CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-348

Actelion Pharmaceuticals US, Inc.
Attention: Thomas Lategan, Ph.D.
Vice President, Regulatory Affairs
56 Huckleberry Lane
North Andover, MA 01845

Dear Dr. Lategan:

Please refer to your new drug application (NDA) dated April 20, 2001, received April 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zavesca (miglustat) 100 mg Capsules.

We acknowledge receipt of your submissions dated June 27 and October 14 and 16, 2002, and February 7, March 6 and 31, April 2, 8, and 9, May 27 and 28, June 10 and 13, and July 31, 2003.

The February 7, 2003, submission constituted a complete response to our June 20, 2002, action letter.

This new drug application provides for the use of Zavesca (miglustat) 100 mg Capsules for the treatment of mild to moderate Type I Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access).

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below:

1. On the **Blister** and **Carton labels**, the word "Capsules" should be moved to immediately follow "(miglustat)".

2. On the **Carton label**, the storage statement should be changed to read, "Store at 20° to 25° C (68° to 77°F). Brief exposure to 15° to 30° C (59° to 86° F) permitted (see USP Controlled Room Temperature)".

3. On the **Carton label**, the statement (b)(4)---------- (b)(4)-------- should be changed to "Rx only".

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert and patient package insert, submitted July 31, 2003). The final printed labeling FPL must be identical to the enclosed labeling (the blister and carton label, submitted April 9, 2003) except for inclusion of the revisions listed above. These revisions are terms of the NDA approval.

Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-348.**" Approval of this submission by FDA is not required before the labeling is used.

We acknowledge your May 28, 2003, voluntary agreement to limit the distribution of Zavesca to qualified physicians.

We remind you of your postmarketing study commitments in your submissions dated July 17 and 24, 2003. These commitments are listed below.

1. To conduct a two-year carcinogenicity study in mice.

Protocol Submission:	January 13, 2003
Study Start:	April 2003
Final Report Submission:	March 2006

2. To conduct a two-year carcinogenicity study in rats.

Protocol Submission:	November 5, 2001
Study Start:	March 2002
Final Report Submission:	January 2005

Submit study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, and any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert
Patient Package Insert
Blister Label
Carton Label

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/s/

Robert Meyer
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APPLICATION NUMBER:

21-348

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-348

6/20/02
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New England Biomedical Research, Inc.
Attention: Bruce Manning, President
Agent for Oxford GlycoSciences (UK) Ltd
96 West Main Street
Northborough, MA 01532

Dear Mr. Manning:

Please refer to your new drug application (NDA) dated August 16, 2001, received August 21, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zavesca (miglustat) Capsules, 100 mg.

We acknowledge receipt of your submissions dated March 28, April 20, July 18, August 1, September 10, October 2, November 14, and December 5, 2001, and January 11 and 25, February 12, 18, 21, and 22, March 12, and May 22, 2002.

We also refer to your two submissions dated May 3, 2002, consisting of a clinical amendment and a 240-day safety update. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

You have not demonstrated through adequate and well-controlled investigations that miglustat is safe and effective for use in the treatment of Type 1 Gaucher disease. The results from Studies 918-001 and 918-003 and their extensions show decreases in liver and spleen volume, but marginal improvement in hematologic parameters with miglustat therapy in treatment-naïve patients. In Study 918-004, conducted in patients who were well-maintained on Cerezyme, switching to miglustat monotherapy resulted in clinical deterioration as measured by hematologic indices and biochemical markers of Gaucher disease. Miglustat monotherapy was not found to be a suitable treatment in these patients. Also in Study 918-004, switching to combination therapy with miglustat + Cerezyme was not associated with a clear benefit over Cerezyme monotherapy in the small number of patients so treated for a limited time (6 months).

Treatment of patients with miglustat was associated with frequent side effects, such as diarrhea in 90% of patients and weight loss in 65% of patients that progressed over the course of the studies. Most concerning, however, is the fact that tremor, paresthesias or numbness, and abnormal electrodiagnostic

test results were reported in a substantial number of patients (a late report of memory loss is still under investigation). The potential neurotoxicity of miglustat must be further investigated. The findings in the clinical trials are especially worrisome given miglustat's neurotoxicity in animals as well as the biologic plausibility of neurotoxicity based on the mechanism of action of the drug.

In sum, the clinical data show marginal benefits associated with miglustat therapy in Gaucher disease coupled with significant adverse effects. This balance of risk and benefit of miglustat treatment in the studied patient population does not warrant approval of the drug. Before this application may be approved, it will be necessary for you to address the following:

Clinical

1. Conduct further studies to address the balance of risk and benefit of miglustat treatment of type 1 Gaucher disease. Such studies:
   a. Must be randomized and controlled, with pre-specified endpoints, sample size calculations, and analysis plans. In mildly affected patients, such as the patients included in Studies 918-003 and 918-001, consideration could be given to a placebo-controlled or active-comparator study. Any study must also include specific guidelines for blinding of radiologists in the reading of MRI and CT films for assessments of liver and spleen volume. Blinding should not allow access to patient treatment assignment or time sequence of the films.

   b. Must address the relationship of dose administered to efficacy and safety, including objective assessments of the effects of dose adjustments during the clinical studies, particularly if you wish to recommend such in the labeling.

   c. Must assess the neurotoxicity of miglustat employing a clinical trial design that incorporates baseline and on-treatment assessments of neurologic and cognitive functions utilizing validated methods, preferably incorporating blinded readings of any electrodiagnostic or cognitive tests, as well as adequate controls. Because neurotoxicity was a late effect in many patients, treatment with miglustat should be for at least 12 months, with a long follow-up phase. In addition, efforts should be made to determine if biochemical markers of disease severity and/or pharmacologic effect of drug are useful as predictors of adverse neurologic outcomes in humans treated with miglustat.

Chemistry, Manufacturing, and Controls

2. Regarding ← acceptance specifications for the starting materials used in drug substance synthesis:

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2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Although not approvability issues *per se*, we have the following comments:

A. You should determine whether the adverse effects on male reproductive function in dogs, rats, and monkeys dosed with miglustat are relevant to humans through semen analysis. The specific nature, frequency, severity, and reversibility of any abnormalities should be assessed.

B. You should revise the dissolution specification to the recommended acceptance criterion of Q= — at— minutes.

C. The results of the Caco-2 cell monolayer experiment indicated activation of P-glycoprotein by miglustat. You should provide confirmatory evidence that miglustat activates P-glycoprotein in Caco-2 cells using other substrate(s).

D. Neurologic histopathologic assessments in animals are limited. If feasible, you should thoroughly re-evaluate brain, spine, and nerve histopathology in the chronic monkey study (SA 4078). Use of special stains for neurologic tissue, neuroanatomical sectioning, and ultrastructural assessments are recommended. If possible, determine ceramide and glucosylceramide plasma and/or tissue concentrations in these monkeys. A dedicated neurologic toxicity study in rodents or other suitable animal model is also recommended to evaluate ceramide and glucosylceramide levels, specific staining for various neurologic tissues (e.g., brain, spine, nerve), extended neuroanatomical sectioning, and ultrastructural assessments in conjunction with a rigorous assessment of learning/memory (e.g. Morris maze).

E. Since miglustat is not an established name as described under section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the USAN Council for adoption of a name that will comply with that section of the Act as provided by 21 CFR 299.4(e). The Council can be reached at the following address:

Secretary
United States Adopted Names (USAN) Council
c/o American Medical Association
P.O. Box 10970
Chicago, Illinois 60610

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Metabolic and Endocrine Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Sandra Kweder, M.D.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sandra L. Kweder
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