

Labeling Changes

The sponsor proposes to use Zavesca (miglustat) for the following indication:

[redacted]

The Division is recommending the following indication:

"ZAVESCA® is indicated for the treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a

therapeutic option (e.g. due to constraints such as allergy, hypersensitivity, or poor venous access)."

Other substantial changes have been made by the different disciplines reviewing this application. These changes are currently under negotiation with the sponsor and final accepted language will be documented in the label attached with the approval letter.

A Patient Package Insert (PPI) has also been reviewed by the Division of Drug Marketing, Advertisement, and Communication (DDMAC) and the final approved version will be attached with the approval letter.

OTHER REVIEW ISSUES

The June 20, 2002 NA letter also included deficiencies in Chemistry, Manufacturing, and Controls and comments from Pharmacology/toxicology and Clinical Pharmacology. These issues have been addressed by the sponsor in this resubmission and are reviewed separately by the appropriate FDA disciplines.

RECOMMENDATION

Pending final labeling negotiations, this application should be approved.

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/s/

Mary Parks
7/14/03 01:30:57 PM
MEDICAL OFFICER

David Orloff
7/21/03 03:49:47 PM
MEDICAL OFFICER
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3/16/02

MEDICAL TEAM LEADER'S MEMO ON NEW DRUG APPLICATION

NDA #: 21-348
Sponsor: Oxford Glycosciences (UK) Ltd.
Drug Name: OGT 918 (Zavesca)
Indication: Type I Gaucher Disease

Date of Submission: August 16, 2001
Primary Medical Officer: Anne R. Pariser, MD
Statistical Reviewer: Lee Pian, PhD

EXECUTIVE SUMMARY

Gaucher disease is a lysosomal storage disease where a deficiency of the enzyme, β-glucocerebrosidase, results in the buildup of glucosylceramide within the lysosomes of reticuloendothelial cells in multiple organs and tissues. There are 3 variants of this disease with Type 1, the nonneuronopathic variant, being the most common. Type 1 Gaucher disease has an estimated birth frequency of 1 in 60,000 to 1 in 360,000 and an even higher frequency (1 in 1200 live births) among Ashkenazi Jews. The clinical manifestations are protean but are a consequence of infiltration into organs and tissues by large macrophages (Gaucher cells) whose lysosomes are filled with glucosylceramide. Patients often present with hepatosplenomegaly, cytopenias, and osteopathic lesions.

Currently approved therapies for Type I Gaucher disease include enzyme replacement with either the placentally-derived form of glucocerebrosidase (Ceredase®) or the recombinant enzyme, Cerezyme®. These treatments are administered intravenously approximately every 2 weeks and clinical studies have shown significant improvements in organomegaly, anemia, and thrombocytopenia.

OGT 918 is a synthetic analogue of D-glucose which competitively and reversibly inhibits glucosylceramide synthase, the enzyme which mediates the transfer of glucose to ceramide to form glucosylceramide. This is the initial reaction in a series of steps involved in the production of glycosphingolipids (GSL). The rationale for its use in Gaucher disease is to reduce the amount of substrate delivered to the deficient glucocererosidase enzyme thereby allowing sufficient degradation of glucosylceramide by any residual activity of this enzyme. The site of action for OGT 918 and a brief overview of GSL production and breakdown are illustrated in the following schematics from Dr. Pariser's review:

Figure 1. Site of Action of OGT 918 (from Anne Pariser, MD FDA Medical Review of 21-348)

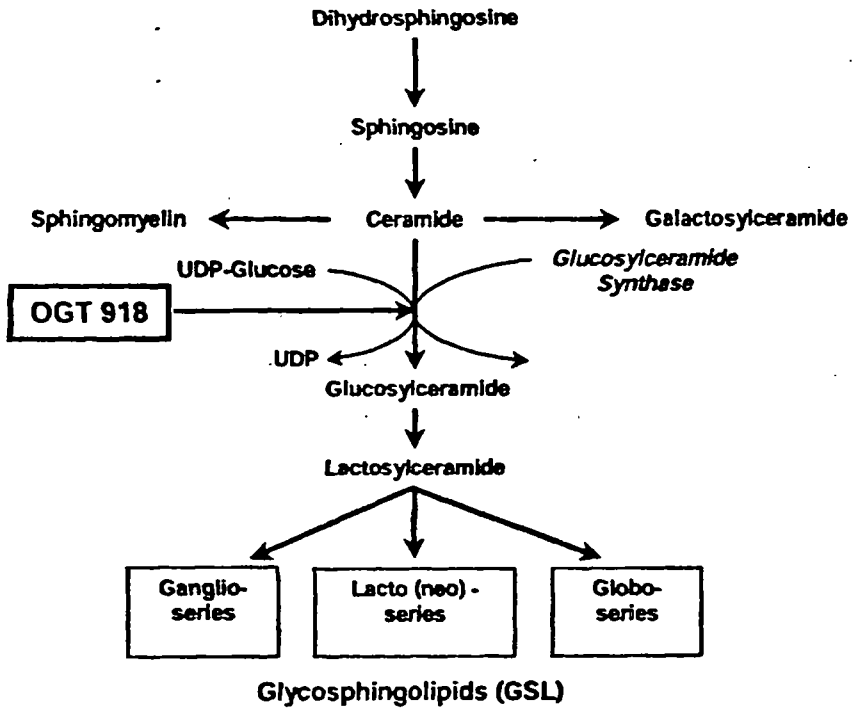
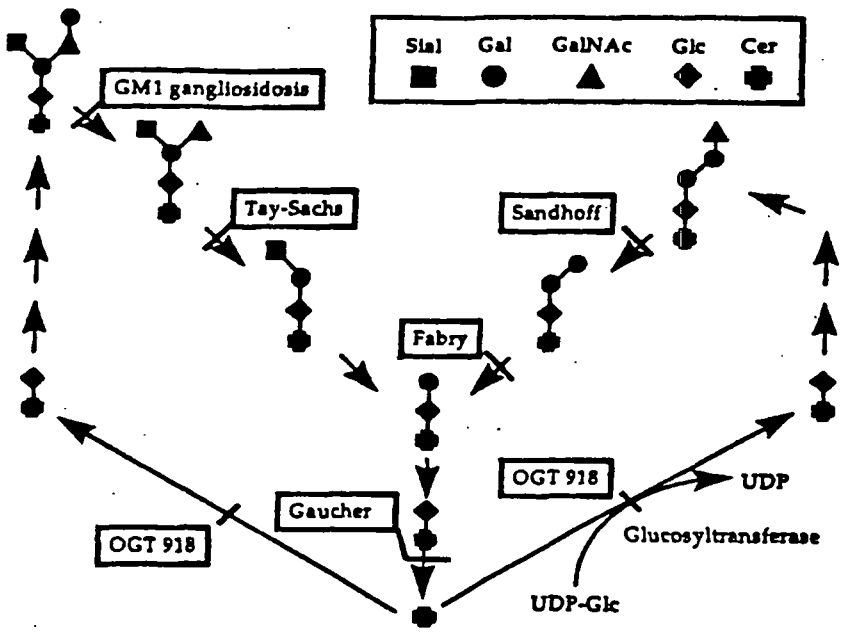


Figure 2. Glycolipid Biosynthetic and Catabolic Pathway (from Anne Pariser, MD FDA Medical Review of NDA 21-348)



The clinical development program for OGT 918 in Type I Gaucher disease included evaluation of its use as monotherapy in treatment-naïve patients or patients who had discontinued ERT for at least 3 months and its combined use with Cerezyme in patients who had stable disease with at least 2 years ERT. The efficacy endpoints of interest for this condition are reduction in organ volume and improvements in anemia and thrombocytopenia. Improvements of osteolytic lesions and reductions in risks of skeletal fractures are also clinically relevant endpoints but studies evaluating these measures require much longer periods of observation and were not comprehensively evaluated in this development program. No pediatric patients with Type 1 Gaucher disease have been studied with OGT 918.

Given the low prevalence of this disease, the studies in this NDA enrolled small numbers of patients and two of the three studies had no concurrent controls. Although such designs are typical for studies of rare disorders, they may also preclude definitive conclusions on the drug's effect on efficacy and safety. Such is the case with the studies submitted to this NDA.

