CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

CHEMISTRY REVIEW(S)

NDA 21-348

Zavesca™ (miglustat) 100 mg capsules

Actelion Pharmaceuticals U.S., Inc.

Mike Adams
Division of Metabolism and Endocrine Drug Products, HFD-510

NDA 21-348

Zevesca (miglustat) 100 mg capsules

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Actelion Pharmaceuticals, US, Inc.
601 Gateway Blvd.
South San Francisco, CA 944080

Former sponsor:
Oxford Glycosciences

Indication: Treatment of Type 1 Gaucher Disease

Presentation: Blisters

EER Status: Final overall recommendation from Compliance:
acceptable 28-MAY-2003

Consults: DMETS – ZAVESCA unacceptable 1-APR-2002, but was found to be acceptable by the 510 DD. Second review 23-JUL-2003 maintains the recommedation against use of Zavesca. Additional comments are discussed below – see labeling section.
DDMAC – ZAVESCA acceptable from a promotional perspective.
USAN – miglustat is pending (miglustat is INN)
Statistics – none
EA – no consult - waiver requested – granted
OCPB – dissolution is acceptable

Phase IV Commitments: none

The original NDA was received 21-AUG-2001

The **drug substance** is manufactured by: Lonza, Visp, SZ - acceptable GMPs 7-JUN-2002.

Structural characterization of the drug substance, and chirality determination was satisfactory. The manufacturing process and controls were found to be acceptable. Satisfactory work was performed to characterize the impurity profile and the impurity tests and acceptance criteria were found to be acceptable.

Other specifications were found acceptable. Based upon microbial testing of 11 batches, routine testing will be dropped. Residual solvent testing (IPA, EtOH) and acceptance criteria have been revised and are acceptable. [redacted] is requested, and is supported by data from 5 batches. The stability testing protocol is considered adequate

Conclusion
Drug substance information is acceptable.

The **drug product** is an immediate release 100 mg capsule.

Manufacturer:

Galen Group
Craigavon, IR

The manufacturing method is [redacted] capsule filling process. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable. The dissolution test and acceptance criteria were found acceptable by OCPB – see review dated 26-APR-2002. [redacted] The stability testing protocol is considered adequate. The established name Miglustat is pend designation from USAN. Miglustat has been adopted by INN. Compliance recommendation is acceptable 28-MAY-2003.

All associated DMFs are acceptable.

Labeling is satisfactory with the exception of the storage statement and the absence of the Rx Only statement on the blister and carton label. Additional revisions as recommended in the DMETS review dated 23-JUL-2003 should be conveyed in the AP letter.

It is recommended that the storage statement be revised to:

Store at 20° to 25°C (68 to 77°F). Brief exposure to 15° to 30°C (59° to 86°F) permitted (see USP Controlled Room Temperature).

The blister and carton label should be revised to delete the Caution statement and replace it with "Rx Only". [redacted]

The comment re the small circular design in front of the trade name – the design can remain.

Deficiencies
Minor CMC deficiencies have been resolved from review #2.

Labeling should be revised as follows:

It is recommended that the storage statement be revised to:

Store at 20° to 25°C (68 to 77°F). Brief exposure to 15° to 30°C (59° to 86°F) permitted (see USP Controlled Room Temperature).

Overall Conclusion
From a CMC perspective the application is recommended for approval with the recommendation to revise the storage statement and to complete the USAN process.

Eric P Duffy, PhD

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/s/

Eric Duffy
7/30/03 03:41:50 PM
CHEMIST

NDA 21-348

Zavesca™ (miglustat) 100 mg capsules

Actelion Pharmaceuticals U.S., Inc.

Mike Adams
Division of Metabolism and Endocrine Drug Products, HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-348

2. REVIEW #3

3. REVIEW DATE: 20 Jun 2003

4. REVIEWER: Mike Adams

5. PREVIOUS DOCUMENTS:

Document	Document Date
BI Amendment	27 May 2003
BL Amendment	28 May 2003
BC Amendment	10 Jun 2003

6. SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Document Date
Original Submission	16 Aug 2001
NDA Filing	21 Aug 2001
BL Amendment	02 Oct 2001
CMC Review #1	22 Apr 2002
NA Letter	20 Jun 2002
Correspondence	31 Mar 2002
BZ Amendment	07 Feb 2003
CMC Review #2	29 Apr 2003
IR Letter	29 May 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Actelion Pharmaceuticals U.S., Inc.
Address	56 Huckleberry Lane North Andover, MA 01845
U.S. Representative:	Tom Lategan, Ph.D.
Telephone:	978-682-3999
Fax:	309-216-7012

