Memo to File

NDA #:	21-348
Sponsor:	Actelion Pharmaceuticals US, Inc.
Drug:	Zavesca (miglustat)
Memo Date:	16-Jul-03
Office/Division:	OCPB / DPE–2
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.
Issue:	Labeling for effect of Zavesca on Cerezyme

The sponsor claimed no significant effect of Zavesca on Cerezyme because the drug interaction results were confounded by the dose proportionality (Attachment, letter date of July 9, 2003). [redacted] which covers doses in the drug interaction study [redacted] by the sponsor. In this regard, the company's argument is not acceptable.

The proposed labeling is as follow:
(Underline text is recommended to add and ~~strikethrough~~ is recommended to delete.)

CLINICAL PHARMACOLOGY

Drug Interactions

[redacted]

PRECAUTIONS

Drug Interactions

[redacted]

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

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

/s/

Sang Chung
7/17/03 05:35:37.PM
PHARMACOLOGIST

Hae-Young Ahn
7/21/03 06:17:35 PM
BIOPHARMACEUTICS

NDA 21348

Memorandum of Consultation

To: Anne Pariser, MD (Medical Officer – HFD 510)
David Orloff, MD (Division Director – HFD – 510)
From: George S. Benson, MD (Medical Officer – HFD 580)
Through: Mark S. Hirsch, MD (Team Leader, Urology HFD – 580)
Daniel Shames, MD (Acting Director – HFD – 580)

Re: consultation regarding male reproductive toxicity issues with Zavesca (miglustat)

Date consultation received by DRUDP: March 21, 2002
Medical officer review: March 27, 2002

Background: NDA 21348 (Zavesca, miglustat) was submitted to HFD-510. This drug is an NME and the proposed indication is Gaucher's disease. Pre-clinical studies have revealed "possible" adverse effects on male reproduction. The consultation requests the answers to 2 questions:

1) How relevant are these findings to reproductive safety issues in humans?
2) Would you suggest any warning, practical monitoring or Phase IV commitments? If approved the drug will be administered chronically to young individuals of reproductive age. If further studies are recommended, what specifically would you recommend (i.e., motility, morphology, reversibility, histopathology)?

Medical officer review:

Materials reviewed: A summary from HFD-510, but not the original pre-clinical study reports, of the effect of miglustat on reproductive parameters in the rat and monkey was reviewed.

The sponsor has reported that pre-clinical reproductive data show possible effects on male reproduction in the rat. In dose-ranging studies, there were effects on sperm morphology at all dose levels. Specifically, there were increases in the proportion of abnormal sperm, principally headless sperm, and sperm with chromosomal abnormalities. Sperm motility was also affected. There were no treatment-related histological changes in the testes or the epididymis. The review also states that "similarly, other male reproductive phenomena were observed in long-term treatments." These "phenomena" are not further described. The sponsor claims that these findings are reversible.

Two tables with some data concerning pre-clinical reproductive toxicity are provided:

Rat: "1,3 month toxicity, male fertility"

	Animal dose	Animal exposure (mg/M^2)	Human multiple
"Motility, aberrant morphology (headless, reduced hook)"	20 mg/kg/day	120	<1X
"testes, epididymides, prostate weight, aspermatogenesis, hypospermia, seminal vesicle/prostate atrophy, fertility index (40%)"	200 mg/kg/day	600	<3X

"The effects on spermatogenesis/fertility appear to reverse following a 13-week recovery period." Furthermore, "it is unknown if the histopathology is reversible since this was not examined."

Reviewer's comment: "There were no treatment-related histological changes in the testes or the epididymis" (see above). The meaning of "it is unknown if the histopathology is reversible since this was not examined" is unclear.

Studies were also performed with the miglustat pro-drug SC 49483. The following table of results with SC 49483 in the rat and monkey was provided:

	Animal dose	Animal exposure (mg/M^2)	Human multiple
"Rat: motility, concentration, aberrant morphology (headless, reduced hook)"	300 mg/kg/day	1800	<10X
"Monkey: concentration"	750 mg/kg/day	9000	<50X

Reviewer's comment: This reviewer assumes that "monkey concentration" referred to in the table refers to an abnormal sperm concentration. The severity of this abnormality related to the pro-drug 49483 is not further described.

No reproductive studies have been performed in humans. In one clinical trial, a man treated with miglustat 100 mg tid for Gaucher's disease withdrew from the study, was off study drug for approximately 3 months, and fathered a normal child.

Reviewer's comments: From scant data provided, miglustat may have an adverse effect on semen parameters in both rats and monkeys. In the rat, aspermatogenesis with a human multiple dose of <3X is described. In addition, prostate and seminal vesicle atrophy in the rat suggests a hormonal mechanism. No monkey data on the effect of miglustat on reproductive function is provided. The severity of the effect of the "pro-drug" 49483 on monkey sperm concentration can not be ascertained.

Responses to questions:

1) If adverse effects on semen parameters are seen in both the rat and a non-human primate, the findings may be relevant to humans. Unfortunately, this reviewer can not provide a more definitive assessment at this time due in large part to the limited pre-clinical and clinical information provided and to the inherent difficulty in predicting risk to human spermatogenesis based on pre-clinical findings.
2) Because of the intended chronic drug use of the drug in young men of reproductive age, studies of the effect of miglustat on human reproduction appear appropriate. However, the timing of conducting these studies is dependent on many variables, including among others, the risk/benefit ratio of miglustat in patients with Gaucher's disease, the actual pre-clinical findings in the monkey, the rate of conversion of the pro-drug SC 49483 to miglustat in the monkey, and the actual safety margin between expected human blood levels and toxic exposure levels and NOAEL exposure levels in the monkey. If human studies are to be conducted, they should evaluate semen analyses (to include sperm concentration, motility, and morphology) and the trials should be placebo controlled and powered for non-inferiority to placebo for a clinically meaningful endpoint (e.g. the percentage of patients with at least 50% decrease in sperm concentration). DRUDP would be pleased to assist in the design of such a trial.

/S/

George S. Benson, MD
Medical Officer
Division of Reproductive and Urologic Drugs

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

/s/

George Benson
5/13/02 03:19:50 PM
MEDICAL OFFICER

Mark S. Hirsch
5/13/02 05:03:07 PM
MEDICAL OFFICER
I concur.

Daniel A. Shames
5/13/02 05:11:04 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 11, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-348
Zavesca (Miglustat)
Actelion
Treatment of Type 1 Gaucher disease

SUBJECT: NDA review issues and recommended action

Background

The original NDA for Zavesca was received August 21, 2001. A "Not Approvable" letter was issued June 20, 2002 citing multiple deficiencies, both related to clinical efficacy and safety and chemistry, manufacturing, and controls. The letter stated that safety and efficacy in the target population and under conditions of use proposed had not been satisfactorily demonstrated. The initial review raised concerns over the general utility (and acceptability with regard to risk versus benefit) of this proposed new therapy in Gaucher disease. Specifically, while decreases in liver and spleen volume were demonstrated in patients naïve to therapy for their disease or off enzyme replacement therapy (ERT) for $\geq$ 3 months, the modest increases (up to 25%) in hemoglobin and platelet concentrations occurred late in the course of 2 years of treatment and the statistically significant mean changes from baseline were driven by a small number of responders. Furthermore, when patients stable on ERT were switched to Zavesca, platelet counts fell over the course of 1 year of treatment, suggesting some deterioration in the control of their glycogen storage disease.