OGT 918 therapy in treatment-naïve or patients off ERT for ≥ 3 months was associated with reductions in liver and spleen volume in 2 uncontrolled studies evaluating doses of 100 mg tid and 50 mg tid. These effects were evident after 6 months of therapy and further reduction in organ size continued out to 12 months. In one study which collected data beyond 12 months, the effects of OGT 918 at a dose of 100 mg tid persisted but no further reductions were obtained. The mean percent decrease in liver volume was -14.5% and -6.2% at the end of study for the 100 mg tid and 50 mg tid groups, respectively. The mean percent decrease in spleen volume was –26.4% and –10.1% at the end of study in the two respective treatment groups. No significant changes were observed in Hb and Plts in these studies except after 18 months of therapy with the 100 mg tid dosed group. Even then, these changes are clinically minor with a mean actual increase in Hb of 0.91 g/dL and 13.6 x 10^9/L increase in platelets. The changes in organ volume likely represent true responses to treatment; however, the changes in hematologic parameters may be confounded by variabilities in disease course or fluctuations in laboratory values not related to treatment.

OGT 918 therapy added on to stable treatment with Cerezyme (combination therapy) and switching from stable Cerezyme therapy to OGT 918 therapy was not associated with any significant changes in organ volume when compared to baseline. A between treatment comparison reveals a statistically significant decrease in liver volume with combination therapy versus Cerezyme therapy; however, these apparent positive results were not accompanied by improvements in anemia and thromybocytopenia. Conversely, there was a worsening in hematologic parameters when patients were switched from Cerezyme to OGT 918 therapy. Patients switched from Cerezyme to OGT 918 had a mean reduction of up to -3.1% in Hb levels and -9.6% in Plts counts. These findings do not support a benefit in switching to or adding on OGT 918 in patients whose disease is stable on Cerezyme therapy.

Complicating the risk-benefit profile of OGT 918 in Type 1 Gaucher disease were the unexpected findings of tremors, paresthesias/neuropathy, and memory loss. Tremors occurred in 29% of the patients and appeared while on treatment or were exacerbated with treatment. However, this AE often resolved while therapy continued or resolved with treatment discontinuation. Paresthesias and neuropathy were reported in 8% and 10% of the cohort, respectively. Electrodiagnostic (EDX) tests were added to the safety

monitoring which revealed abnormal results in 19 of 60 (32%) patients who underwent evaluation but establishing a causal role of drug was hindered by the absence of baseline tests, co-existing medical conditions which may be associated with similar neurologic signs and symptoms, and the absence of a control group. Recently the sponsor has submitted AEs of memory loss in 5 patients with the findings in one patient prompting the Institutional Review Board (IRB) overseeing the Israel study site to halt drug administration until the neurotoxicity AEs are further evaluated.

Although the safety signals from these studies are confounded by numerous factors, preclinical studies have demonstrated neurotoxicity in several animals although at higher exposures than those at the therapeutic doses proposed in humans. Vascular mineralization of the brain and spinal cord as well as necrosis and mineralization of the white matter in rats and monkeys have been observed at approximately 4-times the therapeutic dose. Ataxia and loss of reflexes without histopathologic findings have also been observed in dogs exposed to more than 50-times the therapeutic dose.

Overall, this application is approvable based on the results of the clinical studies demonstrating a marginal clinical benefit that does not outweigh the potential for neurotoxicity associated with OGT 918 therapy. OGT 918 was associated with a clinical benefit only with regard to liver and spleen volume reduction but had no benefit with regard to anemia and thrombocytopenia. This reduction in organomegaly was only evident in the uncontrolled studies (Studies 918-001, 003, and their extensions) of patients who were treatment-naïve or had discontinued Cerezyme for ≥ 3 months. The results from the controlled study (Study 918-004/004x) with Cerezyme do not support the replacement of Cerezyme therapy with OGT therapy in patients who have demonstrated adequate control with the former agent. The hematologic profile in each treatment group worsened with the initiation of OGT 918 monotherapy. The addition of OGT 918 to stable Cerezyme therapy resulted in a greater liver size reduction compared to Cerezyme monotherapy; however, a similar finding was not observed for spleen size. Further complicating these conflicting efficacy results, are the findings of tremors, parethesias/neuropathy, and memory loss which highlight concerns for drug-related neurotoxicity. These concerns are borne out in preclinical pharmacology/toxicology findings as well as the pharmacologic action of the drug which inhibits the production of glycosphingolipids, an essential component of eukaryotic cell function and structural integrity.

In order to address the deficiencies of this application, the sponsor needs to prospectively conduct a clinical trial that demonstrates improvements in bone marrow involvement as observed by increases in hemoglobin and platelets in addition to improvements in organomegaly. These benefits should not be outweighed by signs of neurotoxicity. Evaluation of neurotoxicity requires a prospectively designed study with monitoring for neuropathy and memory loss established at baseline and throughout the study.

CLINICAL STUDIES SUBMITTED

The sponsor conducted 3 clinical trials which all continued into extension phases of 6 to 12 months duration. All the studies were open-labeled and uncontrolled except for the first 6 months of one study which had active controls with Cerezyme alone or a combination of Cerezyme and OGT 918. These 3 studies are summarized in the following table:

Table 1. Studies Conducted in Support of NDA 21-348

Study No.	N	Treatment and Duration*	Extension	N	Treatment and Duration
918-001	28	OGT 918 100 mg tid x 12 mos	918-001X	18	OGT 918 100 mg tid x 12 mos
918-003	18	OGT 918 50 mg tid x 6 mos	918-003X	16	OGT 50 mg tid x 6 mos
918-004	12	OGT 918 x 6 mos	918-004X	10	OGT 918 → OGT 918 x 6 mos
	12	Cerezyme x 6 mos		10	Cerezyme → OGT 918 x 6 mos
	12	OGT 918 + Cerezyme x 6 mos		9	OGT 918 + Cerezyme → OGT 918 x 6 mos

*patients were randomized to OGT 918 at the protocol-specified doses but titration in dose was allowed depending on patient tolerability and response to therapy

All patients in these 3 studies were adults (18 yrs or older) with Type I Gaucher disease. The first two studies (918-001/001x and 918-003/003x) were conducted in patients who were, for the most part, treatment-naïve. Patients treated with ERT in the past had to be off therapy for at least 3 months prior to study enrollment. In Study 918-004/004x, patients had been treated with ERT for at least 2 years prior to enrollment. In the treatment-naïve studies, the patients tended to have larger baseline organ (liver and spleen) volumes and lower hematologic indices (Hb and Plts) compared to the patients who had been treated with ERT for a minimum of 2 years. These differences are summarized in Dr. Pariser's review (Table 1, page 18).

In addition, safety data from HIV and Fabry's disease trials were summarized by Dr. Pariser in her review.

EFFICACY RESULTS

Uncontrolled Studies 918-001/001X and 918-003/003X

The primary efficacy variables for Studies 918-001/001x and 918-003/003x were percentage change from baseline in liver and spleen organ volume and the actual change from baseline in hemoglobin and platelets. In both these studies, mean and median percent reductions in liver and spleen organ sizes were achieved at the end of the first period and were maintained or continued in the extension period. The following tables summarize these results:

Table 2. Changes in Liver Organ Size in Studies 918-001 and 003

	Liver Volume			
	Actual vol (L) chg	Mean % chg (SD)	95% CI	Median % chg
Study 918-001/001x				
Month 12	-0.28	-12.1% (9.4)	-16.4, -7.8	-12.6%
Month 24	-0.36	-14.5% (7.6)	-19.3, -9.6	-13.3%
Study 918-003/003x				
Month 6	-0.14	-5.9% (7.8)	-9.9, -1.9	-6.7%
Month 12	-0.17	-6.2% (9.6)	-12.0, -0.5	-4.1%

Table 3. Changes in Spleen Organ Size in Studies 918-001 and 003

	Spleen Volume			
	Actual vol (L) chg	Mean % chg (SD)	95% CI	Median % chg
Study 918-001/001x				
Month 12	-0.32	-19.0% (9.5)	-23.7, -14.3	-19%
Month 24	-0.42	-26.4% (5.5)	-30.4, -22.4	-26.3%
Study 918-003/003x				

Month 6	-0.09	-4.5% (5.6)	-8.2, -0.7	-4.8%
Month 12	-0.23	-10.1% (13)	-20.1, -0.1	-11.1%

From the above two tables, the 100 mg tid dosing (Study 918-001/001x) appears to achieve greater mean and median changes from baseline in liver and spleen organ size than the 50 mg tid dosing regimen.