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zavesca™
b) Non-Proprietary Name (USAN): miglustat 100 mg capsules
c) Code Name/# (ONDC only): OGT 918
d) Chem. Type/Submission Priority

- Chem. Type: NME
- Submission Priority: 1V

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: treatment of type 1 Gaucher Disease

11. DOSAGE FORM: ——— HG capsule

12. STRENGTH/POTENCY: 100 mg

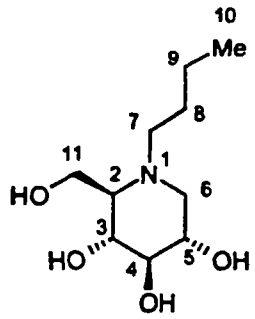
13. ROUTE OF ADMINISTRATION: oral

14. DISPENSED: Rx

15. SPOTS: XX Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula:	$C_{10}H_{21}NO_4$
Molecular Weight:	219.28
Chemical Abstract Index:	[2R,3R,4R,5S]-1-butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol
Chemical name:	1,5-(butylimino)-1,5-dideoxy-D-glucitol or N-butyldeoxynojirimycin (*N*B-DNJ)
Code Names:	OGT 918 (Oxford GlycoSciences) SC-48334 (G.D. Searle)
CAS number:	72599-27-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Type	Holder	Item Referenced	Code[1]	Status[2]	Review Date	Comment
—	III	———	———	4	N/A	—	—

		Europe	Blister film				
—	III	—	—	4	N/A	—	—

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application#	Description
IND	—	
IND	60,197	Treatment of Gaucher Disease (OGT 918)
IND		
IND		

18. STATUS:

Consults/CMC Related Reviews	Recommendations	Date	Reviewer
Biometrics	N/A		
EES	Acceptable	05/28/03	OC
Pharm/Tox	N/A		
Biopharm	Accepted with comments	06/05/03 telcon	S.Chung
DMETS/ODS	Trade name accepted by Clinical Division Director	06/05/02 memo	D.Orloff
Methods Validation	To be sent	—	—
OPDRA	N/A		
EA	Excluded	04/22/02	M.Adams
Microbiology	N/A		

The Chemistry Review for NDA 21-348

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application should be APPROVED.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no proposed phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Zavesca™ (miglustat) 100 mg capsule is an immediate release oral product intended for an orphan indication. The pre-clinical studies by G.D. Searle and clinical studies by Oxford Glycosciences were performed on the same drug formulation. NDA ownership was transferred to Actelion Pharmaceuticals U.S., Inc. in Nov-2002.

DRUG SUBSTANCE: Miglustat, [2R,3R,4R,5S]-1-butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol, is a new molecular entity manufactured by Lonza Ltd (Visp, SZ). The API is essentially a re-organized, N-substituted glucose molecule synthesized by .

Lonza IP/QC specifications, synthesis method, and reprocessing procedure have been described in detail. The proposed release specifications address molecular and configuration identity; molecular assay; and purity for metals, chiral process impurities (and residual solvents Due to the high water solubility, particle size distribution is not addressed. The proposed regulatory methods have been adequately validated. The impurity and degradation profiles have been investigated at length. Oxidative degradation is to be studied further and the results submitted at an unspecified time after NDA approval. Reference standards for API and the identified process impurities have been developed and characterized. Based on data from ICH stability studies on 5 lots, the NDA has established that API is stable for 24 months at room temperature when stored

DRUG PRODUCT: The proposed drug product is manufactured by Galen Ltd (Craigavon, Northern Ireland). The dosage form is 100 mg API hard gelatin capsule. Excipients are USP/NF grade based on Galen's acceptance specifications. The manufacturing process and IP/process controls are described in detail. There is no provision for reprocessing. The proposed release specifications address molecular identity, molecular assay USP content

uniformity/EP uniformity of mass, USP dissolution —— /EP disintegration, residual moisture (—— and process impurities & degradants (———— The proposed regulatory methods have been adequately validated. The market package is stated to be child resistant/senior friendly and consists of an opaque, 3x7 count ———— blister package in a cardboard carton. Ten months into their stability studies the firm was forced to change their blister pack to use equivalent blister and lidding films. As a result, the pivotal stability studies are being repeated using the first 3 commercial capsule lots in the newly proposed blister package at ICH conditions. The repeat stability study contains 12-month data.

temperature (package insert) or at 20-24°C (patient information leaflet) ——— The claim is supported by the repeat study (three 100 mg capsule lots at ICH conditions in the proposed commercial blister package); the pivotal study (three 100 mg capsule lots at ICH conditions in the original blister package); support studies (bulk capsules and 50 mg capsules at ICH conditions); and a photostress study using ICH conditions. The NDA has claimed a categorical exclusion from filing an environmental assessment under 21 CFR 25.31(b). All manufacturing and control sites listed in the NDA have been found to meet current GMP requirements.