With regard to safety and tolerability, up to 30% of patients on Zavesca experienced tremor, though it appeared to be reversible or self-limited; and up to 20% of patients experienced paresthesias and possible peripheral neuropathy suggested by abnormal electrodiagnositic test results. These findings were of particular concern given the finding of neurotoxicity in animals as well as biological plausibility based on the mechanism of action of the drug. It is important to note, however, that no formal baseline assessments of neurological status were made as part of the protocol.

The sponsor was asked to conduct further studies to address risk and benefit in Gaucher, with particular attention to possible neurotoxicity.

An end-of-review meeting took place on September 24, 2002 to discuss the sponsor's proposals to address the NA letter. In lieu of additional trials as first-line therapy or as a substitute for ERT

as maintenance therapy, the sponsor proposed that Zavesca be indicated only for those patients with mild-to-moderate disease who are unable to take ERT. The sponsor also proposed the submission of updated safety and efficacy data from ongoing studies.

Response to NA

Efficacy

The sponsor submitted a complete response to the NA letter on February 7, 2003. Dr. Pariser has conducted a thorough review of the submission. The information updating the efficacy and safety information are further summarized in Dr. Parks memo. As is shown in figure 2 of Dr. Parks' review, the small group of individuals from the trial in treatment naïve (or off ERT for ≥ 3 months) remaining on therapy for 3 years showed progressive mean decreases in liver and spleen size. Similarly, effects on hemoglobin and platelet counts, a measure of disease activity in the marrow space, were persistent, if not progressive over 3 years in the small cohort who remained on therapy for that period of time. Essentially, then, these data support the durability of efficacy in this population and support use in the treatment of mild to moderate patients with type I Gaucher who are unable to take ERT.

An additional subject requires review and comment. In patients originally treated with combination Zavesca and Cerezyme, in whom a small incremental liver volume decrease was the only apparent advantage over Cerezyme alone in a 6 month treatment protocol, discontinuation of Cerezyme (leaving patients on Zavesca alone) resulted in a decrease in platelet counts over the ensuing six months, suggesting deterioration in control of the disease. Given the established efficacy and safety of Cerezyme monotherapy, the lack of data to support dose (thus convenience and cost) sparing with combination therapy, unresolved concerns about the potential adverse effects of Zavesca, [redacted]

Safety

With regard to additional safety information and insight into the adverse effect profile of Zavesca, the sponsor did provide follow up of patients with tremor as well as data from surveys of Gaucher patients suggesting that at least some of the neurological abnormalities might be part and parcel of the disease itself. Dr. Pariser remains unconvinced that drug is without a potential role in at least some patients, and recommends inclusion of information on the observed neurological AEs in the label. I concur with inclusion of information in labeling but do feel more comfortable (though not completely so) with the neurological safety profile of Zavesca. Unfortunately, the clinical experience is limited; the observations are essentially uncontrolled, so definitive conclusions regarding causality are not possible.

The updated safety data are as follows, in brief: 1) The spectrum and frequency distribution of reported AEs has not changed substantially with further follow up of patients. Approximately 30% of patients experienced tremor and 15-20% experienced paresthesia or neuropathy. 2) Follow up of patients with tremor revealed resolution in virtually all cases and detailed work up of 3 patients was not supportive of a primary CNS or neurological cause that might plausibly implicate Zavesca as causative. 3) Weight loss noted in the initial review and attributed to the GI

side effects of Zavesca did not appear to be progressive over long-term follow up. Most patients lost weight relative to baseline but remained within 5-10% of baseline after 3 years. Regardless, this is a monitorable side effect. 4) While neurological symptoms as paresthesias may be a feature of Gaucher, the data are insufficient to conclude that Zavesca has no role in the exacerbation of symptoms or in their primary genesis in at least some patients.

[redacted]

Labeling

[redacted]

Biopharmaceutics

The issue of an interaction resulting in a marked increase in the clearance of Cerezyme in patients treated with Zavesca was raised by the biopharm reviewer. The sponsor has presented data and discussion that such a conclusion is not justified because of variable doses of Cerezyme used by the study participants. Dr. Chung points out that Cerezyme has dose-linear PK, so this should not matter. However, OCPB concedes that the data are not conclusive of a significant interaction. Regardless, combination therapy with Cerezyme and Zavesca is not indicated.

Pharmacology/Toxicology

The team wishes to re-emphasize the commitment by the sponsor to conduct a rat carcinogenicity study. The division would like to make this a formal phase 4 commitment.

Chemistry/ Microbiology

NDA #
Drug:
Proposal:
07/17/03

All deficiencies have been resolved.

DSI/Data Integrity
No audits were conducted

Financial disclosure
No new information has been submitted. Information is complete and satisfactory.

ODS/DMETS
Zavesca is acceptable to the division

Summary
Zavesca is modestly effective in the control of Gaucher disease, presumably acting via depletion of substrate for beta-glucocerebrosidase, the enzyme whose deficiency results in lysosomal accumulation of glucosylceremide and clinical disease in these patients. It is not a substitute for enzyme replacement therapy, as deterioration in disease control may be expected in this instance. Furthermore, there are insufficient data to support its use as add-on therapy for ERT, either to enhance control of the disease or to spare ERT dose. There are incompletely resolved safety concerns, notably tremor and paresthesias, arising from the clinical trial experience, that merit inclusion in labeling and to some extent guide the restriction of recommended use to those patients unable to take ERT. Tremor, if indeed caused by drug, appears self-limited. There is some information to suggest that paresthesias may be an aspect of the disease itself, though there are insufficient data to permit a conclusion that drug might not exacerbate these symptoms or constitute a primary cause in some patients with Gaucher.

Recommendation
Pending final labeling, this application may be approved.

NDA #
Drug:
Proposal:
07/17/03

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

/s/

David Orloff
7/17/03 12:06:29 PM
MEDICAL OFFICER

Robert Meyer
7/17/03 12:14:29 PM
MEDICAL OFFICER
I agree with this summary memo by Dr. Orloff
and it will stand as the summary memo
of record for this application.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: June 13, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-348
Zavesca (miglustat, OGT-918)
Oxford Glycosciences
Treatment of type 1 Gaucher disease

SUBJECT: NDA review issues and recommended action

Background

The enzymology and pathophysiology of Gaucher disease has been well summarized in the reviews by Drs. Pariser, Parks, and by Dr. Tremblay of HFD-120. Briefly, it is a lysosomal storage disease resulting from deficient or absent glucocerebrosidase, an enzyme responsible for the breakdown of glycosphingolipids. The accumulation of lipid-laden macrophages (Gaucher cells) in multiple tissues leads to the primary pathology associated with this recessively inherited metabolic disease. Patients with Type 1 Gaucher disease have residual enzymatic activity (~15% of normal), do not have neurological involvement with the disease, and in recent years have been successfully treated with enzyme replacement therapy (ERT) by intravenous injection. Successful therapy with involution of the infiltrates of Gaucher cells results in reductions in liver and spleen size (these organs can become markedly enlarged), restoration of bone marrow function with return toward normal of blood counts, predominantly red cells and platelets, reduction in bone pain, and presumed reduction in risk for the pathologic fractures due to Gaucher cortical bone lesions.

ERT is expensive and arguably a cumbersome therapy. The subject drug of this NDA, OGT-918, has been developed as a potential oral therapy for the disease. OGT-918 is one of a class of competitive inhibitors of glucosylceramide synthase, and thus has a hoped-for action in Gaucher disease to reduce amounts of glycosphingolipid (GSL) accumulating in macrophages, thus, so-called "substrate depletion." That is, by inhibiting the synthesis of GSLs, presumably not to the point of disruption of cellular function, there is less GSL delivered to macrophages for degradation, which is impaired, but not absent, in Type 1 Gaucher disease. Thus, residual endogenous enzyme (or perhaps a lower dose of ERT) may be sufficient to prevent lysosomal accumulation of GSLs. Certain related compounds have apparently been shown to be cytotoxic.