The effects of OGT 918 on hemoglobin and platelets were also evaluated in these studies and are summarized in Tables 4 and 5 below.

Table 4. Changes in Hb in Studies 918-001and 003

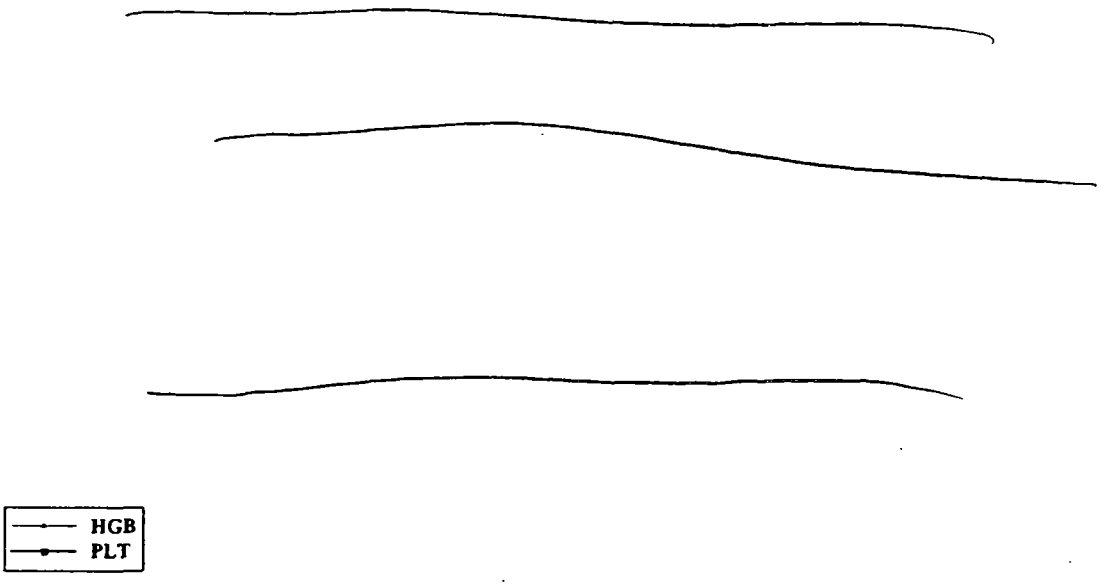
	Hemoglobin Changes				
	Mean Hb, g/dL (SD)	Mean Actual Chg, g/dL	Mean % Chg (SD)	95% CI	Median % Chg
Study 918-001/001x					
Baseline	12.0 (1.8)	–	–	–	–
Month 12	12.2 (1.6)	+0.26	+2.6% (6.9)	-0.5, 5.7	+1.3%
Month 24	12.4 (1.4)	+0.91	+9.0% (10.2)	+2.9, +15.2	+10.1%
Study 918-003/003x					
Baseline	11.6 (1.6)	–	–	–	–
Month 6	11.5 (1.8)	-0.13	-1.3% (6.0)	-0.5, +0.2	-3.9%
Month 12	11.8 (1.5)	+0.06	+1.2% (10.6)	-5.2, +7.7	+0.9%

Table 5. Changes in Plts in Studies 918-001 and 003

	Platelet Changes				
	Mean Plts, 10^9/L (SD)	Mean Actual Chg, 10^9/L	Mean % Chg (SD)	95% CI	Median % Chg
Study 918-001/001x					
Baseline	77.4 (48.3)	–	–	–	–
Month 12	35.0 (50.4)	+7.6	+16.0% (38.0)	-0.8, 32.8	+7.5%
Month 24	90.6 (54.1)		+26.1% (18.9)	+14.6, +37.5	+30.8%
Study 918-003/003x					
Baseline	116.5 (104.1)	–	–	–	–
Month 6	121.8 (113.4)	+5.35	+2.0% (17.2)	-6.3, +17.0	+4.8%
Month 12	127 (115.9)	+14.0	+14.7% (26.5)	-1.4, +30.7	+8.7%

As in the changes in organ volume size, the changes in the hematologic profile appear more responsive to the 100 mg tid dosing than to 50 mg tid dosing. Increases in Hb and Plts were not statistically significantly changed except in the 100 mg tid treatment group and this was only after 18 months of therapy and continued until Month 24 (data shown in Table 5 and 6). The changes in Hb and Plts from Study 918-001X do not appear clinically relevant as illustrated in the following figure obtained from Lee Pian, PhD, FDA statistical reviewer:

Figure 3. Hemoglobin and Platelet Changes by Patient in Study 918-001X (from Lee Pian, PhD FDA Statistical Review of NDA 21-348)



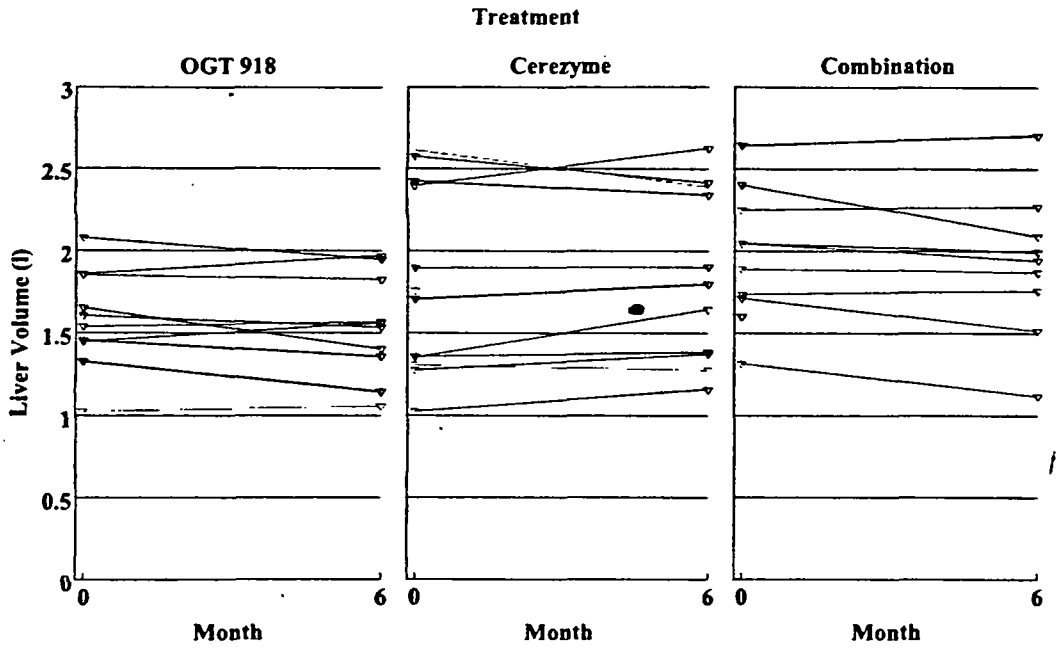
Indeed, this illustration suggests that the majority of patients treated with OGT 918 had flat responses over the course of treatment with the overall mean likely affected by a few apparent responders.

Controlled Study 918-004

The primary objective of this study was to evaluate the tolerability of combined OGT 918 and Cerezyme therapy to the individual constituents. A protocol amendment submitted in February 2000 later added the percentage change in liver volume from baseline at 6 months as a primary efficacy endpoint. Although this trial also included an extension phase of 6 months' duration, all but 2 patients were switched to treatment with OGT 918. Hence, the results of 918-004X (6-month extension period) reflect only treatment with OGT 918 and the changes in efficacy after receiving Cerezyme monotherapy or Cerezyme/OGT 918 combined therapy.

Compared to baseline, liver volume changes were not significant in any treatment group. However, between group analyses reveal a statistically significant reduction in liver volume between the Cerezyme/OGT 918 combination group versus the Cerezyme group alone (-8.45%; p=0.031). The actual changes in liver volume are displayed in the following figure from Dr. Pian's review:

Figure 4. Liver volume by patient and treatment group in Study 918-004



Although the difference in the mean percent change between combination therapy and Cerezyme favors Cerezyme/OGT 918, this figure illustrates an overall similar range of liver volumes for these treatment groups. Concerns were raised during this review that the radiologists reading the CTs and MRIs to assess organ size were not blinded. This would include blinding not only to treatment group but also to time sequence of the films being read. The absence of such blinding may introduce an observer (reader) bias which may affect the efficacy outcome. During a teleconference, the sponsor reassured the FDA that the radiologists did not have access to the initial films during the post-baseline readings. Treatment assignments were not revealed to the radiologists but this does not exclude the possibility of patients revealing their treatment regimen during the evaluation.