B. Description of How the Drug Product is Intended to be Used

The proposed drug product is intended to be used for the treatment of mild to moderate type 1 Gaucher Disease in patients for whom enzyme replacement therapy is not a therapeutic option due to constraints such as allergy, hypersensitivity, poor venus access ———— The recommended treatment regime for adults is 1 capsule taken 3 times daily. The dose may be reduced by the taking fewer capsules per day. The applicant has no drug experience with patients under 18 years old.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved and the application should be approved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CMC/M.Adams/20 Jun 2003
CMC-TL/S.Moore/20 Jun 2003

C. CC Block

PM/P.Matara
ONDC/DNDC2-Dir/E.Duffy
ONDC/DNDC2-DepDir/D.Wu

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

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/s/

Mike Adams
6/20/03 03:25:53 PM
CHEMIST

Stephen Moore
6/20/03 03:30:22 PM
CHEMIST

NDA 21-348

Zevesca (miglustat) 100 mg capsules

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Oxford Glycosciences

Address:
The Forum
86 Milton Park, Abingdon
Oxon OX12 4RY
United Kingdom

U.S.Representative:
Bruce R. Manning
New England Biomedical Research, Inc.
96 West main Street, PO Box 809
North Borough, MA 01532
Telephone: 508-393-3100

Indication: Treatment of Type 1 Gaucher Disease

Presentation: Blisters

EER Status: Final overall recommendation form Compliance is pending. Testing facility has a withold recommendation. Final results from the inspection of drug product manufacturer Galen Group, Craigavon NIR are missing.

Consults: OPDRA – ZEVESCA unacceptable 1-APR-2002
Statistics – none
EA – no consult - waiver requested – granted

Phase IV Commitments: none

The original NDA was received 21-AUG-2001

The **drug substance** is manufactured by: Lonza, Visp, SZ - acceptable GMPs 7-JUN-2002. The drug substance is manufactured from D-glucose by a

Structural characterization of the drug substance, and chirality determination was satisfactory. The manufacturing process and controls were found generally acceptable with a few comments being offered. Satisfactory work was performed to characterize the impurity profile and the impurity tests and acceptance criteria were found to be acceptable. Other specifications were found acceptable. A re-submitted stability data – additional data are requested. The stability testing protocol is considered adequate

Conclusion
Drug substance is approvable pending resolution of minor issues.

The **drug product** is an immediate release 100 mg tablet

Manufacturer:

Galen Group
Craigavon, IR

The manufacturing method is a standard and capsule filling process. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable. The dissolution test and acceptance criteria were found acceptable by OCPB – see review dated 26-APR-2002. The – additional data have been requested. The stability testing protocol is considered adequate. The established name Miglustat should be made official though USAN. Testing facility has a withold recommendation, final results from the inspection of Galen Group, Craigavon NIR are missing as is the overall Compliance recommendation.

Minor deficiencies have been cited.

All associated DMFs are acceptable.

Deficiencies

Application for an official USAN name should be made.

Please be aware that all manufacturing and testing facilities should have a satisfactory GMP compliance status for approval.

Overall Conclusion
From a CMC perspective the application is approvable.

Eric P Duffy, PhD
Final overall recommendation form Compliance is pending Director, DNDC II/ONDC

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/s/

Eric Duffy
6/17/02 05:26:44 PM
CHEMIST

NDA 21-348

Zavesca™ (miglustat) 100 mg capsules

Actelion Pharmaceuticals U.S., Inc.