As is discussed in detail in the safety section of Dr. Pariser's review and in Dr. Tremblay's consult memo, this mechanistic approach to therapy of this disease carries theoretical risks related to depletion of GSLs, critical components of all cell membranes, as well as to

accumulation of ceramide, which is cytoxic through induction of apoptosis and thought by some to be responsible for the neurologic pathology in Farber disease, an inherited disease of impaired GSL synthesis. Finally, Dr. Tremblay notes that OGT-918 may indeed mimic ceramide and be directly neurotoxic, though this remains to be demonstrated. These theoretical drawbacks to the use of OGT-918 for substrate depletion in Gaucher disease lend plausibility to a role for the drug in the neurologic adverse events detected in the small clinical trial database of this NDA. In the context of at best marginal efficacy, the finding of significant adverse events plausibly related to drug therapy directs "not approvable" action on this NDA pending more thorough investigation of the safety and effectiveness of the drug and of this mechanistic approach to treatment of Gaucher disease.

The previous experience with this drug has been in HIV patients where it was investigated as antiretroviral therapy. Development was terminated due to the poor tolerability of the high doses of drug required to achieve presumed virucidal/static plasma concentrations of OGT-918. Adverse GI events predominated.

Clinical

In the studies of OGT-918 monotherapy in patients naïve to therapy for their Gaucher disease or off ERT for at least 3 months, which enrolled 46 patients total with follow up of up to 2 years, there were statistically significant reductions in liver and spleen size (up to ~25% reduction in spleen size at 2 years) with a dose-response suggesting greater efficacy at the higher dose (100 mg tid). There were likewise modest increases in hemoglobin and platelet concentrations (up to 25% increases in platelet counts) that reached statistical significance only at the 2-year timepoint with the overall results driven by a small number of late responders, as shown in Dr. Parks review on page 7. This may indicate that the bone marrow response is delayed relative to the more readily measurable response in terms of liver and spleen size. The clinical significance of these responses is not clear, insofar as the patients enrolled were clearly clinically stable off all therapy.

A single study compared OGT-918 monotherapy to ERT to the combination of the two for 6 months in 12 patients per arm. The study enrolled patients stable on ERT for at least 2 years. At the end of 6 months, all patients were switched to OGT-918 therapy. There were no clinically significant changes in liver or spleen volume either within treatment groups from baseline or between treatment groups from baseline to 6 months. With regard to hematologic indices, there were no statistically significant changes from baseline at 6 months, though platelet counts fell from baseline to the end of the 6-month OGT-918-only extension phase in all groups. On balance, the medical reviewers' conclusions that there are no data to support a switch to OGT-918 from ERT appear well founded.

Dr. Pariser has summarized the safety findings beginning on page 223 of her review.

The most common side effects of OGT therapy were gastrointestinal in nature, diarrhea in 90% of patients. Weight loss was also a common finding, occurring in 65% of patients.

The most troublesome safety findings in the studies of OGT-918 relate to the nervous system, and include tremor in up to 30% of patients (which appears reversible or self-limited, at least in

the relatively short trials to date), paresthesias in up to 20% of patients, possible neuropathy suggested by on-treatment electrodiagnostic testing in a subset of patients (without baseline studies), and memory loss reported in 6 patients. Drs. Tremblay and Pariser have discussed in detail this neurological safety "signal" and have concluded, as mentioned above, that a causal relationship to the drug and its mechanism of action is plausible, and that further, careful investigations of the preclinical neurotoxicity and of the clinical neurological safety are required.

Based on preclinical toxicological findings, Dr. Pariser recommends investigation of the possible reproductive toxicity of OGT-918 in males. In addition, potential bone marrow effects of OGT-918 are suggested by animal studies, and may necessitate assessment in the future of bone marrow effects in patients (e.g., by biopsy). Such effects may counterbalance any benefit of OGT-918 with regard to reduction of the marrow burden of Gaucher cells.

In sum, the drug has been shown to have marginal efficacy in a small number of treatment-naïve patients treated to date. The trial of OGT-918 as add-on or as a substitute for ERT suggest that patients may well deteriorate over time. Treatment with OGT-918 was associated with tremor in a substantial proportion of patients treated, with new paresthesias, and with abnormal findings on electrodiagnostic testing in a large percentage of those so studied. Further investigations of efficacy and safety are required which should include, in all patients, baseline and on-treatment assessments of neurologic (including cognitive) function, and measurements of glycosphingolipid and ceramide plasma/tissue levels if possible.

Labeling
No labeling has been negotiated at this time.

Biopharmaceutics
OCPB finds the biopharmaceutics portion of the application acceptable. A change in the dissolution specification is required and described in the action letter.

Pharmacology/Toxicology
Findings consistent with neurotoxicity were found in dog, rat, and monkey. These include clinical signs as well as histopathologic lesions. The 510 pharm-tox team as well as the 120 pharmacologist have recommended a more thorough histopathologic examination of the central and peripheral nervous system tissues from the completed preclinical studies as well as further studies in rodents. These comments are conveyed in the action letter.

Chemistry/ Microbiology
The application is approvable from the standpoint of ONDC, pending satisfactory response to certain deficiencies identified. These are listed in the letter.
A final recommendation on GMP compliance has not been made at this time (6-6-02). The following summarizes the status of the establishment inspections currently.

Galen Ltd (microbiological testing) is WITHHOLD (06/04/02) as they are in the process of moving.

[redacted] is PENDING a district office (DO) conclusion to the 05/08/02 inspection (no 483 indicated)

[redacted] is PENDING a DO conclusion to the 05/09/02 inspection (483 issued)

Lonza [redacted] is PENDING a DO conclusion to the 04/20/02 inspection (483 issued)
Lonza [redacted] is ACCEPTABLE after an inspection
Galen Group (DP mfg, package & label) is awaiting an inspection scheduled for 06/13/02

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by ONDC.

DSI/Data Integrity
There were no DSI audits performed, in part because of the difficulties and dangers of travel to Israel at this time.

Financial disclosure
The financial disclosure information is in order. And is reviewed in Dr. Pariser's review. The information provided does not raise concerns about data integrity or bias in the conduct of the clinical studies.

ODS/nomenclature
DMETS recommends against the name Zavesca because of the potential for "sound-alike, look-alike" confusion with marketed drugs. Zavesca will be used by a very small number of patients, under the care of specialists in a few academic medical centers, and will not be stocked routinely by pharmacies. I have no objection to the name at this time. The division will reconsult DMETs should we consider approval at a later date.

Recommendation
This application is "not approvable."

Further preclinical and clinical investigation of the potential neurological toxicity of the drug/mechanistic approach is required. An assessment of the potential neurotoxicity of the drug in the setting of further, controlled studies of efficacy and safety will permit an assessment of benefit versus risk of OGT-918 in the treatment of Type 1 Gaucher disease.

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

/s/

David Orloff
6/13/02 06:58:58 PM
MEDICAL OFFICER

Sandra L. Kweder
6/18/02 12:37:13 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 19, 2003

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Pat Madara, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Zavesca (miglustat) Oral capsules, 100 mg, NDA 21-348

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Zavesca (miglustat) Oral capsules, 100 mg, NDA 21-348. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

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

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

/s/

Jeanine Best
5/19/03 08:33:50 AM
CSO

Toni Piazza Hepp
5/19/03 02:35:00 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 15, 2002

TO: File; NDA 21-348 Zavesca (miglustat) Capsules

FROM: Samuel Wu, Regulatory Project Manager, HFD-510

SUBJECT: **DSI Inspection Status**

A DSI consult was requested on 13-SEP-2001 for the Israel study site, where the majority of the subjects were enrolled for studies OGT 918-001, -003, and -004. According to an e-mail dated 03-DEC-2001, from Dr. Joanne Rhoads, DSI, both Drs. Rhoads and Orloff decided that an inspection will not be conducted due to the political situation in that geographical area.