There were no significant changes in spleen volume from baseline at 6 months in any treatment group and between treatment groups. Similarly, there were no significant changes from baseline in Hb or Plts at 6 months in any treatment group or between treatment groups. The mean % change in treatment groups is summarized in Table 6.

Table 6. Changes in Hb and Plts by Treatment Group in Study 918-004

	OGT 918 N=10	Cerezyme N=12	Combination N=11
Hemoglobin			
Baseline mean value (g/dL)	12.44	13.18	12.38
6 mo mean value (g/dL)	12.13	13.01	12.29
Mean % Chg	-2.4%	-1.2%	-0.5%
p-value	0.101	0.198	0.815
Platelets			
Baseline mean value ($x10^9$/L)	170.55	165.75	152.14
6 mo mean value ($x10^9$/L)	148.95	181.04	154.86
Mean % Chg	-9.6%	+10.1%	+3.2%
p-value	0.073	0.59	0.577

Although none of these changes were statistically significant it is interesting to note that switching from stable therapy with Cerezyme to OGT 918 resulted in a reduction in platelets counts compared to those who continued with Cerezyme either alone or in combination. This observation is particularly impressive in the extension period where all patients are switched to OGT 918 therapy.

Table 7. Change in Platelets during Extension period of Study 918-004X

	OGT 918 N=10	Cerezyme N=12	Combination N=11
Platelets			
Mean % Chg from Baseline	-10.4%	-3.2%	-8.3%

For patients who had been receiving Cerezyme during the controlled period as either monotherapy or combination therapy, switching to OGT 918 monotherapy during the extension period resulted in a reduction in platelet counts. Dr. Pariser's review points out that this decrease in platelet count is particularly evident in the subgroup of patients with Plts $\geq 150 \times 10^9$/L; however, the small sample sizes preclude any definitive conclusion on this observation.

Table 8: 918-004X Mean Change Platelet Count by Baseline Value (<150 $X10^9$/L vs ≥150 $X10^9$/L)

Change from Baseline	Plt <150 $X10^9$/L			Plt ≥150 $X10^9$/L		
	n =	Mean (10^9/L)	p-value	n =	Mean ($X10^9$/L)	p-value
Month 6						
OGT 918	5	-0.10	.979	5	-43.10	.093
Cerezyme	4	8.13	.490	6	24.75	.116
Combination	5	-5.20	.493	4	26.13	.222
Month 12						
OGT 918	4	1.25	.880	5	-50.30	.032
Cerezyme	4	-3.75	.410	6	-3.75	.712
Combination	5	-11.10	.180	4	-13.63	.434

Other Efficacy Measures

Biochemical markers for Gaucher disease were evaluated in both studies. These included chitotrisadase and hexosaminidase levels. In the treatment-naïve patient (uncontrolled studies) population, OGT 918 therapy appears to be associated with reductions in these markers. Interestingly, these same markers increased in the controlled study when patients were switched from stable therapy with Cerezyme to OGT 918. This finding is suggestive of a detrimental effect in switching from stable ERT to OGT 918 treatment and appears to correlate with the worsening hematologic profile after patients are switched to OGT 918.

Table 9 : Chitotriosidase and Hexosaminidase Changes, Studies 918-004 and 918-004X (from Anne Pariser, MD FDA Medical Review)

	Chitotriosidase	Hexosaminidase
	Mean % Change	
Month 6		
OGT 918	+33.0	+17.8
Cerezyme	-0.3	+5.0
Combination	-3.9	+5.5
Month 12**		
OGT 918→OGT 918	+84.5	+42.1
Cerezyme→OGT 918	+11.7	+13.0
Combination→OGT 918	+28.6	+31.1

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

The skeletal assessments, quality of life assessments, and bone marrow fat fraction were not consistently obtained at all study sites thereby limiting any conclusions made of OGT 918 on these efficacy measures.

SAFETY RESULTS

A total of 82 patients were enrolled in the 3 trials with all but 2 patients receiving OGT 918. The most common adverse events reported in the combined safety data set occurred in the gastrointestinal system with diarrhea and weight loss being reported in 90% and 65% of the patients, respectively. Similar findings were also reported in the clinical trials involving HIV+ patients where doses up to 5 g tid were evaluated. In the active-control study, all the patients randomized to OGT 918 and 83% of those receiving combination therapy reported diarrhea. In contrast, only 25% of the Cerezyme reported this AE. This incidence increased to 80% when the Cerezyme-treated patients switched to OGT 918 therapy in the extension period. In all the studies, these symptoms decreased over time, coinciding with an increase in use of anti-diarrheals.

Safety findings of potential neurotoxicity were reported in all 3 Gaucher clinical trials and consisted of: tremors; neuropathy and paresthesias; and memory loss. These 3 findings are reviewed separately in this memo. The findings of electrodiagnostic and nerve conduction velocity studies will also be discussed under this section.

Tremors

In the combined safety data set, tremor was reported in 29% (23/80) of the patients receiving OGT 918 with 3 (4%) patients discontinuing therapy as a result of this AE.

This was an unexpected finding and initially reported in the first study conducted, 918-001. As a result there were protocol amendments adding EMG/NCV assessments either during or after drug treatment; no baseline evaluations were conducted. The following table summarizes the incidence of tremors across all the studies. It is possible that the rising incidence is a result of greater vigilance for detecting this AE.

Table 10. Reports of Tremor in Combined Safety Dataset

Study	Dose of OGT	Incidence of Tremor n (%)
918-001 (n=28)	100 mg tid	4 (14%)
918-003 (n=18)	50 mg tid	8 (44%)
918-004		12 (33%)
OGT 918 alone (n=12) → OGT 918 alone (n=10)	100 mg tid	5 (42%)
Cerezyme alone (n=12) → OGT 918 alone (n=10)		3 (25%)
Combination tx (n=12)→ OGT 918 alone (n=9)	100 mg tid	4 (33%)

None of the patients in the Cerezyme-only group of Study 918-004 developed tremors until they were switched to OGT 918 treatment during the extension period (918-004x). According to Dr. Pariser's review, tremors occurred within the first month of treatment and resolved between Month 1 and 3 with resolution occurring in 13 patients while still on therapy. Tremor usually resolved within days of discontinuing therapy in 8 patients.

Paresthesias/Neuropathy

Paresthesias were reported in 6 (8%) and neuropathy was reported in 8 (10%) of the 80 patients exposed to OGT 918. The breakdown of neuropathy reports by study is summarized below:

Table 11. Reports of Neuropathy in Combined Safety Dataset

Study	Dose of OGT	Incidence of neuropathy
918-001 (n=28)	100 mg tid	4 (14%)
918-003 (n=18)	50 mg tid	2 (11%)
918-004		2 (6%)
OGT 918 alone (n=12) → OGT 918 alone (n=10)	100 mg tid	1 (8%)
Cerezyme alone (n=12) → OGT 918 alone (n=10)		0
Combination tx (n=12)→ OGT 918 alone (n=9)	100 mg tid	1 (8%)

Only 60/82 (73%) of the cohort underwent EDX testing during the study; none of these patients had a baseline evaluation. Of these 60, 19 (32%) were reported to have an abnormal result. The data were confounded in certain individuals by the presence of diabetes, vitamin B12 deficiency, or other conditions which may present with peripheral neuropathy. The individual results of these tests were reviewed by the primary medical reviewer and 5 cases were identified as definite sensorimotor peripheral neuropathy. Even in these 5 cases summarized in Table 141 of Dr. Pariser's review, there are confounders with one patient having a history of IgA hypergammaglobinemia and reports of the neurologic signs and symptoms resolving while on therapy.