Mike Adams
Division of Metabolism and Endocrine Drug Products, HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-348

2. REVIEW #2

3. REVIEW DATE: 29 Apr 2003

4. REVIEWER: Mike Adams

5. PREVIOUS DOCUMENTS:

Document	Document Date
Original Submission	16 Aug 2001
NDA Filing	21 Aug 2001
BL Amendment	02 Oct 2001
CMC Review #1	22 Apr 2002
NA Letter	20 June 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Correspondence	31 Mar 2002
BZ Amendment	07 Feb 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Actelion Pharmaceuticals U.S., Inc.
Address	56 Huckleberry Lane North Andover, MA 01845
U.S. Representative:	Tom Lategan, Ph.D.
Telephone:	978-682-3999
Fax:	309-216-7012

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zavesca™
b) Non-Proprietary Name (USAN): miglustat 100 mg capsules
c) Code Name/# (ONDC only): OGT 918
d) Chem. Type/Submission Priority

- Chem. Type: NME
- Submission Priority: 1V

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: treatment of type 1 Gaucher Disease

11. DOSAGE FORM: immediate release HG capsule

12. STRENGTH/POTENCY: 100 mg

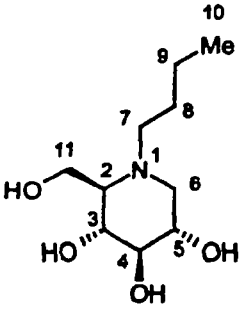
13. ROUTE OF ADMINISTRATION: oral

14. DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]: XX Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: $C_{10}H_{21}NO_4$
Molecular Weight: 219.28
Chemical Abstract Index: [2R,3R,4R,5S]-1-butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol
Chemical name: 1,5-(butylimino)-1,5-dideoxy-D-glucitol
or N-butyldeoxynojirimycin (*N*B-DNJ)
Code Names: OGT 918 (Oxford GlycoSciences)
SC-48334 (G.D. Searle)
CAS number: 72599-27-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENT
—	III	—	—	4	N/A	—	—
—	III	—	—	4	N/A	—	—

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION#	DESCRIPTION
IND		
IND	60,197	Treatment of Gaucher Disease (OGT 918)
IND		
IND		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	07/30/02	OC
Pharm/Tox	N/A		
Biopharm	Accepted with comments	04/26/02	S.Chung
DMETS/ODS	Trade name accepted by Clinical Director	memo not yet filed in DFS	D.Orloff
Methods Validation	To be sent	—	—
OPDRA	N/A		
EA	Excluded	04/22/02	M.Adams
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-348

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending submission of further CMC information cited in review section H.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no proposed phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Zavesca™ (miglustat) 100 mg capsule is an immediate release oral product intended for an orphan indication. The pre-clinical studies by G.D. Searle and clinical studies by Oxford Glycosciences were performed on the same drug formulation. NDA ownership was transferred to Actelion Pharmaceuticals U.S., Inc. in Nov 2002.

DRUG SUBSTANCE: Miglustat, [2R,3R,4R,5S]-1-butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol, is a new molecular entity manufactured by Lonza Ltd (Visp, SZ). The API is essentially a reorganized glucose molecule synthesized by a [redacted]

[redacted]

. Lonza IP/QC specifications, synthesis method, and reprocessing procedure have been described in detail. The proposed release specifications address molecular and configuration identity; molecular assay; and purity for metals, chiral process impurities [redacted] residual solvents [redacted] and microbiological contamination. Due to the high water solubility, particle size distribution is not addressed. The proposed regulatory methods have been adequately validated. The impurity and degradation profiles have been investigated at length. Oxidative degradation is to be studied further and the results submitted at an unspecified time after NDA approval. Reference standards for API and the identified process impurities have been developed and characterized. Based on data from ICH stability studies on 5 lots, the NDA has established that API is stable for 24 months at room temperature when stored [redacted]

DRUG PRODUCT: The proposed drug product is manufactured by Galen Ltd (Craigavon, Northern Ireland). The dosage form is 100 mg API [redacted] hard gelatin capsule. Excipients are USP/NF grade based on Galen's acceptance specifications. The manufacturing process and IP/process controls are described in detail. There is no provision for reprocessing. The proposed release specifications

address molecular identity, molecular assay ——— USP content uniformity/EP uniformity of mass, USP dissolution ——— /EP disintegration, microbiological content, residual moisture ——— and process impurities & degradants (——— The proposed regulatory methods have been adequately validated. The market package is stated to be CR/SF and consists of an opaque . ——— blister pack in a cardboard carton. Ten months into their stability studies the firm was forced to change their blister pack to use equivalent blister and lidding films. As a result, the pivotal stability studies are being repeated using the first 3 commercial capsule lots in the newly proposed blister package. Initial data has been submitted. Based on data from ICH stability studies on three 100 mg capsule lots in the original blister package and supported by ICH studies for bulk capsules, 50 mg capsules and ICH photostress conditions, ——— ——— temperature or below 25°C. The NDA has claimed a categorical exclusion from filing an environmental assessment under 21 CFR 25.31(b). Except for the contract microbiology laboratory, the manufacturing and control sites listed in the NDA have been found to meet current GMP requirements.