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

/s/

Samuel Wu
5/16/02 09:33:49 AM
CSO

ADRA Review #1 of Action Package for NDA 21-348, Zavesca (miglustat) Capsules, 100 mg

Reviewer: Lee Ripper, HFD-102
Date received in HFD-102: June 7, 2002
Date Review Completed: June 10, 2002

Date original NDA received: August 21, 2001
Action goal date: June 14, 2002
UF GOAL DATE: June 21, 2002 (10 mo)

Indication: Treatment of type 1 Gaucher disease

RPM: Samual Wu x7-6416/KJ
Action type: AE
Drug Classification: 1SV
505(b)(1) application

Patent Information: Submitted

Clinical Inspection Summary: Inspection of the Israel site, which had a majority of the patients enrolled, was requested. Subsequently, a decision was made not to inspect based on the political situation in the area.

OPDRA review of tradename: DMETS recommends against use of "Zavesca." DD review considers it to be acceptable.

DDMAC review of PI: Not done
Debarment statement: Acceptable
Financial disclosure information/review: Acceptable
Safety Update: COMIS shows SU submitted 2/22/02, received 2/25/02. MOR p. 169 says SU received 1/02 was incorporated into MOR.
EA: Categorical exclusion, page 89 of CMC review #1

1. "Miglustat" is not listed in the 2002 USAN dictionary. Emailed Dan Boring on 6/10/02 asking if name has been submitted to/approved by USAN Council.

2. EER: One inspection pending (scheduled for 6/13/02) (Galen, Group, Northern Ireland, finished dosage manufacturer), one inspection with withhold recommendation (6/4/02) [redacted]. Satisfactory inspection requirement needs to be added to letter.

3. See comments on letter.

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

/s/

Leah Ripper
8/15/02 11:17:55 AM
CSO
No action by FDR required.

ADRA Review #2 of Action Package for **NDA 21-348, Zavesca (miglustat) Capsules,** 100 mg

Reviewer: Lee Ripper, HFD-102
Date received in HFD-102: July 17, 2003, w/o action letter
Date Review Completed: July 18, 2003

Date original NDA received: August 21, 2001
Date resubmission received: February 12, 2003
Action goal date: July 31, 2003
UF GOAL DATE: August 12, 2003

Indication: Treatment of mild to moderate type 1 Gaucher disease

RPM: Pat Madara X 7-6380
Action type: AP
Drug Classification: 1SV
505(b)(1) application

Patent Information: Submitted

Clinical Inspection Summary: Inspection of the Israel site, which had a majority of the patients enrolled, was requested. Per 12/3/01 email, a decision was made not to inspect based on the political situation in the area.

Review of Tradename: DMETS recommends against use of "Zavesca." DD review #1 considers it to be acceptable. 7/18/03: No updated DMETS review in package; email out to Jerry Phillips. *DMETS review dated 7/23/03 added to action package. Email out asking if label and labeling comments had been considered.*
DDMAC Review of PI: No review in original action package or in resubmission action package.
DSRCS Review of PPI: 5/19/03
Debarment Statement: See #1 below.
Financial Disclosure Information/Review: Acceptable, no new clinical studies submitted
Safety Update: See MOR #2, page 9, safety cut-off date was 3/20/02. No SU after RS.
EA: Categorical exclusion, page 89 of CMC review #1

1. The applicant has changed since the NDA letter. Emailed PM 7/17/03 to request a debarment statement from the new applicant. *Copy received by email dated 7/22/03.*

2. I added the 2/13/03 ECAC Review from IND 60,197. Also, the DD NDA review which was signed by the OD and will stand as the summary memo of record. DOrloff needs to sign MParks TL review. *Done 7/21/03. Added to action package.*

3. Exclusivity Summary and Pediatric Page need signatures.

4. The 4/02 BPh review, page 3, says

"The results of Caco-2 cells monolayer experiment indicated activation of P-gp by miglustat. Transporters become increasingly important as a mechanism of drug interaction. In this regard, OCPB-DPEII recommends to provide confirmatory evidence that miglustat activate P-gp in Caco-2 cells using other substrates(s).

The 5/03 P/T review, page 35 says

"Reviewer agrees with sponsor's proposition to use the human PGP ATPase assay to demonstrate interaction of miglustat with P-glycoprotein because this assay provides a compound-independent measure of the concentration dependence of any interaction of a drug with P-glucoprotein, but we defer to biopharm to make this assessment."

"Human PGP ATPase assay is fine. Since the sponsor is doing it, Biopharm does not need to ask an additional PGP activation study using Caco2 cells."

5. Email to Marlene Haffner on 7/18/03 re: orphan designation:

"Oxford GlycoSciences has orphan designation for Zavesca (miglustat, 1,5-(Butylimino)-1,5 dideoxy, D-glucitol) for Tx of Gaucher disease and submitted the NDA on 8/16/01. They received an NA letter and subsequently transferred all rights to the NDA to Actelion Ltd. We expect to approve the NDA for Tx of mild to moderate type 1 Gaucher disease about July 31. How will approval as an orphan drug work in this case? Does Oxford need to transfer its orphan designation to Actelion in order for Actelion to receive 7 years of orphan exclusivity? Please advise as to documentation needed for Actelion to receive exclusivity."

Dr. Haffner replied that Jeff Fritsch would arrange for the transfer. *Pending as of 7/29/03.*

6. Comments on letter and labeling to Dr. Meyer 7/22/03. Comments on letter to RPM 7/28/03.

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

/s/

Leah Ripper
7/29/03 11:27:42 AM
CSO

Filing Meeting Minutes

Meeting Date: October 1, 2001 @ 4:00 pm

Location: PKLN 14B45

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

Applicant: Oxford GlycoSciences (UK) Ltd
New England Biomedical Research, Inc. – U.S. Agent

Attendees:

David Orloff, M.D., Division Director
Mary Parks, M.D., Medical Team Leader
Eric Duffy, Ph.D., Director, DNDCII
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader
John Colerangle, Ph.D., Pharmacology Reviewer
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Wei Qiu, Ph.D., Biopharmaceutics Reviewer
Todd Sahlroot, Ph.D., Biostatistics Team Leader
Lee-Ping Pian, Ph.D., Biostatistics Reviewer
Kati Johnson, R.Ph., Supervisory Project Manager
Samuel Wu, Pharm.D., Regulatory Project Manager

FILING DISCUSSION

- Clinical – No filing issues. Financial disclosure information was submitted.
- Pharmacology/Toxicology – No filing issues. Carcinogenicity study was waived as phase 4 commitment, per a phone conversation between Dr. Ron Steigerwalt and OGS on August 4, 1999. However, the firm needs to submit the protocol and dose-selection study reports prior to approval.
- Micro – Not applicable.
- Devices – Not applicable.
- Chemistry – No filing issues.
- Biopharmaceutics – No filing issues.
- Biostatistics – No filing issues.

- DSI – Not likely, according to Roy Blay, due to restrictions on international travel and the safety concerns at the clinical site in Israel.