Memory Loss

These adverse events were only recently submitted to the NDA. One patient in Study 918-001 (Patient 411) is a 67-year [redacted] who

[redacted] He was treated with OGT 918 for 3 years and discontinued treatment approximately 7 months ago. Two years ago, coincident with an episode of tinnitus and vertigo, the patient complained of memory loss which was attributed to this acute illness. The tinnitus recurred in September of that year and the patient complained of memory loss again 9 months ago. Memory testing on 10/18/01 revealed above-average memory recall. A repeat memory test on 4/22/02 reveals 'memory and executive dysfunction with early language problems and mild idiomotor apraxia', possibly early Alzheimer's but drug toxicity could not be ruled-out. This patient's history is also complicated by the presence of vitamin B12 deficiency. CT scan was reported as normal and MRI and SPECT scans are pending. Due to this adverse event, the IRB for the Israeli site has suspended drug treatment until further investigation of this potential toxicity is conducted and the results evaluated.

Dr. Pariser's review of the safety database has revealed 5 other reports of memory loss including one from the Fabry disease IND. These 5 cases are summarized in Table 142 of her review. These cases either lack detailed information, are confounded by the presence of low vitamin B 12 levels, or have normal neuropsychological tests. In addition, there are no baseline memory function tests in any of these patients.

Overall, a signal for drug-related neurotoxicity was detected in the review of this NDA. Since this was an unexpected AE, the clinical studies were not designed to adequately evaluate the findings of tremor, paresthesias/neuropathy, and memory loss. Given the marginal clinical benefit demonstrated with this product, additional studies will be needed to address potential for neurotoxicity associated with OGT 918 use.

OTHER ADMINISTRATIVE ISSUES

DSI Audits

No clinical audits were conducted for this NDA. All study sites were foreign with the largest enrollment occurring in Israel. Although the Review Division felt that a site inspection of the Israeli center was important for establishing data integrity and good clinical practices, in the immediate aftermath of the September 11, 2001 terrorist attack, the Office of Scientific Investigations (OSI) raised concerns for the safety of federal employees traveling to the Middle East. The Review Division concurred with OSI not conducting an inspection of this site and did not feel that inspection at the other centers would yield meaningful information.

Financial Disclosure

These documents were evaluated by Dr. Pariser and summarized in her review.

Pediatric Rule

[redacted]

RECOMMENDATION

Overall, this application is approvable based on the results of the clinical studies demonstrating a marginal clinical benefit that does not outweigh the potential for

neurotoxicity associated with OGT 918 therapy. OGT 918 showed a clinical benefit only with regard to liver and spleen volume reduction but no benefit with regard to anemia and thrombocytopenia. This improvement in organomegaly was only evident in the uncontrolled studies (Studies 918-001, 003, and their extensions) of patients who were treatment-naïve or had discontinued Cerezyme for ≥ 3 months and were not accompanied by clinically relevant increases in Hb and Plts. The results from the controlled study (Study 918-004/004x) with Cerezyme do not support the replacement of Cerezyme therapy with OGT therapy in patients who have demonstrated adequate control with the former agent. The hematologic profile in each treatment group worsened with the initiation of OGT 918 monotherapy. The addition of OGT 918 to stable Cerezyme therapy resulted in a greater liver size reduction compared to Cerezyme monotherapy; however, a similar finding was not observed for spleen size. Contrasting with these efficacy results, are the findings of tremors, parethesias/neuropathy, and memory loss which highlight concerns for drug-related neurotoxicity.

In order to address the deficiencies of this application, the sponsor needs to prospectively conduct a clinical trial that demonstrates improvements in bone marrow involvement as observed by increases in hemoglobin and platelets in addition to improvements in organomegaly. These benefits should not be outweighed by signs of neurotoxicity. Evaluation of neurotoxicity requires a prospectively designed study with monitoring for neuropathy and memory loss established at baseline and throughout the study.

/S/

Mary H. Parks, MD
Medical Team Leader
Deputy Director
HFD-510

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/s/

Mary Parks
5/16/02 09:34:51 AM
MEDICAL OFFICER

David Orloff
5/16/02 07:46:52 PM
MEDICAL OFFICER
Concur with Dr. Parks

ACTELION
Creative Science for Advanced Medicine

July 22, 2003

Patricia J. Madara
Consumer Safety Officer
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20851

DUPLICATE
N-000-C

RECEIVED
JUL 24 2003
FDR/CDER

Re: NDA 21-348 - Zavesca® (miglustat) 100 mg Capsules
Debarment Certification

Actelion Ltd hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Sincerely,

Tom Lategan

Tom Lategan, Ph.D.
VP, Regulatory Affairs

Actelion Pharmaceuticals US, Inc.
601 Gateway Boulevard, Suite 100
South San Francisco, CA 94080

Tel: (978) 682 3999
Fax (309) 216 7012
Cell: (978) 902 8446
e-mail:tom.lategan@actelion.com
URL: www.actelion.com

Item 16 DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Oxford GlycoSciences did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.

C. Moyses

17/5/02.

Dr Chris Moyses
Chief Medical Officer and Development Director
Oxford GlycoSciences (UK) Ltd
The Forum
86 Milton Park
Abingdon
Oxon
OX14 4RY
United Kingdom

Date

Bruce R. Manning

22 May 2002

Mr. Bruce R. Manning
President
New England Biomedical Research, Inc.
96 West Main Street
PO Box 809
Northborough, MA 01532
(Resident US Agent for Oxford GlycoSciences)

Date

MEMORANDUM OF PRE APPROVAL SAFETY CONFERENCE MINUTES

MEETING DATE: June 24, 2003

TIME: 8:30 AM

LOCATION: Parklawn Conference Room 14B45

APPLICATION: NDA 21-348 (Zavesca)

TYPE OF MEETING: Pre Approval Safety

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Pat Madara

ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Metabolic and Endocrine Drug Products	**Title**
Mary Parks, M.D.	Medical Officer Team Leader
Anne Pariser, M.D.	Medical Officer
Enid Galliers	Chief, Regulatory Project Management Staff
Pat Madara	Regulatory Project Manager

Office of Drug Safety

Division of Medical Errors and Technical Support	**Title**
Denise Toyer, Pharm. D.	Team Leader

Division of Surveillance, Research and Communication Support	**Title**
Leslie Stephens, R.N., M.S.N.	Project Manager

Division of Drug Risk and Evaluation	Title
Mark Avigan, M.D.	Acting Director
Allen Brinker, M.D.	Epidemiologist
Sandra Birdsong, RN	Project Manager
Lanh Green, RPh., MPH	Safety Evaluator Team Leader

Background:

NDA 21-348 (Zavesca) was originally submitted as a rolling NDA between March and August of 2001 for the treatment of Gaucher disease. Due to unacceptable risk/benefit concerns, an NA letter was issued on June 20, 2001. The sponsor responded to our NA letter on February 7, 2003 with a complete response. [redacted] use of the drug to those patients unable to take enzyme replacement therapy (ERT). The purpose of this meeting was to discuss any safety concerns that may require monitoring if Zavesca is approved.

Gaucher disease is caused by a defect in the next to last enzyme required in the breakdown of glycosphingolipids. The disease has a variable presentation and treatment is often based on the severity of the clinical signs and symptoms. The current standard of care is enzyme replacement therapy with Cerezyme®. This is an injectible drug which replaces the defective enzyme and, in general, works well. Problems with this drug include high cost, the fact that it involves long-term injections, and, rarely, severe allergic reactions.

Zavesca (miglustat) is proposed for the treatment of mild to moderate Type I Gaucher disease in adults who cannot take enzyme replacement therapy. A possible advantage of Zavesca is that it is administered orally. Zavesca works by inhibiting the formation of sphingolipids.

Discussion:

Clinical trials using Zavesca showed a reduction in splenomegaly and hepatomegaly. However, mild increases in Hgb and Hct were seen after 18 – 24 months of treatment, and platelet counts were unchanged. Cerezyme probably decreases bone crises while it is not known if Zavesca effects bone crises or not.

The Medical Officer pointed out that there are many safety issues with this drug. Possible side effects of Zavesca include stomach pain, weight loss, diarrhea and tremor. Some of these symptoms may decrease over time. The tremor tended to stop when the drug was halted. Peripheral neuropathy was a surprise finding seen in clinical trials. It is not clear if this is reversible. In addition, patients maintained on Cerezyme and switched to Zavesca deteriorated, particularly in hematologic parameters, especially platelet counts.

Zavesca has been approved for use in Europe since October, 2002 and there have been no indications of "off-label" use. However, there is concern that the drug could be used to treat other storage diseases for which there is no current therapy. In addition, there is concern about use in severely affected Gaucher disease patients and in the pediatric Gaucher disease patient population.

