CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

July 29, 2003

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

Attention: Tom Lategan, PhD
Vice President, Regulatory Affairs

Dear Dr. Lategan:

Reference is made to the designated orphan drug request submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for 1,5-(Butylimino)-1,5 dideoxy, D-glucitol (miglustat) for the treatment of Gaucher disease (request #98-1125).

We also refer to your letter dated July 29, 2003, notifying us that the sponsorship of this application has been transferred to Actelion Pharmaceuticals Ltd from Oxford Glycosciences PLC.

Please be advised that if miglustat is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of miglustat as designated. Also an annual progress report must be submitted annually after the designation date until a marketing application is approved (21 CFR 316.30).

The information required for the complete transfer of the orphan drug application has been submitted. We look forward to your future communication.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-348

4/9/03

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

Dear Mr. Lategan:

We acknowledge receipt on April 1, 2003, of your March 31, 2003 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application:

Name of Drug Product: Zavesca (miglustat) Capsules, 100 mg

NDA Number: 21-348

Name of New Applicant: Actelion Pharmaceuticals US Inc.

Name of Previous Applicant: Oxford Glycosciences PLC

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Actilion Pharmaceuticals US Inc.as the sponsor of record for this application.

All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: New England Biomedical Research, Inc.
Bruce Manning, President
Agent for Oxford Glycosciences PLC
96 West Main Street
P.O. Box 809
Northborough, MA 01532

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/s/

Patricia Madara

4/9/03 11:16:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-348

3/24/03

New England Biomedical Research, Inc.
Attention: Bruce manning, President
U.S. Agent for Oxford Glycosciences Ltd.
96 West Main Street, PO Box 809
Northborough, MA 01532

Dear Mr Manning:

We acknowledge receipt on February 12, 2003 of your February 07, 2003 resubmission to your new drug application for Zavesca (miglustat) Capsules, 100 mg.

We consider this a complete, class 2 response to our June 20, 2002 action letter. Therefore, the user fee goal date is August 12, 2003.

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

Sincerely,

/S/

Pat Madara
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Patricia Madara
3/24/03 11:16:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-348

DISCIPLINE REVIEW LETTER

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

6/5/03

Dear Dr. Lategan:

Please refer to your March 28, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zavesca (miglustat) 100 mg capsules.

We also refer to your submission dated February 7, 2003, containing a complete response to our June 20, 2002 action letter.

Our review of the Patient Package Insert section of your submission is complete, and we have made revisions to the text. Enclosed is a PDF document with the proposed changes included in strike out format.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Revised PPI

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

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

Sincerely,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, for the
Division of Metabolic and Endocrine Drug
Products, (HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Chien-Hua Niu
5/29/03 09:04:40 AM
signed for Stephen Moore, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-348

OCT 26 2001

New England Biomedical Research
U.S. Agent for Oxford GlycoSciences, Ltd.
Attention: Bruce Manning
President
96 West Main Street
PO Box 809
Northborough, MA 01532

Dear Mr. Manning:

Please refer to your August 16, 2001, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zavesca (miglustat) 100 mg Capsules, in which you requested a Priority Review.

We have reviewed the materials and concluded that this application does not qualify for Priority Review status. We refer to the CDER MaPP for Priority Review Policy (MaPP 6020.3, http://www.fda.gov/cder/mapp.htm) which outlines the following criteria for an application to qualify for 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.

Below is the summary of your rationale for requesting Priority Review, as outlined in your April 21, 2000, submission to IND 60,197 and the Agency response:

1. ERT (enzyme replacement therapy) 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. You have stated "Some patients – especially children receiving ERT – require an indwelling cannula to be inserted" which can lead to further problems such as infection, especially in splenectomized patients.

   Agency Response:

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. OGT 918 has not been studied in children, and it has not been determined if the availability of OGT 918 would result in a decreased need for indwelling intravenous access in children.

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.

Agency Response:

The majority of patients treated with ERT are able to tolerate ERT with or without premedication for allergic symptoms. You 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. The 3 main studies contained in your NDA for OGT 918 were all performed outside the United States due to (per the submission) "...the majority of patients in the USA and Europe are already treated with ERT, making it extremely difficult to carry out randomized studies in treatment-naïve patients." You also stated 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 Zavesca."*

In addition, studies –001 and –003 were performed in patients "unable or unwilling" to receive ERT. 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." 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 Zavesca alone arm (one patient for tremor and one patient for viral infection) and 1 patient in the Zavesca + Ceredase arm (for diarrhea). No patient in the Ceredase alone arm discontinued for any reason during study drug treatment.

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."

Agency Response:

No Quality of Life measurements or data were submitted with the application. In the April 21, 2001, submission to IND 60,197 requesting Fast Track designation, you 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. "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".

Agency Response:

Economic considerations are not a valid reason for Priority Review designation. 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. "Recent evidence is coming to light of a possible link between the administration of Cerezyme and the triggering, aggravation or complication of pulmonary hypertension."

Agency Response:

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 point #1, OGT 918 is also associated with treatment-limiting adverse events.

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

Agency Response:.

As previously stated, 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. This submission, therefore, will be reviewed as a standard application.

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

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
10/26/01 11:26:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-348

SEP 7 2001

New England Biomedical Research, Inc.
Attention: Bruce Manning, President
Agent for Oxford Glycosciences
96 West Main Street
PO Box 809
Northborough, MA 01532

Dear Mr. Manning:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Vevesca (miglustat) Capsule, 100 mg

Review Priority Classification: Standard (S)

Date of Application: August 16, 2001

Date of Receipt: August 21, 2001

Our Reference Number: NDA 21-348

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 16, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 21, 2002 and the secondary user fee goal date will be August 21, 2002.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-6431.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Samuel Wu
9/7/01 10:45:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-348

MAY 21 2001

Oxford Glycoscience
Attention: Bruce Manning, Agent
New England Biomedical Research, Inc.
96 West Main Street
PO Box 809
Northborough, MA 01532

Dear Mr. Manning:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Vevesca (miglustat) Capsules 100 mg.

We also refer to our June 15, 2000, letter granting fast track designation for Vevesca (miglustat) Capsules 100 mg for Gaucher Disease and to your April 20, 2001, request for step-wise submission of sections of the New Drug Application (NDA) for this product.

We have reviewed your request and have concluded that the proposed plan for step-wise submission of sections of the NDA is acceptable.

If you pursue a clinical development program that does not support use of Vevesca (miglustat) Capsules 100 mg for Gaucher Disease, the application will not be reviewed under the fast track drug development program and submission of sections of the NDA will not be permitted under this program.

If you have any questions, please call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6431.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
5/21/01 07:41:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

May 29, 1998

Mr. Bruce Manning, President
New England Biomedical Research Inc.
PO Box 809
27 South Street
Northborough, MA 01532

Dear Mr. Manning:

Reference is made to the orphan drug application of March 24, 1998, sponsored by Oxford GlycoSciences, and submitted pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (FFDCA) for the designation of OGT 918 as an orphan drug (application #98-1125).

We have completed the review of this application and have determined that OGT 918 qualifies for orphan designation for the treatment of Gaucher disease. Please note that it is OGT 918 and not its formulation that has received orphan designation.

Please be advised that if OGT 918 were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of OGT 918 as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR

316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Michael W. Dreis, PharmD, MPH at (301) 827-0990.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development