REGULATORY SECTION

1. Priority or Standard Review schedule: Standard

2. Clinical Audit sites (list): N/A

3. Advisory Committee Meeting: No

4. Review Timelines/Review Goal Date (with labeling):

Consults Due (OPDRA):	April 1, 2002
Reviews Due from T/L:	May 3, 2002
To Division Director:	May 16, 2002
To Office Director:	May 32, 2002
10-Month Goal Date:	June 21, 2002

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

/s/

Samuel Wu
11/28/01 11:42:16 AM

NOV 2 8 2001

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-348

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

Sponsor: Oxford GlycoSciences, UK
US Agent: New England Biometidal Research
Bruce Manning, Preseident

Material Reviewed

Type of Submission: Paper

Submission Date: August 16, 2001

Receipt Date: August 21, 2001

Filing Date: October 19, 2001

User-fee Goal Date(s): June 21, 2002

Proposed Indication: Treatment of Type I Gaucher disease

Other Background Information:

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		
2. Form FDA 356h (original signature)	X		Signed by both U.S. agent and NDA sponsor
a. Establishment information	X		Behind cover letter and 356h form
b. Reference to DMF(s) & Other Applications	X		

3. User Fee FDA Form 3397	X		In volume 1.1 of 03.28.01 submission.
4. Patent information & certification	X		Signature needed from US Agent
5. Debarment certification (Note: Must have a definitive statement)	X		Signature needed from US Agent
6. Field Copy Certification	X		
7. Financial Disclosure	X		Not complete. Forms 3454 is needed for each investigator.
8. Comprehensive Index	X		
9. Pagination	X		
10. Summary Volume	X		
11. Review Volumes	X		
12. Labeling (PI, container, & carton labels)			
a. unannotated PI	X		
b. annotated PI	X		
c. immediate container		X	Will request marked-up copy
d. carton		X	Will request marked-up copy
e. patient package insert (PPI)	X		
f. foreign labeling (English translation)			N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		
2. Foreign Marketing History	X		
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		
b. Nonclinical Pharmacology/Toxicology	X		
c. Human Pharmacokinetic & Bioavailability	X		
d. Microbiology			N/A/
e. Clinical Data & Results of Statistical Analysis	X		
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		
5. Summary of Safety	X		
6. Summary of Efficacy	X		

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		

2. Controlled Clinical Studies			
a. Table of all studies	X		
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		
c. Optional overall summary & evaluation of data from controlled clinical studies	X		
3. Integrated Summary of Efficacy (ISE)			
4. Integrated Summary of Safety (ISS)			
5. Drug Abuse & Overdosage Information	X		
6. Integrated Summary of Benefits & Risks of the Drug	X		
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	X		

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Type I occurs only in adults.
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			

a. Proposed unannotated labeling in MS WORD		X	Will request it from the firm.
b. Stability data in SAS data set format (only if paper submission)		X	
c. Efficacy data in SAS data set format (only if paper submission)		X	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)			N/A
3. Exclusivity Statement (optional)		X	

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Name
Regulatory Project Manager

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

/s/

Samuel Wu
11/28/01 12:08:17 PM
CSO

Samuel Wu
11/28/01 12:13:17 PM
CSO

45 Day Meeting Checklist

NDA 21-348, VEVESCA (MIGLUSTAT)

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? No. Carcinogenicity studies have not been submitted: On August 4, 1999, Dr. Ron Steigerwalt told OGS that carcinogenicity studies would be requested as a Phase IV commitment.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?		X	The formulation to be marketed (OGT 918 + sodium starch glycollate, povidone, magnesium stearate, [redacted] and capsule [redacted] is different from the formulation used in the toxicology studies. Except for studies in the dog where OGT 918 in gelatin capsules were used, all other studies used a solution of OGT 918 in distilled or deionized water. The sponsor has not submitted any repeat studies using the marketed product. However, toxicity across species is similar regardless of drug formulation used.
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X X X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

/S/

Reviewing Pharmacologist

/S/

Supervisory Pharmacologist

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

/s/

John Colerangle
10/1/01 04:39:05 PM
PHARMACOLOGIST

Karen Davis-Bruno
10/2/01 10:02:49 AM
PHARMACOLOGIST
Filing

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

.TE RECEIVED: 4/1/03 and 5/22/03	DUE DATE: 7/25/03	ODS CONSULT #: 01-0214-1 and 01-0214-2

TO:

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

Pat Madara
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	**NDA SPONSOR:** Oxford GlycoSciences (UK) Ltd.
Zavesca (Miglustat Capsules) 100 mg **NDA #:** 21-348	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed labels and labeling medication error safety issues. DMETS also conducted a re-review of the proposed proprietary name "Zavesca".

COMMENDATIONS:

1. Although the Division of Metabolic and Endocrine Drug Products is allowing the approval of the name Zavesca, DMETS maintains its initial concerns with the use of the name and does not recommend it.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, "Zavesca", acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

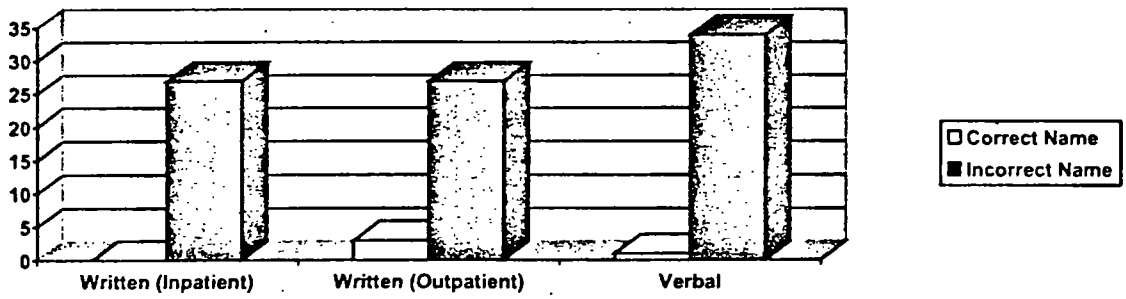
Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: Zavesca 100 mg po tid	*Outpatient Rx:* Zavesca Take 1, by mouth, three times a day. #60
Outpatient Rx: Zavesca 1 po tid #60	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Zavesca"	Incorrectly Interpreted
Written Inpatient	39	27 (69%)	0 (0%)	27 (100%)
Written Outpatient	34	30 (88%)	3 (10%)	27 (90%)
Verbal: Outpatient	40	35 (88%)	1 (3%)	34 (97%)
Total	113	92 (81%)	4 (4%)	88 (96%)



Among the written inpatient prescriptions, 27 (100%) out of 27 respondents interpreted "Zavesca" incorrectly. Interpretations included

Among the written outpatient prescriptions, 27 (90%) out of 30 respondents interpreted "Zavesca" incorrectly. Interpretations included *and Zovira.*

Among the verbal outpatient prescriptions, 34 (97%) out of 35 respondents interpreted "Zavesca" incorrectly. Interpretations included One respondent commented that "Zavesca" sounded similar to *Evista.* Another respondent made a second interpretation of "Zavesca" as *Evista.*

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 23, 2003

NDA NUMBER: 21-348

NAME OF DRUG: Zavesca (Miglustat Capsules) 100 mg

NDA HOLDER: Oxford GlycoSciences (UK) Ltd.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-150) for a review of the sponsor's revised labels and labeling. DMETS also conducted a re-review of the proposed proprietary name "Zavesca". The name "Zavesca" was originally found unacceptable by DMETS on April 1, 2002 (Consult # 01-0214) due to the look sound alike similarities between "Zavesca" and *Zyprexa* as well as "Zavesca" and *Evista*. However, the Division has decided to allow the sponsor the use of the proprietary name, "Zavesca". DMETS also provided comments on the draft labels and labeling in the same consult. Additionally, on June 24, 2003, DMETS participated in a Pre-approval Safety Conference (PSC) with the Division.