Office of Drug Safety Suggestions:

1. Insure that the package insert language is restrictive enough to prevent inappropriate use.
2. Check with the Division of Drug Marketing, Advertising and Communication (contact Debi Nhu Tran) to determine if they have any labeling concerns.
3. Add information to the Information for Patients section of the package insert. It now contains no information.
4. Suggest changes to the label to emphasize that ERT is the standard of care for this disease.
5. Discuss with the sponsor the importance of monitoring sales data and estimates of drug exposure. Report these findings in the quarterly periodic reports.
6. Determine the possibility of using Genzyme's Gaucher disease registry to help track data.
7. Insure that patients are not switched from Cerezyme to Zavesca by their insurance company.

Reviewed by:
Mary Parks, M.D., Medical Officer Team Leader
Anne Pariser, M.D., Medical Officer
Enid Galliers, Chief, Project Management Staff
Denise Toyer, Pharm. D., Team Leader
Leslie Stephens, R.N., M.S.N., Project Manager
Mark Avigan, M.D., Acting Director
Allen Brinker, M.D., Epidemiologist
Sandra Birdsong, RN, Project Manager
Lanh Green, RPh., MPH, Safety Evaluator Team Leader

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/s/

Patricia Madara
8/7/03 01:28:09 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 24, 2002

TIME: 11:00 AM – 12:00 PM

LOCATION: Chesapeake Room

APPLICATION: NDA 21-348

DRUG: Zavesca (miglustat) Capsules, 100 mg

TYPE OF MEETING: End of Review

MEETING CHAIR: David Orloff, M.D., Division Director

MEETING RECORDER: Samuel Wu, Pharm.D., Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Robert Meyer, M.D.	Office Director	ODE-II, HFD-102
2. David Orloff, M.D.	Division Director	DMEDP, HFD-510
3. Mary Parks, M.D.	Deputy Director	DMEDP, HFD-510
4. Anne Pariser, M.D.	Medical Reviewer	DMEDP, HFD-510
5. Kati Johnson, R.Ph.	Chief, Project Management Staff	DMEDP, HFD-510
3. Samuel Wu, Pharm.D.	Regulatory Project Manager	DMEDP, HFD-510

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Chris Moyses, M.D.	Chief Medical Officer/Development Director	Oxford GlycoSciences (OGS)
2. David Ebsworth, M.D.	Chief Executive Officer	OGS
3. Robert Ibbotson	Regulatory Affairs Manager	OGS
4. Bruce Manning	US Agent	New England Biomedical Research
5. Tom Lategan, M.D.	VP Regulatory Affairs	Actelion Pharmaceuticals US Inc.

BACKGROUND:

Oxford GlycoSciences (UK) Ltd submitted a New Drug Application on August 16, 2001, for Zavesca (miglustat) Capsules. The proposed indication was for the treatment of Type 1 Gaucher disease. This application received a non-approval on June 20, 2002, due to the drug's marginal efficacy and its significant adverse effects including neurological disorders such as tremor, paresthesias, and numbness.

On June 27, 2002, the applicant submitted an End-of-Review meeting request to discuss what further steps need to be taken before the application may be approved. The meeting package was submitted on August 23, 2002. In it, the applicant outlined the approach to be taken in response to the Agency's June 20, 2002, action letter. The letter stated that the applicant needs to "conduct further studies to address the balance of risk and benefit of miglustat treatment of type 1 Gaucher disease."

The applicant proposed amending the application to provide a change in the proposed indication. According to the applicant, this would significantly alter the benefit-risk assessment and would lead to approvability of the application. Following are the proposals for the amendment (from the meeting packet):

1. [redacted]
2. An update to the NDA package that will include revised documentation of the ongoing studies and updated safety information (consistent with that recently provided to the EU agencies as part of the MAA review and comprising data already provided to FDA but not reviewed).
3. A comprehensive Post-Marketing Surveillance Plan would be implemented that will combine controlled distribution of Zavesca alongside a tracking system. This plan will actively solicit safety information on all patients who receive Zavesca.
4. [redacted]

MEETING OBJECTIVES:

The objective of the meeting is to determine the acceptability of the proposal outlined above in getting the application approved.

DISCUSSION POINTS (Bullet Format):

Dr. Moyses introduced the proposals outlined above. This was followed by a general discussion based on the slides presented by the firm. However, no direct responses were provided for the two questions in the meeting packet. They are to be included in this meeting minutes following further internal discussion. Below are highlights from the discussion:

- The underlining problems with neuropathy remain even with the new wording for the indication. A study needs to be done on a subset of subjects with unmet medical needs or who are unsuitable for enzyme replacement therapy.

- There is no head-to-head comparison between Zavesca and ERT. While this is understandable, the efficacy response is modest, at best, and takes a long time to show. Having said this, your target population should be ones with mild disease condition.

- While there is organ size reduction, improvement in hemoglobin and platelet count is gradual and slow.

- In addressing the safety issues related to peripheral neuropathy, the firm's responses are as follow (from the slides):
  1. Cross sectional electrodiagnostic (EDX) testing performed in Zavesca clinical trial program following AE reports of peripheral neuropathy in Study OGT 918-001
  2. 'Peripheral neuropathy' on EDX by virtue of having abnormalities in both hands and feet with associated symptoms rather than an isolated finding of a low sural Sensory Nerve Action Potential (SNAP)
  3. Most EDX abnormalities (21 out of 68 cohort total) due to mononeuropathies or isolated EDX abnormality without clinical correlate
  4. Usually sensory only, no evidence of small fiber involvement

- EDX assessment did not include a placebo group in the clinical trials. Results from 40 patients with type 1 Gaucher disease who had not been treated with Zavesca were collected to assess background incidence of EDX abnormalities. The following is the results:
  1. Ten of the patients in the control population were receiving ERT at the time of the EDX and four had EDX abnormalities
  2. Type 1 Gaucher population has an underlying high incidence of EDX abnormalities similar to those seen in the Zavesca trials

- According to the firm, there is no baseline neurological exam in the NDA submission.

- There are still concerns with the safety database:
  1. There is no baseline.
  2. It is not clear when the adverse events started, i.e., while on ERT or on Zavesca.
  3. The cross-over design resulted in all but three receiving Zavesca.

- It is the firm's intention to supplement the NDA to address further in study 018 the relationship between the drug and the neurological problems.

- Firm stated that there are five reported adverse events affecting cognitive function in the Gaucher disease studies:
  1. Three had transient symptoms only with no deficit on formal testing.
  2. One had a transient mild cognitive deficit.

3. One had a mild cognitive deficit and a clinical picture consistent with early Alzheimer's disease.

- One subject in the Fabry disease study with pre-existing ischemic cerebral disease and end stage renal disease had mild memory impairment.

- Specific cases discussed (from the slides):
  1. Subject 001-411: A 66 year old male patient with no family history of dementia who complained of memory loss in association with tinnitus and vertigo about 16 months after starting Zavesca. Approximately 2.5 years later, patient again complained of problems with memory. The drug was discontinued after three years with significant deterioration, but cognitive deficit has remained throughout.

     a. SPECT scan showed changes predominantly in the frontal lobe
     b. MRI showed no significant sulcal widening but some subtle white matter abnormalities.
     c. CT scan showed mild cerebral atrophy consistent with age
     d. Patient had a know history of vitamin B_{12} deficiency – low serum vitamin B_{12} accompanied with high MMA for at least 3 years.

     Firm stated that according to the experts, this patient exhibited early signs of dementia and could be attributed to an early Alzheimer's disease.

  2. Subject 001-105: A 48 year [redacted] complained of possible cognitive dysfunction several months after stopping drug. Neuropsychological profile showed possible "mild compromise of cognition." In a repeat assessment, there was an improvement in concentration.

- [redacted]

- Firm proposed a limited distribution of the drug perhaps requiring physicians to register their patients.

- There will be a standard monitoring in clinics for responses. This would include yearly organ scans and more frequent hematological exams to monitor hemoglobin and platelets.

- Firm stated that there are currently 11 patients enrolled in the New York study who are unable or unwilling to receive ERT.

- In summary:
  1. The indication needs to be revised to address unmet medical needs.
  2. [redacted]
  3. Data should be collected on population with unmet medical needs and be used to amend the NDA.