B. Description of How the Drug Product is Intended to be Used

The proposed drug product is intended to be used for the treatment of mild to moderate type 1 Gaucher Disease in patients for whom enzyme replacement therapy is not a therapeutic option due to constraints such as allergy, hypersensitivity, poor venus access ———
The recommended treatment regime for adults is 1 capsule taken 3 times daily. The dose may be reduced by the taking fewer capsules per day. The applicant has no drug experience with patients under 18 or over 70 years old.

C. Basis for Approvability or Not-Approval Recommendation

The additional information required for NDA approval consists of additional CMC documentation, data to support a regulatory specification, information to support drug product stability and revised labels.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CMC/M.Adams/29 Apr 2003
CMC-TL/S.Moore/29 Apr 2003

C. CC Block

PM/S.Wu/
ONDC/DNDC2-Dir/E.Duffy
ONDC/DNDC2-DepDir/D.Wu

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

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/s/

Mike Adams
4/30/03 05:18:20 PM
CHEMIST

Stephen Moore
4/30/03 05:22:24 PM
CHEMIST

NDA 21-348

Zevesca™ (miglustat) 100 mg capsules

Oxford Glycosciences

Mike Adams
Division of Metabolism and Endocrine Drug Products, HFD-520

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-348

2. REVIEW #1

3. REVIEW DATE: 04/22/02

4. REVIEWER: Mike Adams

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	08/16/01
BL Amendment	10/02/01

7. NAME & ADDRESS OF APPLICANT:

Name:	Oxford Glycosciences
Address	The Forum 86 Milton Park, Abingdon Oxon OX12 4RY United Kingdom
U.S. Representative:	Bruce R. Manning New England Biomedical Research, Inc. 96 West main Street, PO Box 809 North Borough, MA 01532
Telephone:	508-393-3100

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zevesaca
b) Non-Proprietary Name (USAN): miglustat 100 mg capsules
c) Code Name/# (ONDC only): OGT 918
d) Chem. Type/Submission Priority
- Chem. Type: NME

- Submission Priority: 1V

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: treatment of type 1 Gaucher Disease

11. DOSAGE FORM: HG capsule

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:
_____SPOTS product – Form Completed
__XX__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: $C_{10}H_{21}NO_4$
Molecular Weight: 219.28
Chemical Abstract Index: [2R,3R,4R,5S]-1-butyl-2-(hydroxymethyl)3,4,5-piperidinetriol
Chemical name: 1,5-(butylimino)-1,5-dideoxy-D-glucitol or N-butyldeoxynojirimycin (*N*B-DNJ)
Code Names: OGT 918 (Oxford GlycoSciences)
SC-48334 (G.D. Searle)
CAS number: 72599-27-0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENT
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—	III			4	N/A	—	—

[1] Action codes for DMF Table:
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6 – DMF not available
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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION#	DESCRIPTION
IND	[redacted]	Treatment of [redacted] Disease (OGT 918)
IND	60,197	Treatment of Gaucher Disease (OGT 918)
IND	[redacted]	Treatment of [redacted] /GT 918)
IND	[redacted]	Treatment of [redacted]

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	09/25/01	OC
Pharm/Tox	N/A		
Biopharm	Accepted with comments	04/26/02	S.Chung
DMETS/ODS	Not Accepted	03/13/02	J.Fan
Methods Validation	To be sent	---	---
OPDRA	N/A		
EA	Excluded	CMC #1	M.Adams
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-348

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending submission of further CMC information cited in review section H.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no proposed phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Zavesca™ (miglustat) 100 mg capsule is an immediate release product intended for the treatment of type 1 Gaucher Disease, an orphan indication. The pre-clinical studies by G.D. Searle and clinical studies by OGS were performed on the same drug formulation.

DRUG SUBSTANCE: Miglustat, [2R,3R,4R,5S]-1-butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol, is a new molecular entity manufactured for Oxford Glycosciences (OGS) by Lonza Ltd (Visp, SZ). The API is essentially a reorganized glucose molecule synthesized by [redacted]

[redacted] Lonza IP/QC specifications, synthesis method, and reprocessing procedure have been described in detail. The proposed release specifications address molecular and configuration identity; molecular assay; and purity for metals, chiral process impurities [redacted] residual solvents [redacted], and microbiological contamination. Due to the high water solubility, particle size distribution is not

addressed. The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated at length. Oxidative degradation is to be studied further and the results submitted at an unspecified time after NDA approval. Reference standards for API and the expected process impurities have been developed and characterized. Based on data from ICH stability studies on 5 lots, OGS claims that API is stable for 24 months at room temperature when stored

DRUG PRODUCT: The proposed drug product is manufactured for OGS by Galen Ltd (Craigavon, Northern Ireland). The dosage form is 100 mg API hard gelatin capsule. Excipients are USP/NF grade based on Galen's acceptance specifications. The manufacturing process and IP/process controls are described in detail. There is no provision for reprocessing. The proposed release specifications address molecular identity, molecular assay , USP content uniformity/EP uniformity of mass, USP dissolution, , microbiological content, residual moisture and process impurities and degradants The proposed regulatory methods have been validated. The market package is stated to be CR/SF and consists of an opague blister pack with carton having a tamper evident seal. Ten months into their stability studies the firm was forced to change their blister pack to use equivalent blister and lidding films. As a result, the pivotal stability studies will be repeated using the first 3 commercial capsule lots in the newly proposed blister package. Based on data from ICH stability studies on three 100 mg capsule lots in the original blister package and supported by ICH studies for bulk capsules, 50 mg capsules and ICH photostress conditions, OGS claims that their market product is when stored below 25°C.
OGS has claimed a categorical exclusion from filing an environmental assessment under 21 CFR 25.31(b).
The manufacturing and control sites listed in the NDA have been found to meet current GMP requirements.

B. Description of How the Drug Product is Intended to be Used

The proposed drug product is intended to be used for the treatment of type 1 Gaucher Disease. The recommended treatment regime is 1 capsule taken 3 times daily with a one week supply

of drug product being provided ———— . Dose is redused by the taking fewer capsules per day.

C. Basis for Approvability or Not-Approval Recommendation

The additional CMC information required for NDA approval consists of product qualification information (completed API and drug product stability studies, a packaging qualification study) and information required for completeness (API and drug product manufacturing controls or regulatory specifications).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CMC/M.Adams/04/22/02
CMC-TL/S.Moore/

C. CC Block

PM/S.Wu/
ONDC/DNDC2-Dir/E.Duffy
ONDC/DNDC2-DepDir/D.Wu

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

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

/s/

Mike Adams
5/1/02 04:07:30 PM
CHEMIST

Stephen Moore
5/1/02 04:30:20 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

plication : NDA 21348/000 Sponsor: ACTELION PHARMACEUTICALS US IN
Org Code : 510 601 GATEWAY BLVD STE 100
Priority : 1S SOUTH SAN FRANCISCO, CA 94080

Stamp Date : 21-AUG-2001 Brand Name : ZAVESCA (MIGLUSTAT) CAPSULE
PDUFA Date : 12-AUG-2003 Estab. Name:
Action Goal : Generic Name: MIGLUSTAT CAPSULES; 100MG;
District Goal: 22-APR-2002 OGT 918
Dosage Form: (CAPSULE)
Strength : 100 MG

FDA Contacts:	P. MADARA	Project Manager (HFD-510)	301-827-6380
	W. ADAMS	Review Chemist (HFD-510)	301-827-9088
	S. MOORE	Team Leader (HFD-510)	301-827-6430

Overall Recommendation: ACCEPTABLE on 28-MAY-2003by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 30-JUL-2002by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 25-SEP-2001by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : 9616676 FEI : 3001079059
GALEN GROUP
SEAGOE INDUSTRIAL ESTATE
CRAIGAVON, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile : CHG OAI Status: NONE
st Milestone: OC RECOMMENDATION
Milestone Date: 25-JUL-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [illegible] FEI : 3002303[illegible]

LONZA AG

WALLISER WERKE

VISP CH-3930, , SZ

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JUL-02

Decision : ACCEPTABLE

Reason : DUPLICATE MILESTONE FROM FACTS

Establishment : CFN : 9613429 FEI : 3001224264

LONZA BIOTEC SRO

281 61 KOURIM, , EZ

SUMMARY REPORT

DMF No: AADA:

Responsibilities:

Profile : CFN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-APR-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No:

sponsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUN-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No:

Responsibilities:

.rofile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUN-02