PRODUCT INFORMATION

"Zavesca" is the proposed proprietary name for miglustat capsules. It is an inhibitor of the enzyme glucosylceramide synthase, a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycolipids. It also inhibits α-glucosidase I and was found to possess anti-human immunodeficiency virus (HIV-1) activity *in vitro*. "Zavesca" is indicated for the oral treatment of type 1 Gaucher disease. This drug product will be available as a 100 mg capsule. The recommended starting dose is 100 mg three times a day for treatment-naïve patients, patients switching from enzyme replacement therapy (ERT), and as an add-on therapy in patients currently receiving ERT. The maximum dose is 200 mg three times a day.

II. RISK ASSESSMENT:

DMETS re-reviewed the proposed proprietary name, "Zavesca", to identify any additional safety concerns since the initial review. The Expert Panel identified *Celexa* as a potential sound-alike name to "Zavesca".

Celexa sounds similar to "Zavesca". It is the proprietary name for citalopram hydrobromide and is indicated for the treatment of major depression. The recommended initial dose is 20 mg once a day. It can be increased to 40 mg/day. *Celexa* is available as a 10 mg, 20 mg, and 40 mg tablet as well as a 2 mg/mL oral solution. The "ce" and "xa" in *Celexa* sounds similar to the "za" and "sca" in "Zavesca", respectively. However, the "le" and "ve" may differentiate the two proprietary names from each other.

Both products are oral dosage forms (capsule vs. tablet). *Celexa* is administered once a day while "Zavesca" is administered three times a day. However, the difference in dosage directions can be negated if the prescriber states the directions as "use as directed". Even though *Celexa* and "Zavesca" are available in different strengths (10 mg, 20 mg, 40 mg, and 2 mg/mL vs. 100 mg), they share numerical similarities. Although Zavesca is considered an orphan drug, it will be dispensed in a retail and/or hospital setting. A pharmacist who is familiar with the name "Zavesca" may misinterpret a verbal prescription of *Celexa* for "Zavesca" or vice versa. A pharmacist who is unfamiliar with the name "Zavesca" may misinterpret a "Zavesca" prescription as *Celexa*. If a patient mistakenly received "Zavesca" instead of *Celexa*, then the patient's depression would not be adequately treated. Also, the patient may experience unnecessary side effects such as diarrhea and weight loss. If a patient mistakenly received *Celexa* instead of "Zavesca", then the patient's Type I Gaucher disease would not be treated. Also, the patient may experience unnecessary side effects such as hyponatremia, tachycardia, paresthesia, and nausea. The similarities between *Celexa* and "Zavesca" could potentially increase the risk of medication errors occurring between these two drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft labels and labeling of "Zavesca", DMETS has focussed on safety issues relating to possible medication errors, and has identified several areas of possible improvement, which might minimize potential user error.

A. BLISTER LABEL

1. Increase the prominence of the product strength.

2. The HOW SUPPLIED section of the package insert states the product will be available in blisters containing— capsules. However, from the draft provided, the label information only appears on 18 individual capsule blisters rather than — Revise accordingly.

3. —

B. CARTON LABELING

1. Increase the prominence of the proprietary name, "Zavesca", and the strength, "100 mg". This can be done by increasing their font size.

2. The blue design/graphic logo a "ZA" covers more than half of the principal display panel of the carton. The design detracts attention from the name of the product, "Zavesca". The logo should be decreased in size or deleted from the principal display panel.

3.

4. The statement "This pack contains 90 Zavesca™ 100 mg capsules for oral use" is inconsistent with the HOW SUPPLIED section where it states that the pack contains — capsules. Revise accordingly.

5. The statement "Caution: Federal law prohibits dispensing without prescription" should be revised to state "Rx Only".

6. [redacted]

C. INSERT LABELING (Package Insert and Patient Information Insert)

1. [redacted]

2 [redacted]

IV. RECOMMENDATIONS:

A. Although the Division of Metabolic and Endocrine Drug Products is allowing the approval of the name Zavesca, DMETS maintains its initial concerns with the use of the name and does not recommend it.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name, "Zavesca", acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Alina Mahmud
7/23/03 08:33:19 AM
PHARMACIST

Carol Holquist
7/23/03 09:29:18 AM
PHARMACIST

Jerry Phillips
7/23/03 10:43:22 AM
DIRECTOR

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

ATE RECEIVED: 10/15/01	DUE DATE: 4/1/02	ODS CONSULT #: 01-0214

TO:

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

Samuel Wu
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	**NDA SPONSOR:** Oxford GlycoSciences (UK) Ltd.
Zavesca (Miglustat Capsules) 100 mg **NDA #:** 21-348	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Zavesca" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS does not recommend the use of the proprietary name, "Zavesca". In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 13, 2002

NDA NUMBER: 21-348

NAME OF DRUG: Zavesca (Miglustat Capsules) 100 mg

NDA HOLDER: Oxford GlycoSciences (UK) Ltd.

****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename "Zavesca", regarding potential name confusion with other proprietary/established drug names.

PRODUCT INFORMATION

"Zavesca" is the proposed proprietary name for miglustat capsules. It is an inhibitor of the enzyme glucosylceramide synthase, a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycolipids. It also inhibits α-glucosidase I and was found to possess anti-human immunodeficiency virus (HIV-1) activity *in vitro*. "Zavesca" is indicated for the oral treatment of type 1 Gaucher disease. This drug product will be available as a 100 mg capsule. The recommended starting dose is 100 mg three times a day for treatment-naïve patients, patients switching from enzyme replacement therapy (ERT), and as an add-on therapy in patients currently receiving ERT. The maximum dose was 200 mg three times a day.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Zavesca" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the data provided by Thomson & Thomson's

[1] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K, (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support (DMETS) name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov.

SAEGIS™ Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Zavesca". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel had concerns with the pending name [redacted] and sound-alike concerns with *Evista*. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

2. DDMAC does not have a problem with the proposed proprietary name "Zavesca".

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Zavesca	Miglustat (Rx) Capsule: 100 mg	1 capsule 3 times a day.	
Evista	Raloxifene Hydrochloride (Rx) Tablet: 60 mg	1 tablet daily.	*SA
[redacted]			

*Frequently used, not all-inclusive.
**SA (sound-alike). LA (look-alike)

3. Further research revealed other proprietary names that were of concern. Those name are listed in Table 2.

[5] WWW location http://www.thomson-thomson.com.

Table 2

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Zavesca	Miglustat (Rx) Capsule: 100 mg	1 capsule 3 times a day.	
Zovirax	Acyclovir (Rx) Tablet: 400 mg and 800 mg Capsule: 200 mg Suspension: 200 mg/5 mL Injection: EQ 500 mg base/vial and EQ 1 g base/vial Ointment: 5%	Capsules, Tablets, and Suspension *Acute Treatment of Herpes Zoster*: 300 mg every 4 hours orally, five times daily for 7-10 days *Genital Herpes*: 200 mg every 4 hours, five times daily for 10 days *Chronic Suppressive Therapy for Recurrent Disease*: 400 mg twice daily for up to 12 months. *Chicken Pox*: (Children 2 years or older) 20 mg/kg per dose orally 4 times a day for 5 days. (Adults and Children over 40 kg) 800 mg 4 times a day for 5 days. Injection *Herpes Simplex Infection*: 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days. *Herpes Simplex*: 10 mg/kg infused at a constant rate over at least 1 hour, every 8 hours for 10 days. *Varicella Zoster*: 10 mg/kg at a constant rate over 1 hour every 8 hours for 7 days. Ointment Apply over lesions every 3 hours, 6 times a day for 7 days	*LA