QUESTIONS (post-meeting internal discussion):

1. Does the Agency concur with the OGS position that the proposals outlined in the Briefing pack could lead to the NDA for Zavesca being deemed approvable?

2. On the assumption that the answer to Q1 is positive, does the Agency concur with the OGS position that the content of the proposed amendment to the NDA is appropriate?

Agency Response (to both questions):
Given the toxicities associated with this drug and its marginal efficacy, the Agency is concerned with the off-label use. Although the Agency realizes the low prevalence of Gaucher disease and the low abuse potential of the drug, it is not known whether the toxicities are reversible.

[redacted] *The Agency recommends that you revise the labeling to identify a target population who cannot take ERT such as patients intolerable to ERT or patients with poor vascular access. The term "unsuitable" should not extend to patients who refuse to take ERT for personal reasons or whose disease is not severe enough to warrant treatment with ERT. Instead, the patient population for which Zavesca should be targeted will be the limited number of patients who are incapable of receiving ERT due to medical reasons (e.g., hypersensitive or adverse reactions to ERT). The burden remains on you to demonstrate that this drug is sufficiently safe for its intended use.*

DECISIONS (AGREEMENTS) REACHED:
None.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:
None.

ACTION ITEMS:
None.

/S/

Minutes Preparer: _____
Samuel Y. Wu, Pharm.D.
Regulatory Project Manager

Chair Concurrence: /S/
David G. Orloff, M.D.
Division Director

Drafted by: S. Wu/November 1, 2002
Initialed by: K. Johnson/November 11, 2002
R. Meyer/November 13, 2002
M. Parks/November 13, 2002
A. Pariser/November 13, 2002
D. Orloff/November 18, 2002
Final: S. Wu/November 18, 2002

MEETING MINUTES

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/s/

Samuel Wu
11/18/02 04:58:39 PM

David Orloff
11/19/02 07:36:15 PM

Pre-NDA meeting minutes for IND 60,197

Date: January 9, 2001
Time: 2:00 – 3:30 pm
Location: Parklawn Building 3rd fl c/r "Chesapeake"
Drug Product: OGT 918
Proposed Indication: Treatment of Gaucher disease
Attendees:

FDA:

John Jenkins, M.D., Director, Office of Drug Evaluation II
David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products
Mary Parks, M.D., Medical Team Leader, DMEDP
Moshe Zilberstein, M.D., Medical Officer, DMEDP
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP
Sharon Kelly, Ph.D., Chemist, DMEDP
Karen Davis-Bruno, Ph.D., Pharm/Tox Team Leader, DMEDP
John Colerangle, Ph.D., Pharmacologist, DMEDP
Todd Sahlroot, Ph.D., Statistical Team Leader, Division of Biometrics II
Lee Pian, Ph.D., Statistician, DOB II
Hae-Young Ahn, Ph.D., Clin Pharm Team Leader, DPE II
Sang M. Chung, Ph.D., Clin Pharm Reviewer, DPE II
Janet Whitley, Ph.D., Division of Orphan Drug Products
Julie Rhee, Regulatory Project Manager, DMEDP

Oxford GlycoSciences, Ltd.:

Chris Moyses, M.D., Clincal and Development Director
Dr. Sandy Kenndy, Director of Pharmacoproteomics and Preclinical Development
Robert Ibbotson, Regulatory Affairs Manager
Darrell Morgan, Pharmaceutical Development Manager

New England Biomedical Research, Inc.

Bruce Manning, President

Discussion:

1. Dose selection and study design for carcinogenicity studies will be needed for Executive CAC review at NDA submission. Submission of carcinogenicity data as a Phase 4 commitment is acceptable based on previous communications with the sponsor.

2. Patients enrolled in OGT studies were either unwilling or unable to receive enzyme replacement therapy.

3. Two patients have reached 30-months treatment. Twenty-two patients have completed 1-year treatment by February 2000.

Questions and FDA's Responses:

1. **OGS consider that no additional *in vitro* or *in vivo* estimation of bioavailability is necessary to support an NDA filing. Does the Agency concur with this view?**

FDA response:

As long as to-be-marketed formulation is studied in clinical studies, bioavailability testing is not needed. However, if to-be-marketed formulation is not used in clinical studies, bioavailability/bioequivalence studies are necessary when NDA is submitted.

2. **OGS considers that sufficient clinical safety, efficacy, and pharmacokinetic data are being provided to evaluate the clinical significance of a food effect on OGT 918. Does the Agency agree?**

FDA response:

Since OGT 918 demonstrated food effect, high-fat meal study should be conducted. The conduct of this study is not a filing requirement.

3. **We would like to ask for confirmation from FDA that the proposed format for the Clinical Section (Item 8) and the Statistical section (Item 10) as presented in this document is acceptable for submission of this NDA for OGT 918?**

FDA response:

a. *In Study 004, statistical tests for subgroup-by-treatment interactions should use alpha =0.1 (not 0.05).*

b. *Include one or more references for the minimization procedure used in Study 004 to assign patients to a treatment group.*

4. **We would like to ask FDA whether they concur with the OGS view on the format of the proposed ISE presented in Section 6.5 of this document.**

FDA Response:

It appears to be acceptable.

5. **We would like to ask FDA whether they concur with the OGS view on the format of the proposed ISS presented in Section 6.6 of this document.**

FDA Response:

It appears to be acceptable.

6. **To support the Clinical and Statistical sections of the NDA we propose to supply FDA with SAS transport files in Item 11. Can FDA confirm that this proposal is acceptable?**

FDA Response:

a. *Refer to the "Guidance for Industry Providing Regulatory Submissions in Electronic Format --- NDAs" for Item 11: Case Report Tabulations (CRTs). Also, follow Appendix 2: EXAMPLE CONTENT OF SPECIFIC CLINICAL DATASETS in the above guidance document for the organization of variables.*

b. *The Agency would like to request a reviewer's aid for clinical reports and labeling sections in MS Word.*

7. **OGS propose to include only relevant CRFs from the OGS sponsored studies in the NDA submission.**

FDA response:

The sponsor should include narrative summaries for death and drop-outs generated by G. D. Searle in their HIV studies, if they are available.

8. **OGS would like to discuss the proposed submission timetable with FDA at the pre-NDA meeting.**

FDA response:

The review clock does not start until the complete submission is received.

Decisions (agreements) reached:

The Agency recommended and the sponsor agreed to conduct a pilot high-fat study before the NDA submission.

Unresolved issues or issues requiring further discussion:

None.

Drafted by: JRhee 2-8-01
Initialed by: KDavis-Bruno 2-9-01/TSahlroot 2-9-01/Pian 2-9-01/Moore 2-9-01/Zilberstein 2-12-01/Ahn 2-12-01/Parks 2-16-01/Kelly 2-16-01/Moore 2-23-01/Orloff 2-26-01
Comments not received by 2/26/01: from JColerangle, SChung, and JWhitley
F/T by: JRhee 2-27-01

/s/

David Orloff
2/27/01 11:26:01 AM

DEC 27 2001

MEMORANDUM OF TELECON

DATE: November 28, 2001

APPLICATION NUMBER: NDA 21-348, Zavesca (miglustat) 100 mg Capsules

BETWEEN:

Name: Bob Ibbotson, Regulatory Affairs Manager
Lloyd Curtis, MD, Director of Medical Affairs
Irene Gow, Clinical Operations Manager
Phone: +44 1235 207622
Representing: Oxford GlycoSciences (UK) Ltd

AND

Name: Samuel Y. Wu, Pharm.D., Regulatory Project Manager
Anne Pariser, M.D., Medical Reviewer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Clarification of Clinical Data

This is a brief telephone call to OGS seeking clarification on some issues related to Dr. Pariser's review of the application. The firm was asked to respond in writing in a formal submission. Below is a list of issues that were communicated to the sponsor:

1. The firm is to provide information on screen failure patients and patients who failed to enter the extension studies.
2. The firm is to provide information on medication compliance in the trial.
3. The firm is to clarify the links between the "define.pdf" file and the SAS transport file.

/S/

Samuel Y. Wu, Pharm.D.
Regulatory Project Manager

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/s/

Samuel Wu

12/27/01 03:42:21 PM

CSO

Samuel Wu

12/27/01 03:44:12 PM

CSO

10/11/01

Memo to File

To:	David Orloff, M.D., Division Direction, DMEDP, HFD-510
From:	Anne Pariser, M.D., Medical Officer, DMEDP, HFD-510
Re:	Request for Priority Review for Unmet Medical Need in the Treatment of Gaucher Disease
Submission:	NDA #21-348, dated 01-Aug-2001
Sponsor:	Oxford Glycosciences Ltd
Drug:	OGT 918 (Zevesca) for Oral Administration
Date:	04-Oct-2001

The purpose of this memo is to address the sponsor's request for a priority review for OGT 918 (Zevesca formerly known as Vevesca), NDA # 21348, so that a decision can be made as to whether this application should undergo a standard vs priority review.

Background

The sponsor has requested a priority review for OGT 918 (for oral administration) because of its potential to address an unmet medical need in the treatment of Gaucher disease. Current treatment for Gaucher disease consists of parenteral administration of enzyme replacement therapy (ERT) with either Cerezyme or Ceredase. Three (3) main studies were submitted to the NDA in support of this application. Briefly, these studies are:

1) OGT 918-001 - a non-comparative open-label study of OGT 918 in 28 adult patients with type 1 Gaucher disease.
2) OGT 918-003 - a non-comparative, open-label study of OGT 918 in 18 adult patients with Type 1 Gaucher disease.
3) OGT 918-004 - an open-label, randomized, active comparator study in 36 adult patients with type 1 Gaucher disease who had received ERT for a minimum of 2 years. Patients were randomized to Cerezyme alone, Zevesca alone, or Cerezyme + Zevesca combination therapy.

Reference will be made to the CDER MaPP for Priority Review Policy (MaPP 6020.3) which includes as criteria for a priority review:

1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;
2) elimination or substantial reduction of a treatment-limiting drug reaction;
3) documented enhancement of patients compliance; or
4) evidence of safety and effectiveness of a new subpopulation.

Rationale

The sponsor cites problems with ERT administration in a letter requesting Fast Track Designation, dated 21-Apr-2000. The problems with ERT are summarized as follows:

1. ERT requires "...repeated parenteral access which can present a significant burden to the patient." Patients have reported problems with parenteral administration including discomfort, pruritis, burning, swelling and sterile abscess at the site of venipuncture, and problems with repeated venous access such as hematoma and

thrombophlebitis. The sponsor states "Some patients - ERT – require an indwelling cannula to be inserted" which can lead to further problems such as infection, especially in splenectomized patients.

2. "The most common and most serious adverse effects associated with Cerezyme infusions have been allergic reactions." Anti-Cerezyme IgG antibody occurs in about 15% of patients during the first year of therapy and 46% of these patients experience symptoms of hypersensitivity. Allergic reactions are mainly cutaneous symptoms (urticaria, flushing, pruritis and angioedema); however, more severe allergic reactions such as airway constriction and anaphalactoid reactions have been observed. Some patients require pretreatment with antihistamines or other interventions. In some patients, the more severe allergic reactions have resulted in the reduction of Cerezyme dose and frequency, and in some cases, cessation of ERT.

3. OGT 918 is an oral drug which may offer a "beneficial impact on the patients overall Quality of Life compared to a patient receiving enzyme replacement."

4. "Wider benefits to the overall healthcare system" were also proposed. Factors associated with ERT that burden the healthcare system include: patients need to be treated in designated treatment centers for intravenous ERT therapy; the expense of ERT; and patients receiving ERT risk losing their healthcare coverage secondary to exceeding the financial limits of their health insurance plans, "resulting in significant patient anxiety".

5. "Recent evidence is coming to light of a possible link between the administration of Cerezyme and the triggering, aggravation or complication of pulmonary hypertension."

6. The sponsor states that "an oral therapy offers the potential of easier administration, improved quality of life and an alternative therapy for patients."

Discussion
Responses to above rationale:

1. Whether or not parenteral administration of ERT was a burden to patients was not addressed by any of these studies. No Quality of Life assessments were performed and studies –001 and –003 were non-comparative. In addition, while these are known side effects of parenteral administration of almost any drug, OGT 918 also is associated with significant side effects that may limit treatment, especially diarrhea, weight loss, other GI complaints, and neurologic complaints such as tremor. On preliminary review of the safety data, diarrhea in particular led to OGT 918 discontinuation in some patients, and decreases or interruption of study medication treatment in others. Many Gaucher disease patients are splenectomized, and it is not known if treatment with ERT results in an increase in infections.

2. The majority of patients treated with ERT are able to tolerate ERT with or without premedication for allergic symptoms. The sponsor did not provide any information on the number of patients who cannot tolerate Cerezyme or Ceredase due to severe allergic reactions, and it is not known how many patients are unable to receive ERT in the United States. In fact, the 3 main studies submitted to the NDA for OGT 918 were all performed outside the United States due to (per the sponsor) "...the majority of patients in the USA and Europe are already treated with ERT, making it extremely difficult to carry out randomised studies in treatment-naïve patients" [in NDA #21-348, volume 2.1, page 29, section 8.2.1.8.2 Clinical Development Plan for the Gaucher Disease Indication]. The sponsor went on to note that for patients in the United States "...not receiving ERT, tend to be less severly (sic) affected and have a limited capacity for improvement, making treatment effects more difficult to see", and "...it is notable that none of the treatment centers in the USA who were approached felt able to participate in a clinical trial of Vevesca".

   In additional, studies –001 and –003 were performed in patients "unable or unwilling" to receive ERT. The sponsor, when contacted, was unable to provide reasons as to why patients were unable or unwilling to receive ERT, for example, due to intolerance, unavailability or for financial reasons. It is, however, noted in the NDA submission that studies were carried out "...in patients with measurable disease who were unable or unwilling to receive ERT; thereby including patients who required treatment but wished to defer ERT in order to try an experimental oral therapy, or were unable to obtain ERT for economic reasons, as was the case for the majority of the South African patients" [in NDA #21-348, volume 2.1, page 29, section 8.2.1.8.2 Clinical Development Plan for the Gaucher Disease Indication]. This suggests that economic, not medical or quality of life, factors were the reason for not receiving ERT in a number of patients included in these studies.

   Finally, study –004 required as an inclusion criterion for patients to have "received continuous Ceredase or Cerezyme therapy for a minimum of 2 years prior to screening and had received their current dose for a minimum of 6 months". Therefore, this study did not include patients who were unable to tolerate ERT and does not provide information on alternative therapy for patients who cannot tolerate or receive currently available therapy. As this study was a comparative study, however, discontinuations in the 3 treatments could be assessed. Three (3) patients discontinued study medication prior to study completion: 2 patients in the Zevesca alone arm (one patient for tremor and one patient for viral infection) and 1 patient in the Zevesca + Ceredase arm (for diarrhea). No patient in the Ceredase alone arm discontinued for any reason during study drug treatment.

3. No Quality of Life measurements or data were submitted with the NDA. In the Application for Fast Track Designation letter, the sponsor outlined plans for Quality of Life Assessments to be made in study OGT 918-004. These assessments do not appear in the study protocol, efficacy parameters, nor the study report. It is therefore

not possible at this time to assess the impact of OGT 918 on patients' quality of life vs ERT.

4. Economic considerations are not listed as a reason for Priority Review Designation in the MaPP for Priority Review. It is also not known what the costs would be for OGT 918 oral therapy vs ERT. Anxiety about the loss of healthcare coverage was also not assessed in the studies submitted.

5. Pulmonary hypertension is a known consequence of Gaucher disease in some patients. A possible link to ERT is suspected but not proven, and the mechanism for the triggering, aggravation or complication of pulmonary hypertension is not known. It is therefore not known if pulmonary hypertension is a result of treatment or of the natural progression of disease. It is also not known if the same association will be found with OGT 918. As previously mentioned in #1, OGT 918 is also associated with treatment-limiting side effects.

6. As previously stated in # 4, quality of life was not measured in the OGT 918 studies.

Summary

OGT 918 does not appear to meet the MaPP for Priority Review Policy definition of a drug product qualifying for Priority review. Preliminary review of the efficacy and safety data does not provide evidence of increased effectiveness vs ERT, nor elimination or substantial reduction in treatment-limiting drug reactions. Enhancement of compliance was not assessed, and there is no evidence of safety and effectiveness of OGT 918 in a new subpopulation of patients. It is the recommendation of this Reviewer that NDA #21-348 be evaluated as a Standard Review.

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/s/

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10/9/01 02:38:51 PM
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