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Zavesca	Miglustat (Rx) Capsule: 100 mg	1 capsule 3 times a day.	
Zyprexa	Olanzapine (Rx) Tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg Tablet, orally disintegrating: 5 mg, 10 mg, 15 mg, and 20 mg	*Schizophrenia* Initial dose: 5-10 mg once daily. *Bipolar mania* Initial dose: 10-15 mg once daily.	*SA
Survanta	Beractant (Rx) Suspension: 25 mg/mL	100 mg of phospholipids/kg birth weight. Four doses can be administered in the first 48 hours of life; give doses no more frequently than every 6 hours. Intratracheal administration only.	*SA

*Frequently used, not all-inclusive.
**SA (sound-alike), LA (look-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by DMETS and involved a total of 113 health care professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of "Zavesca" with other drug names due to the similarity in visual appearance with handwritten prescriptions and verbal pronunciation of the name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for "Zavesca" (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Zavesca", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names include *Zovirax, Zyprexa, Survanta,* and *Evista.* Also of concern is [redacted] which is under review in the Agency. **(Not FOI Releasable)**

Zovirax is the proprietary name for acyclovir and is indicated for the treatment of herpes zoster infections, genital herpes, and chickenpox. It is available as a 400 mg and 800 mg tablet, 200 mg capsule, 200 mg/5 mL suspension, 5% ointiment, and EQ 500 mg base/vial and EQ 1 g base/vial injection. The dose and dosing interval of *Zovirax* depends on the disease being treated. *Zovirax* looks somewhat similar to "Zavesca". The "zov" in *Zovirax* can resemble "zav" in "Zavesca" since the scripted "o" can look like a scripted "a". The "ir" in *Zovirax* can also resemble the "es" in "Zavesca" if the "i" was not dotted. The "c" can look like an "a" if the "c" was closed off by the second letter. In the written outpatient portion of the DMETS study, one respondent interpreted "Zavesca" as *Zovira,* which is similar in spelling to *Zovirax.* However, even though both drug products are available in an oral formulation (tablet, capsule, and suspension vs. capsule), there are no overlapping strengths and no overlapping directions of use. These differences would decrease the potential risk of a medication error occurring between these two drug products.

Zyprexa is the proprietary name for olanzapine and is indicated for the treatment of schizophrenia and short-term treatment of acute manic episodes associated with Bipolar I disorder. The usual recommended dose, depending on the disease, is 5-15 mg once a day. It is available as a 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablet. It is also available as a 5 mg, 10 mg, 15 mg, and 20 mg orally disintegrating tablet. *Zyprexa* sounds similar to "Zavesca" since "zy" in *Zyprexa* and "za" in "Zavesca" sounds similar. "Exa" in *Zyprexa* and "esca" in "Zavesca" also sounds similar. Even though both products do not have the same dosage form (tablet vs. capsule), both products have the same route of administration (oral). The "10 mg" of *Zyprexa* can sometimes by misinterpreted as "100 mg" if the "10 mg" was written as "10.0 mg" and vice versa when "100 mg" is mistaken as "10 mg" due to a stray mark. Even though there are no overlapping strengths, a prescription written as "*Zyprexa* 10.0 mg" or "Zavesca 100 mg" with a stray mark in the "100 mg" may be verbally communicated as "*Zyprexa* 100 mg" or "Zavesca 10.0 mg". Since *Zyprexa* and "Zavesca" sound alike, the possible confusion between "10.0 mg" and "100 mg" and vice versa would increase the potential risk of a medication error occurring between these two drug products. The directions of use are different; however, a prescriber may give the directions as "use as directed". If the patient mistakenly receives *Zyprexa* instead of "Zavesca", then the patient's Gaucher disease would not be treated. Also, the patient may experience unnecessary adverse effects of *Zyprexa* such as headaches, somnolence, insomnia, agitation, hostility, dystonic reactions, Parkinsonian events, and abdominal pain. If the patient mistakenly receives "Zavesca" instead of *Zyprexa,* then the patient's schizophrenia would not be managed. Also, the patient would be exposed to unnecessary side effects of "Zavesca" such as diarrhea, flatulence, abdominal pain, nausea, weight loss, headache, influenza-like symptoms, and tremors.

Survanta is the proprietary name for beractant and is indicated for the prevention and treatment ("rescue") of RDS (hyaline membrane disease) in premature infants. It is only available as a 25 mg/mL suspension. Even though *Survanta* sounds somewhat similar to "Zavesca", the dosage form (suspension vs. oral) and route of administration (intratracheal vs. oral) would differentiate the two drug products. Also, *Survanta* is limited to the premature infant population (specific and

small in size) while "Zavesca" has not been used in patients under 18 years. These differences would decrease the potential risk of a medication error between the two drug products.

Evista is the proprietary name for raloxifene hydrochloride and is indicated for the prevention and treatment of osteoporosis in postmenopausal women. It is available as a 60 mg tablet, and the recommended dosage of *Evista* is 1 tablet (60 mg) once a day. Even though *Evista* does not look like "Zavesca", it sounds similar to "Zavesca". In the verbal portion of the DMETS study, some respondents interpreted "Zavesca" as . These different interpretations have a similar pronunciation with *Evista*. The "sca" in "Zavesca" can sound like "sta" in *Evista*. The majority of the respondents (33 out of 35 or 94% of the respondents) in the verbal portion of the study did not hear the "z" sound in the beginning of "Zavesca". One respondent commented that "Zavesca" was similar to *Evista* while another respondent made a second interpretation as *Evista*. Even though *Evista* is available in tablet form and "Zavesca" is available in capsule form, they both have the same route of administration (oral). There is no overlap in strength; however, they are only available in one strength. When a prescriber communicates an *Evista* or a "Zavesca" prescription verbally, he or she may not indicate a strength since there is no other strength for *Evista* and "Zavesca" other than 60 mg and 100 mg, respectively. The directions of use are different (once a day vs. three times a day), but a prescriber may communicate the directions as "use as directed". If "Zavesca" was mistakenly given instead of *Evista*, then the patient's osteoporosis would not be treated. Also, the patient would be exposed to unnecessary side effects of "Zavesca" such as diarrhea, flatulence, abdominal pain, nausea, weight loss, headache, influenza-like symptoms, and tremors. If the patient mistakenly receives *Evista* instead of "Zavesca", then the patient's Gaucher disease would not be treated. The patient would also be exposed to unnecessary side effects of *Evista* such as hot flashes and leg cramps in women.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. BLISTER LABEL (100 mg)

The expiration date should be on each unit dose tablet with the lot number.

B. BLISTER PACK CARTON (100 mg:

[redacted]

C. CARTON LABELING (100 mg: [redacted]

1. The statement "Caution: Federal law prohibits dispensing without prescription" should be revised to state "Rx only".

[redacted]

IV. COMMENTS TO THE SPONSOR:

In reviewing the proprietary name "Zavesca", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names include *Zovirax, Zyprexa, Survanta,* and *Evista.*

Zovirax is the proprietary name for acyclovir and is indicated for the treatment of herpes zoster infections, genital herpes, and chickenpox. It is available as a 400 mg and 800 mg tablet, 200 mg capsule, 200 mg/5 mL suspension, 5% ointiment, and EQ 500 mg base/vial and EQ 1 g base/vial injection. The dose and dosing interval of *Zovirax* depends on the disease being treated. *Zovirax* looks somewhat similar to "Zavesca". The "zov" in *Zovirax* can resemble "zav" in "Zavesca" since the scripted "o" can look like a scripted "a". The "ir" in *Zovirax* can also resemble the "es" in "Zavesca" if the "i" was not dotted. The "c" can look like an "a" if the "c" was closed off by the second letter. In the written outpatient portion of the DMETS study, one respondent interpreted "Zavesca" as *Zovira*, which is similar in spelling as *Zovirax.* However, even though both drug products are available in an oral formulation (tablet, capsule, and suspension vs. capsule), there are no overlapping strengths and no overlapping directions of use. These differences would decrease the potential risk of a medication error occurring between these two drug products.

Zyprexa is the proprietary name for olanzapine and is indicated for the treatment of schizophrenia and short-term treatment of acute manic episodes associated with Bipolar I disorder. The usual recommended dose, depending on the disease, is 5-15 mg once a day. It is available as a 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablet. It is also available as a 5 mg, 10 mg, 15 mg, and 20 mg orally disintegrating tablet. *Zyprexa* sounds similar to "Zavesca" since "zy" in *Zyprexa* and "za" in "Zavesca" sounds similar. "Exa" in *Zyprexa* and "esca" in "Zavesca" also sounds similar. Even though both products do not have the same dosage form (tablet vs. capsule), both products have the same route of administration (oral). The "10 mg" of *Zyprexa* can sometimes by misinterpreted as "100 mg" if the "10 mg" was written as "10.0 mg" and vice versa when "100 mg" is mistaken as "10 mg" due to a stray mark. Even though there are no overlapping strengths, a prescription written as "*Zyprexa* 10.0 mg" or "Zavesca 100 mg" with a stray mark in the "100 mg" may be verbally communicated as "*Zyprexa* 100 mg" or "Zavesca 10.0 mg". Since *Zyprexa* and "Zavesca" sound alike, the possible confusion between "10.0 mg" and "100 mg" and vice versa would increase the potential risk of a medication error occurring between these two drug products. The directions of use are different; however, a prescriber may give the

directions as "use as directed". If the patient mistakenly receives *Zyprexa* instead of "Zavesca", then the patient's Gaucher disease would not be treated. Also, the patient may experience unnecessary adverse effects of *Zyprexa* such as headaches, somnolence, insomnia, agitation, hostility, dystonic reactions, Parkinsonian events, and abdominal pain. If the patient mistakenly receives "Zavesca" instead of *Zyprexa*, then the patient's schizophrenia would not be managed. Also, the patient would be exposed to unnecessary side effects of "Zavesca" such as diarrhea, flatulence, abdominal pain, nausea, weight loss, headache, influenza-like symptoms, and tremors.

Survanta is the proprietary name for beractant and is indicated for the prevention and treatment ("rescue") of RDS (hyaline membrane disease) in premature infants. It is only available as a 25 mg/mL suspension. Even though *Survanta* sounds somewhat similar to "Zavesca", the dosage form (suspension vs. oral) and route of administration (intratracheal vs. oral) would differentiate the two drug products. Also, *Survanta* is limited to the premature infant population (specific and small in size) while "Zavesca" has not been used in patients under 18 years. These differences would decrease the potential risk of a medication error between the two drug products.

Evista is the proprietary name for raloxifene hydrochloride and is indicated for the prevention and treatment of osteoporosis in postmenopausal women. It is available as a 60 mg tablet, and the recommended dosage of *Evista* is 1 tablet (60 mg) once a day. Even though *Evista* does not look like "Zavesca", it sounds similar to "Zavesca". In the verbal portion of the DMETS study, some respondents interpreted "Zavesca" as [redacted] These different interpretations are similar pronunciation with *Evista*. The "sca" in "Zavesca" can sound like "sta" in *Evista*. The majority of the respondents (33 out of 35 or 94% of the respondents) in the verbal portion of the study did not hear the "z" sound in the beginning of "Zavesca". One respondent commented that "Zavesca" was similar to *Evista* while another respondent made a second interpretation as *Evista*. Even though *Evista* is available in tablet form and "Zavesca" is available in capsule form, they both have the same route of administration (oral). There is no overlap in strength; however, they are only available in one strength. When a prescriber communicates an *Evista* or a "Zavesca" prescription verbally, he or she may not indicate a strength since there is no other strength for *Evista* and "Zavesca" other than 60 mg and 100 mg, respectively. The directions of use are different (once a day vs. three times a day), but a prescriber may communicate the directions as "use as directed". If "Zavesca" was mistakenly given instead of *Evista*, then the patient's osteoporosis would not be treated. Also, the patient would be exposed to unnecessary side effects of "Zavesca" such as diarrhea, flatulence, abdominal pain, nausea, weight loss, headache, influenza-like symptoms, and tremors. If the patient mistakenly receives *Evista* instead of "Zavesca", then the patient's Gaucher disease would not be treated. The patient would also be exposed to unnecessary side effects of *Evista* such as hot flashes and leg cramps in women.

RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name "Zavesca".

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3231.

/S/

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Jennifer Fan
3/29/02 04:18:28 PM
PHARMACIST

Carol Holquist
4/1/02 07:50:40 AM
PHARMACIST

Requested in AE Letter

COMIS shows SU Submission
dated 2/22/02 rec'd 2/25/02

MOR p. 169 says SU rec'd 1/02
incorporated into safety review

MOR
pg 9
6/16/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-348	Efficacy Supplement Type SE-	Supplement Number	
Drug: Zavesca (miglustat)		Applicant:Actelion Pharmaceuticals US, Inc.	
RPM: Patricia Madara		HFD-510	Phone # 301-827-6416
Application Type: (X)505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(XX) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	ORPHAN
❖ User Fee Goal Dates	8·13·03
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) (X) 21 CFR 314.520 (restricted distribution) (X) Fast Track (X) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	( ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) N/A ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	pending
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	July 9, 2003; June 10, 2002

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA, June 20, 2002
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	✓
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC review 5/19/03 DMETS review 4/01/02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	✓
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	XX
• Documentation of discussions and/or agreements relating to post-marketing commitments	pending
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	XX
❖ Memoranda and Telecons	XX
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	January 9, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	June 24, 2003
• Other End of Review Meeting	September 24, 2002
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	~~pending~~
❖ Clinical review(s) *(indicate date for each review)*	May 2, 2002; June 16, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Page 9 of MOR of 6/16/03
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	XX
❖ Statistical review(s) *(indicate date for each review)*	April 27, 2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	May 6, 2002; June 17, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	N/A
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	5/01/02; 4/30/03; 6/20/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Pg 89 CMC Review
• Review & FONSI *(indicate date of review)*	↓
• Review & Environmental Impact Statement *(indicate date of each review)*	↓
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 5/28/03 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5/6/02; 5/10/02; 6/16/02 INDs: — 60,197; —
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	XX

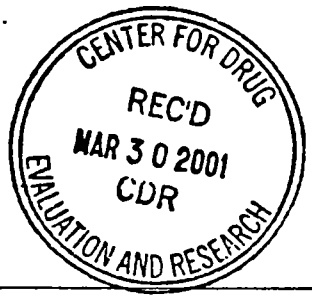
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S AND ADDRESS

Oxford GlycoSciences (UK) Ltd
The Forum
86 Milton Park
Abingdon
Oxon
OX14 4RY
United Kingdom



2. TELEPHONE NUMBER *(Include Area Code)*
(+44 1235) 208000

3. PRODUCT NAME
VEVESCA (miglustat)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
N021-348

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory.)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REEQUIRE A FEE *(See item 7, reverse side before checking box.)*

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHROIZED COMPANY REPRESENTATIVE	TITLE	DATE
R M IBBOTSON	MR R M IBBOTSON REGULATORY AFFAIRS MANAGER OXFORD GLYCOSCIENCES	28th MARCH 2001

FORM FDA 3397 (5/98)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF