CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-393

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-393 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: ISTODAX Established/Proper Name: romidepsin Dosage Form: lyophilized powder to be reconstituted for solution dosage form Strengths: 10 mg per 2 mL in single-use vial		
Applicant: Gloucester Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: January 12, 2009 Date of Receipt: January 12, 2009 Date clock started after UN:		
PDUFA Goal Date: November 12, 2009	Action Goal Date (if different):	
Filing Date: March 23, 2009	Date of Filing Meeting: February 25, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): IND 63,573, DMF [redacted] and DMF 2315				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	√			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	√			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	√			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		√		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	√			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).	

b(4)

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		√		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		√		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		√		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		√		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***		√		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		√		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		√		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		√		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	√			
Index: Does the submission contain an accurate comprehensive index?	√			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	√			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? *If yes, date consult sent to the Controlled Substance Staff:*				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	√			
Are all establishments and their registration numbers listed on the form/attached to the form?	√			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	√			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** *Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.*	√			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	√			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** *Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*	√			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		√		This is an electronic submission.

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		√		Orphan designation 9-30-2004
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		√		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	√			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☒ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	√			
Is the PI submitted in PLR format?	√			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	√			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	√			
REMS consulted to OSE/DRISK?			√	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	√			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	√			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	√			QT IRT and Pediatrics-Maternal Health Team

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** July 13, 2005 ***If yes, distribute minutes before filing meeting***	√			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 10, 2007 ***If yes, distribute minutes before filing meeting***	√			
Any Special Protocol Assessments (SPAs)? **Date(s):** September 5, 2006 (Agreement) December 22, 2006 (NonAgreement) ***If yes, distribute letter and/or relevant minutes before filing meeting***	√			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 25, 2009

BLA/NDA/Supp #: NDA 22-393

PROPRIETARY NAME: romidepsin

ESTABLISHED/PROPER NAME: ISTODAX

DOSAGE FORM/STRENGTH: ISTODAX for injection, 10mg per 2 mL single-use vial

APPLICANT: Gloucester Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy.

BACKGROUND: Gloucester Pharmaceuticals Inc submitted an NDA for ISTODAX. Romidepsin is an anti-neoplastic agent that has been identified as a novel histone deacetylase (HDAC) inhibitor. It is a new molecular entity. Romidepsin is being evaluated in the treatment of cutaneous T-cell lymphoma.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Y
	CPMS/TL:	Frank Cross	Y
Cross-Discipline Team Leader (CDTL)	V. Ellen Maher,		Y
Clinical	Reviewer:	Qin Ryan	Y
	TL:	V. Ellen Maher	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial*	Reviewer:	NA	

products)			
	TL:	NA	

0

Clinical Pharmacology	Reviewer:	Lillian Hua Zhang; Nitin Mehrotra	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Huanyu Chen	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alexander Putnam; Todd Palmby	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Ying Wang	Y
	TL:	Hari Sarker/Sarah Pope Miksinski	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Bryan S. Riley	N
	TL:	James McVey	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:	John Lee	Y
	TL:	Tejashri Purohit-Sheth	N
OSE/DMEPA (proprietary name)	Reviewer:	Cathy Miller	N
	TL:	Kellie Taylor Denise Toyer	N
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:	Claudia Karwoski	N
Bioresearch Monitoring (DSI)	Reviewer:	NA	

	TL:	NA	

Other reviewers	Suchitra Balakrishnan - QT IRT Elektra Papadopoulos – SEALD Endpoints Jeanine Best – Maternal Health Team	N N N
Other attendees	NA	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a***	☒ YES Date if known: ☐ NO ☒ To be determined Reason: new molecular entity

disease	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:** The Pharmacokinetics dataset for study AN10018a is not in SAS transport file (*.xpt)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments:**	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments:**	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Director, OODP **21st Century Review Milestones (see attached)** (optional): **Comments:**	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

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/s/

LISA M SKARUPA
10/21/2009

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******Pre-decisional Agency Information******

Memorandum

Date: October 19, 2009

To: Lisa Skarupa, Project Manager, DDOP

From: Stephanie Victor, Regulatory Review Officer, DDMAC

CC: Robert Dean, DTC Group Leader, DDMAC
JuWon Lee, Regulatory Review Officer, DDMAC
Catherine Gray, Professional Group Leader, DDMAC
Wayne Amchin, Project Manager, DDMAC

Subject: NDA # 22-393
DDMAC comments for Istodax (romidepsin) for Injection
Patient Labeling

DDMAC has reviewed the proposed Patient Labeling for Istodax (romidepsin) for Injection submitted for consult via email on January 12, 2009, and offers the following comments. Comments regarding the proposed PI were previously provided on September 18, 2009 by JuWon Lee.

The version of the draft PI and patient labeling used in this review is titled, "NDA 22393 Labelversion Oct142009.doc" sent via email on October 16, 2009.

General Comment

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the patient labeling, please contact Stephanie Victor at 301-796-3693 or Stephanie.Victor@fda.hhs.gov.

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews- 1

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/s/

STEPHANIE L VICTOR
10/19/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 15, 2009
To:	Robert Justice, MD, Director
	Division of Drug Oncology Products (DDOP)
Through:	Mary Willy, PhD, Deputy Director
	Division of Risk Management (DRISK)
	LaShawn Griffiths, MSHS-PH, BSN, RN
	Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Sharon R. Mills, BSN, RN, CCRP
	Senior Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Istodax (romidepsin) for injection
Application Type/Number:	NDA 22-393
Applicant/sponsor:	Gloucester Pharmaceuticals, Inc.
OSE RCM #:	2009-346

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Istodax (romidepsin) for injection. We used the Zolinza (vorinostat) capsules approved PPI as a comparator for our review. Please let us know if DDOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Istodax (romidepsin) for injection Prescribing Information (PI) submitted January 12, 2009 and revised by the Review Division throughout the current review cycle, the most recent version dated October 6, 2009.
- Draft Istodax (romidepsin) for injection Patient Package Insert (PPI) submitted on January 12, 2009 and revised by the review division throughout the review cycle, the most recent version dated October 6, 2009.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews Section- 2

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/s/

SHARON R MILLS
10/15/2009

MARY E WILLY
10/16/2009
I concur

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-393
APPLICANT	GLOUCESTER PHARMS
DRUG NAME	ISTODAX
SUBMISSION DATE	January 12, 2009
SEALD REVIEW DATE	September 17, 2009
SEALD REVIEWER(S)	Abiola Olagundoye, PharmD
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

10 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews Section- 3

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/s/

ABIOLA OLANGUNDOYE
09/29/2009

LAURIE B BURKE
09/29/2009

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2009.002.A.00058
APPLICATION NUMBER	NDA 22393
PDUFA date	November 12, 2009
Advisory Committee Meeting	August 3, 2009
DATE OF CONSULT REQUEST	June 12, 2009
DUE DATE	July 30, 2009
REVIEW DIVISION	DDOP
MEDICAL REVIEWER/TEAM LEADER	Qin Ryan/ Ellen Maher
REVIEW DIVISION PM	Lisa Skarupa
SEALD REVIEWER	Elektra J. Papadopoulos
REVIEW COMPLETION DATE	July 21, 2009
NAME	Romidepsin (depsipeptide)
APPLICANT	Gloucester Pharma
ENDPOINT(S) CONCEPT(S)	Pruritus
INSTRUMENT(S)	VAS
INDICATION	Cutaneous T-cell lymphoma
INTENDED POPULATION	Patients with CTCL who have received at least one prior systemic therapy

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Oncology Drug Products regarding NDA 22393 for the use of Romidepsin for infusion for the treatment of Cutaneous T-cell lymphoma (CTCL) patients.

The primary objective of the study is to assess the rate of objective response, defined as the proportion of patients with confirmed CR, CCR, or PR, as determined by the OPDREC.

The sponsor also seeks a labeling claim of Romidepsin for the relief of pruritus in CTCL on the basis of results obtained from a single open-label, single arm study.

The review concludes that a "relief of pruritus" claim (as stated in proposed labeling) is not justified.

There are several important concerns when considering the utility of PRO data derived from a non-randomized, open-label study. These are described in the draft PRO Guidance for industry and are also described in Section 2 of this review.

The measurement of itch is important in this patient population and is encouraged in future studies, especially randomized, well-controlled clinical studies. As with pain measurement, concomitant medications need to be taken into account in evaluation of response. If patients' tumors are painful (or may become painful over the course of the study), then pain should be measured as well as pruritus.

2 SEALD COMMENTS

- The phase 2 study supporting product registration (GPI-04-0001) was an open-label, single-arm study. As noted in the draft Guidance for Industry on PROs intended to support labeling claims, PRO-derived data from open-label studies are rarely credible because responses to PRO measures are subjective. The draft guidance recommends, therefore, that every effort should be made to assure that patients are masked to treatment assignment. The study is also nonrandomized and, therefore, there is no concurrent control group from which a treatment effect on pruritus can be ascertained.
- The draft guidance advises that the characteristics of the PRO instrument used should also be considered. For example, questions that ask how patients' current status compares to baseline seem likely to be more influenced by unblinding (optimism can readily be expressed as a favorable comparison) than questions that ask about current status. Questions that ask for current status, or PRO instruments that ask many questions, are harder to answer in a biased way when previous answers are not available. Therefore, it is useful to consider whether patients had access to their previous responses at subsequent assessments.
- The PRO instrument used to quantify itch in this study is a pure VAS scale comprising a line of fixed length with words that anchor the scale at the extreme ends and no words describing intermediate positions. As noted in the draft Guidance for Industry, these scales often produce a false sense of precision. This is because the response is measured in terms of change (in mm) on a 100 mm scale. For this reason, we recommend using instead a numeric rating scale, for example, anchored at 0 and 10 with 0 representing "no itch" and 10 representing "worst itch imaginable," giving patients 11 discrete choices for response.
- Patient instructions were as follows: "indicate the amount of itching you are experiencing by marking a vertical line through the line below." The case report forms should be reviewed in order to ascertain whether patients understood the term "vertical" and responded accordingly with an unambiguous vertical line.
- What was measured was not "relief of pruritus" (as stated in current proposed labeling), but rather pruritus severity (using VAS) at certain points in time. Neither the proposed labeling nor the clinical study protocol defines what constitutes "pruritus relief." A "relief of pruritus" claim is not justified in the absence of empirically-derived response criteria demonstrating that pruritus was, in fact, relieved.

STUDY ENDPOINT REVIEW

- In general, PROs should be measured at clinic visits before other clinical assessments. This is to avoid influencing the patient's responses. It should be clarified whether this was done in this study.
- There are numerous secondary endpoints and the change from baseline in pruritus as measured by VAS was to be assessed at each assessment during the study. As with any endpoint, correction for Type 1 error is an important consideration.

3 ENDPOINT REVIEW

3.1 Instruments

A representation of the VAS used in the case report form is appended.

The pruritus VAS value minus the baseline pruritus VAS value was to be assessed at each assessment during the study.

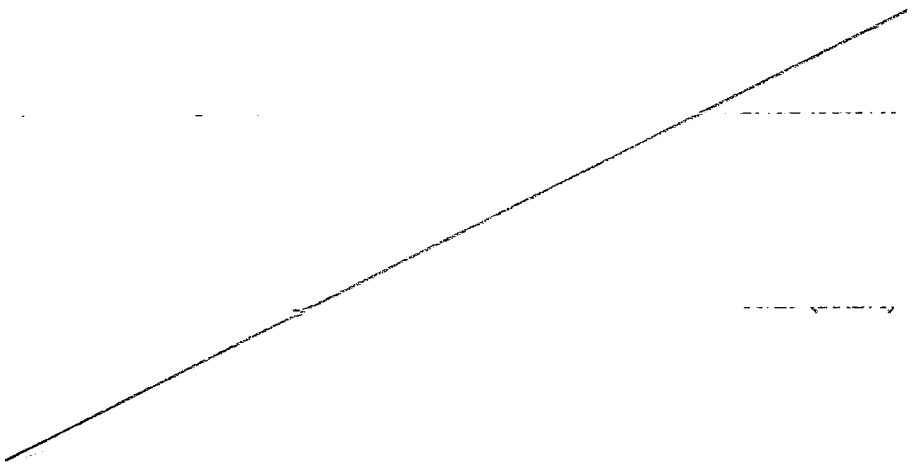
3.2 Claim Structure

The sponsor proposes the following labeling:

INDICATIONS AND USAGE

ISTODAX is indicated for treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy.

The clinical studies section of labeling includes the following table.



b(4)

Comments: Neither the proposed labeling nor the clinical study protocol defines what constitutes "pruritus relief."

3.3 Study Endpoints

Primary Efficacy Endpoint
The primary efficacy endpoint is the rate of objective response, defined as the proportion of patients with confirmed CR, CCR, or PR, as determined by the OPDREC.

The number and percentage of patients with objective disease response will be presented. A two-sided 95% confidence interval will be constructed using exact methods based on the binomial distribution. The primary analysis will be performed using the evaluable population. A secondary efficacy analysis on the primary endpoint will be conducted using the per-protocol set.

Secondary Endpoints

- Rate of objective disease control: Proportion of patients with confirmed CR, CCR, PR, or stable disease (for SD with a duration of at least 3 months) as determined by the OPDREC.
- Duration of objective disease response. For patients with confirmed CR, CCR or PR as determined by the OPDREC criteria, duration of response is defined as the time from the first date of a disease response which is later confirmed, to the first date of diagnosis of progressive disease (confirmed PD or PD leading to permanent treatment withdrawal) or date of last study assessment if no disease progression.
- Time to objective disease response: For patients with confirmed CR, CCR, or PR as determined by the OPDREC criteria, the time from the first date of treatment to the first date of (a later) confirmed disease response.
- Time to objective disease progression: The time from the first date of treatment to the first date of diagnosis of progressive disease (confirmed PD or PD leading to permanent treatment withdrawal), as determined by the OPDREC criteria.
- Time to treatment failure: The time from the first date of treatment to the date of permanent treatment withdrawal (due to objective disease progression, toxicity and/or other treatment-related withdrawal reasons).
- Change from baseline in Weighted Body Surface Assessment (BSA): At each assessment during the study, the BSA value minus the baseline BSA value.
- Change from baseline in Erythroderma Scale: At each assessment during the study, the erythroderma value minus the baseline erythroderma value.
- **Change from baseline in Pruritus VAS: At each assessment during the study, the pruritus VAS value minus the baseline pruritus VAS value.**
- Change from baseline in ECOG performance status: At each assessment during the study, the ECOG performance status value minus the baseline ECOG performance status value.
- Proportion of disease control, response, and progression as determined by RECIST criteria
- Proportion of patients with clearing of Sézary cells from the blood and bone marrow

- Proportion of patients with histone acetylation induction
- Proportion of patients with apoptosis markers
- Summaries of other molecular and disease markers

Comments: A responder definition for the itch endpoint was not specified.

There are numerous secondary endpoints and correction for Type 1 error needs should be considered when considering these. The pruritus VAS value minus the baseline pruritus VAS value was to be assessed at each assessment during the study. A specific time for the analysis should have been pre-specified.

3.4 Content Validity

The VAS instrument was an unmarked horizontal line anchored at the left by "no itching" and at the right by "unbearable itching." The instrument was administered in paper and pen format.

Patients were instructed as follows, "Please indicate the amount of itching you are experiencing by marking a vertical line through the line below..." The patient was to make the vertical line and the investigator (or designee) was to measure the line from left to right and record the measure in mm.

The assessments were to be completed at the clinic visits.

Comment: The case report forms should be reviewed in order to ascertain whether patients understood the term "vertical" and responded accordingly with an unambiguous vertical line.

3.5 Other Measurement Properties

Other measurement properties (e.g., test-retest reliability) for the instrument were not provided.

3.6 Interpretation of Scores

A responder definition was not proposed.

3.7 Language Translation and Cultural Adaptation

Documentation of the translation and cultural adaptation was not provided.

3.8 Study Protocol

Title: A Single Agent Phase II Study of Depsipeptide (FK228) in the Treatment of Cutaneous T-cell Lymphoma

Protocol number: GPI-04-0001

Methodology: The study is a phase 2, international, multi-center, open-label, single-arm study.

Number of patients: A total of 90 patients were to be enrolled to provide data from a total of 64 evaluable patients.

Comment: [redacted] b(4)

Diagnosis and Main Criteria for Inclusion: Males or nonpregnant females ≥18 years of age with histologically confirmed Stage IIA, IIB, III or IVA CTCL at study entry, including mycosis fungoides and Sézary syndrome, who were no longer controlled on standard skin-directed therapy and had received at least 1 course of prior systemic therapy, were candidates for the study.

Test Product, Dose and Mode of Administration:
Patients received 14 mg/m2 of romidepsin IV over 4 hours on Days 1, 8, and 15 of each 28-day treatment cycle.

Duration of Treatment: Treatment was planned for 6 months. Patients could continue to receive treatment until disease progression or other withdrawal criteria were met.

Analysis Populations:

As-treated Population: All patients who received at least 1 dose of romidepsin.

Evaluable Population: All patients who received 2 consecutive cycles of study treatment, with at least 2 of the 3 doses received in each cycle, and had disease assessments performed at Baseline and after the last of the 2 consecutive cycles; and who did not receive concomitant steroid therapy or other therapy for CTCL (whether systemic or topical) that may have biased the assessment of disease response.

Study endpoints are described under section 3.3 of this review.

The PRO measure (pruritus VAS) was to be administered at baseline and at day 1 of each treatment cycle (each clinic visit) post-baseline. There were also discontinuation visit assessments and follow-up assessments that included those who did not continue dosing. (See the table below.)

Schedule of Study Activities

EVALUATIONS	S[3]	Cycles 1 to 6 and Follow-up Visits for Patients who Continue to Dose[11]				Final/Discontinuation Visit[21]	Follow-up Visits for Patients who do not Continue to Dose[12]	Follow-Up Final Visit[10]
		1	8	15	22			
Informed Consent	X							
Medical history	X							
Histology of skin, lymph node and bone marrow, as indicated[8]	X							
Chest x-ray	X							
Physical examination	X	X		X		X	X	X
Concomitant medications	X	X	X	X		X	X	X
Body weight	X	X[13]				X		X
Height	X	X[13]						
Vital signs[2]	X	X	X	X		X	X	X
ECOG Performance Status	X	X	X	X		X	X	X
CBC/Differential/Platelets[3,4]	X	X[4]	X[4]	X[4]	X	X	X[4]	X
Biochemistry[4]	X	X[4]	X[4]	X[4]		X	X[4]	X
Urinalysis	X							
Urine pregnancy test	X	X					X	
Electrocardiogram[5, 6]	X	X	X[4]	X[4]		X	X[4]	X
CT/MRI[5] of chest, abdomen and pelvis[14]	X[5]	X[5,14]				X[5]	X[14]	
QPDREC[7]		X				X	X	
Tumour measurement	X[6]	X				X	X	
Skin lesion severity assessment	X[6]	X				X	X	
Photography	X[6]	X				X	X	
Measurement of Sézary cells	X[6]	X				X	X	
Pruritus VAS assessment	X[6]	X				X	X	
Disease Markers and protein analysis[9]	X	X[9]						
PK samples[19]		X	X	X				
Study drug dosing		X	X	X				
Adverse events		X	X	X		X	X	X

APPENDIX

VISUAL ANALOGUE SCALE (VAS) - PRURITUS

Please indicate the amount of itching you are experiencing by marking a vertical line (I) through the line below (to be completed by patient).

NO ITCHING _____ UNBEARABLE ITCHING

Measurement of VAS ☐☐☐ mm
(measured from left to right by Investigator or designee)

Signature: _____

Confirmation of measurement of VAS (study monitor):

Signature: _____

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

/s/

Elektra Papadopoulos
7/21/2009 08:15:08 PM
MEDICAL OFFICER

Laurie Burke
7/22/2009 02:35:47 PM
INTERDISCIPLINARY

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 5, 2009
To:	Robert Justice, MD, Director Division of Oncology Drug Products
Through:	Kellie Taylor, PharmD., MPH, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Cathy A. Miller, BSN, MPH, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Istodax (Romidepsin) for Injection 10 mg per Vial
Application Type/Number:	NDA# 22-393
Applicant:	Gloucester Pharmaceuticals, Inc.
OSE RCM #:	2009-345

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Oncology Drug Products for DMEPA to evaluate the proposed labels and labeling submitted as part new drug application (NDA 22-393) on January 12, 2009.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the Istodax container labels, carton labeling and insert labeling submitted as part of the February 8, 2009 submission. (See Appendices A through C).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 2.1 *Comments to the Division* for discussion during the review team's label and labeling meetings regarding the presentation of the dosage form currently presented as "for reconstitution" on container labels and on carton labeling. Section 2.2 *Comments to the Applicant* contains our recommendations for the container label, diluent container label and carton labeling. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Sandra Griffith, Project Manager, at 301-796-2445.

3.1 COMMENTS TO THE DIVISION

On June 24, 2009, we consulted with the CMC reviewer via email regarding the presentation of the dosage form (for reconstitution) on container labels and carton labeling. CMC confirmed that the correct presentation of the dosage form for a lyophilized powder requiring reconstitution for intravenous injection is "for injection" and we agree that this should be reflected throughout the labels and labeling.

3.2 COMMENTS TO THE APPLICANT

A. Diluent Container Label

We recommend you revise the following features to provide distinction between the diluent vial and the active drug vial:

1. Increase the prominence of the word 'Diluent' on the diluent container label. Post-marketing experience with intravenous products that have a separate diluent requiring reconstitution has shown that medication errors have occurred involving inadvertent use of the diluent instead of the drug during administration. Providing increased prominence of the word 'Diluent' on the container label may serve to avert confusion such as this during drug preparation and administration of Istodax.
2. Present the word 'Diluent' on a separate line from the proprietary name and use a larger, bolded font size to present the word 'Diluent'.
3. Delete the established name and decrease the prominence of the proprietary name 'Istodax' on the principal display panel of the diluent container label to minimize the potential that the diluent will be mistaken for the active drug.
4. Revise the presentation of the proprietary name 'Istodax' so it is not presented with the same

trade dress as it is presented on the drug vial. This will also serve to help distinguish the active drug vial from the diluent vial.

5. Add quantitative and/or qualitative information regarding the inactive ingredients Propylene Glycol and Deyhdrated Alcohol where they appear on the principal display panel of the diluent container label per 21 CFR 201.100 (b)(5).
6. Revise the presentation of "Inactive Ingredient" to read "Each vial contains" on the principal display panel of the diluent container label.
7. Revise the language accompanying "Dosage and Administration" on the principal display panel of the diluent container label to provide additional emphasis on the need to reconstitute Istodax with the accompanying Diluent. [redacted] and replace it with "Withdraw 2 mL of diluent for use to reconstitute 10 mg vial of Istodax." b(4)

B. Container Label and Carton Labeling

1. Add the final concentration after reconstitution (5 mg/mL) to principal display panel of container label and carton labeling below the strength (10 mg). For example: After reconstitution with 2 mL of Diluent, the final concentration of Istodax is 5 mg/mL. This information should be displayed on the principal display panel of carton labeling and if space permits, it should also be displayed on the principal display panel of the container label.
2. Consider revising the reconstitution and dilution statement on the bottom of the principal display panel of the container label and the side panel of the carton labeling to include reference to the volume of diluent to be added (2 mL of). This may provide clarity to providers calculating the concentration and dose when preparing the drug for administration. We recommend the statement be revised to read: Product MUST be reconstituted with **2 mL of** supplied diluent and then further diluted in 0.9 % Sodium Chloride Injection, USP.
3. Revise the presentation of the dosage form 'For Reconstitution' on container labels to the CDER Dosage Form "For Injection" and add the dosage form "For Injection" after the established name on the carton labeling.
4. Revise the presentation of the strength (10 mg) on the principal display panel of the container label and the carton labeling to read "10 mg per vial" to provide clarity regarding product strength.
5. Add a statement after the language "Single-use vial" on the container label and carton labeling such as "Discard Unused Portion" to provide emphasis in the product being single-use only.
6. Given the limited space available on the Istodax container label, we recommend deleting the statement [redacted] b(4)
7. Since the Istodax carton contains the diluent and the active ingredient for preparing the drug for administration, add the word 'Kit' to the upper section of the principal display panel of the carton labeling above the proprietary name.

8. Add information regarding the components packaged in the Istodax carton to the principal display panel of the carton labeling. We recommend the following:

Each vial contains:

1 single-use vial containing 10 mg of Istodax

1 vial containing 2 mL of Diluent

9. Revise the statement which appears on the principal display panel of the carton labeling that reads "MUST BE RECONSTITUTED AND DILUTED PRIOR TO ADMINISTRATION" to include "WITH ENCLOSED DILUENT" and relocate to directly below the strength (10 m g per vial). We recommend the added language to provide emphasis on the need to use the diluent included in the packaging to reconstitute the product before administration.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews Section- 4

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/s/

CATHY A MILLER
08/05/2009

KELLIE A TAYLOR
08/05/2009

DENISE P TOYER
08/06/2009

CAROL A HOLQUIST
08/06/2009

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 17, 2009

TO: Lisa Skarupa, Regulatory Project Manager
Qin Ryan, MD, Medical Officer
Division of Drug Oncology Products

FROM: John Lee, MD, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

SUBMISSION: NDA 22-393

APPLICANT: Gloucester Pharmaceuticals, Inc.

DRUG: Romidepsin (Istodax)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of cutaneous T-cell lymphoma, including relief of pruritus in patients who have received at least one prior systemic therapy

CONSULTATION REQUEST DATE: February 23, 2009

DIVISION ACTION GOAL DATE: August 5, 2009

PDUFA DATE: November 12, 2009

I. BACKGROUND

Cutaneous T-cell lymphoma (CTCL) is a chronic form of non-Hodgkin's lymphoma (NHL) of helper T-cell origin that typically targets and presents in the skin (tumors, patches, plaques, and erythroderma). It is a chronic, rare disease of the elderly with an incidence of 2-3,000 cases per year in the United States. Lifetime incidence of extracutaneous disease has been estimated to be about 40%, typically visceral tumors preceded by regional lymph node involvement. Common visceral sites include lung, upper digestive tract, brain, spleen, and liver, but any organ may be involved. There is no curative treatment for CTCL. Early stage disease with limited skin involvement is usually treated with skin-directed therapies and/or photopheresis. Late stage disease may be treated with systemic therapy using one or more chemotherapy agents or other immunomodulators, including vorinostat, bexaroteneor, and denileukin diftitox. CTCL treatment is typically associated with high relapse regardless of disease stage. Prognosis is related to disease stage, with 10-year survival ranging from 80% in stage I disease to 5% in stage IV disease. Late-stage disease is associated with declining immunocompetence and death most often results from systemic infection, secondary malignancies (higher-grade NHL, Hodgkin's disease, colon cancer), and cardiopulmonary complications. Romidepsin is a novel histone deacetylase (HDAC) inhibitor. Primary support for its safety and efficacy in CTCL is provided by two phase 2 (pivotal) open-label studies, GPI04-0001 and NCI 1312.

Pivotal Studies

The two studies were similar in design, enrolled similar patients, tested the same dosing regimen, and measured disease improvement using composite efficacy endpoints. Together, the two studies provided a total of 135 and 167 patients for efficacy and safety evaluations, respectively.

- Study GPI-04-0001 was a single-arm study to evaluate the safety and efficacy of romidepsin in CTCL Stages IB, II, III, or IVA refractory to at least one prior systemic therapy. Ninety-six patients were enrolled at 33 domestic and foreign sites. The primary efficacy endpoint was a composite investigator assessment of skin involvement, lymph node involvement, and abnormal circulating Sezary cells. The primary objective was to determine the objective response (OR) rate in patients who received two consecutive cycles of treatment with disease assessments available. The OR included complete response with biopsy confirmation (CR), complete clinical response (CCR), or partial response (PR) as defined by the Objective Primary Disease Response Criteria (OPDREC). Secondary endpoints included response duration, time to response, time to progression, and changes from baseline in severity of pruritus. Over two-thirds of the patients had advanced stage disease (Stage IIB, III, or IVA). Concomitant medication for pruritus was prohibited to permit an assessment of romidepsin efficacy on this symptom.
- Study NCI 1312 was a three-arm study conducted by the NCI to evaluate the efficacy and safety of romidepsin in patients with T-cell lymphomas, including CTCL. Patients with all stages of CTCL were candidates for the study. Seventy-one patients with CTCL were enrolled at 10 sites in the United States and Australia. The 3 study arms were based on the number of prior therapies. Eighty-seven percent of patients had advanced stage disease (Stage IIB, III, or IVA/B). The primary efficacy endpoint was a composite investigator assessment of skin involvement, lymph node involvement, and abnormal circulating Sezary cells. The primary objective was to determine the OR rate in patients who received two consecutive cycles of treatment with at least one non-missing response assessment on or after the second cycle. Secondary endpoints included response duration, time to response, and time to progression.

Clinical Indication

Based on these two pivotal studies, the sponsor proposes the following clinical indication in the draft product label for romidepsin (Istodax), a new molecular entitity (NME):

Istodax is a histone deacetylase (HDAC) inhibitor indicated for the treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy:

- 14 mg/m2 administered intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug.
- If a patient is intolerant to therapy, dose reduction to 10 mg/m2 and further to 8 mg/m2 can be considered.

II. INSPECTION RESULTS

Five inspections were conducted to support the review of this NDA: three domestic clinical sites, one foreign clinical site, and the sponsor site. Many foreign clinical sites participated in both pivotal studies and domestic data alone were insufficient to support this NDA. The clinical sites were selected for inspection based on subject enrollment, study results, the clinical investigator's prior FDA inspection history, and to include at least one foreign clinical site. No financial conflicts were reported for any site in either study. The sponsor site was inspected to support the review of this NDA for a new molecular entity.

Table 1: Summary of Inspection Results

Clinical Study Site	Site Protocol Subjects	Inspection Dates	Result Classification	
			Field	CDER
Adam Lerner, MD Boston Medical Center 732 Harrison Avenue Boston, MA 02118	Site 48 GPI-04-0001 6 subjects	May 5 - 13 2009	NAI	NAI
Susan Bates, MD National Cancer Institute 9000 Rockville Pike Bethesda, MD 20892	NCI Intramural NCI-1312 39 subjects	April 27 - May 15 2009	NAI	NAI
Mark Kirschbaum, MD Hematologic Malignancies Program City of Hope National Cancer Center Duarte, CA 91010	NCI CA-043 NCI-1312 5 subjects	April 14 - 28 2009	VAI	VAI
Sean Whittaker, MD St. Thomas' Hospital Lambeth Palace Road London SEI 7EH, UK	Site 02 GPI-04-0001 12 subjects	June 15 - 18 2009	VAI	VAI
Gloucester Pharmaceuticals, Inc. One Broadway Cambridge, MA 02142	GPI-04-0001 NCI-1312	June 16 - 19 2009	NAI	NAI

NAI: No action indicated (no deviations from regulations)
VAI: Voluntary action indicated (no significant deviations from regulations)
OAI: Official action indicated (significant deviations from regulations)

1. Adam Lerner, MD (Study GPI-04-0001, Site 48)

   Boston Medical Center
   732 Harrison Avenue
   Boston, MA 02118

   a. What was inspected:

      - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations
      - Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
      - Subjects: 7 subjects were screened, 6 enrolled, and 3 completed the study. Complete records were reviewed for all subjects enrolled in the study.

   b. General observations and commentary: All primary efficacy endpoint data were verified to be accurate. No unreported adverse events were noted. Study monitoring oversight appeared to be adequate. No significant deficiencies were observed and a Form FDA 483 was not issued.

   c. Assessment of data integrity: The data from this study site appeared reliable.

2. Susan E. Bates, MD (Study NCI-1312, NCI intramural site)

   National Cancer Institute
   Building 10, Room 12N226
   9000 Rockville Pike
   Bethesda, MD 20892

   a. What was inspected:

      - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations
      - Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
      - Subjects: 128 subjects were screened and 39 enrolled in the study. Complete records were reviewed for 13 subjects.

   b. General observations and commentary: All primary efficacy endpoint data were verified to be accurate. No unreported adverse events were noted. Study monitoring oversight appeared to be adequate. No significant deficiencies were observed and a Form FDA 483 was not issued.

   c. Assessment of data integrity: The data from this study site appeared reliable.

3. Mark H. Kirschbaum, MD (Study NCI-1312, Site CA043)

   City of Hope National Cancer Center
   1500 East Duarte Road
   Duarte, CA 91010-3000

   a. What was inspected:

      - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations
      - Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
      - Subjects: 16 subjects were screened, 15 enrolled, and 14 completed the study. Complete records were reviewed for all 14 subjects enrolled in the study.

   b. General observations and commentary: A Form FDA 483 was issued for failing to report the following two items to the Investigational Review Board (IRB):

      - A serious adverse event of sepsis in Subject 90000-5471, and the hospitalization of this subject on —— to manage sepsis and to rule out viral sepsis owing to Epstein-Barr virus (EBV) reactivation. b(6)
      - Changes to the study protocol, the informed consent document, and the patient information sheet, including changes regarding the serious risk of EBV reactivation associated with the study medication. Of the 14 subjects in the study, seven were enrolled under protocol amendment version I (11/15/06), seven under version J (3/14/07), and one under version K (2/6/09).

      Aside from these isolated instances of failing to report to the IRB, study reporting was otherwise generally adequate. All primary efficacy endpoint data were verified to be accurate. Study monitoring oversight and the reporting of adverse events to the sponsor appeared to be adequate.

   c. Assessment of data integrity: The data from this study site appeared reliable.

4. Sean Whittaker, MD (Study GPI-04-0001, Site 02)

   St. Thomas' Hospital, St. John's Institute of Dermatology
   Lambeth Place Road
   London, SE1 7EH, United Kingdom

   a. What was inspected:

      - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations
      - Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
      - Subjects: 15 subjects were screened, 13 enrolled, and 12 completed the study. Complete records were reviewed for 10 subjects enrolled in the study.

b. General observations and commentary: A Form FDA 483 was issued, which included the following major items:

- Delegation of authority by the principal investigator to other study personnel was not adequately documented in up to 18 of 29 study personnel, and a Form FDA 1572 (Investigator Statement) was not obtained from two clinical investigators until 17 and 23 months after beginning study participation.
- Two laboratory tests (lactate dehydrogenase level, CD4 cell count) were not obtained at subject screening as specified in the study protocol (4 subjects).
- Electrocardiograms (ECGs) were apparently performed but were not available as part of subject records (3 ECGs in 3 subjects).
- Serious adverse events were not promptly reported to the sponsor (6 events in 3 subjects). The two most serious events (in different subjects) were sepsis requiring hospitalization and perineal abscess.

After the inspection was completed, Dr. Whittaker provided study documentation that had not been available at inspections which satisfactorily resolved many of the concerns cited on the Form FDA 483.

Other than as cited on the Form FDA 483, the reporting of adverse events to the sponsor generally appeared to be adequate. All primary efficacy endpoint data were verified to be accurate and study monitoring oversight appeared to be adequate.

c. Assessment of data integrity: The data from this study site appeared reliable.

4. Gloucester Pharmaceuticals, Inc.

One Broadway
Cambridge, MA 02142

a. What was inspected:

- Scope of inspection: an assessment of the sponsor's responsibilities as transferred to multiple contract research organizations (CROs), and an evaluation of the CROs' performance in adhering to the contractual agreements and established standard operating procedures (SOPs) for the transferred study functions, including study drug management, clinical site monitoring, data management and analysis.
- Data verification: data obtained from two clinical sites that participated in Study GPI-04-0001 and linked with this sponsor inspection b(4)

b. General observations and commentary:

Study NCI-1312 was sponsored by NCI and Gloucester provided the data from this study to support this NDA; Gloucester had little control over the conduct of NCI-1312. Study GPI-04-001 was sponsored by Gloucester, and major responsibilities as the sponsor of this study were transferred to the following CROs:

- Study drug management: [redacted]
- Clinical site monitoring: [redacted]
- Data management and analysis: [redacted] b(4)
- Pharmacokinetics assays: [redacted]
- Electrocardiogram interpretation: [redacted]
- Photography services: [redacted]

No major deficiencies were observed and a Form FDA 483 was not issued. The CROs' study records and SOPs ———— indicated adequate performance of clinical site monitoring, data collection and management, and study drug disposition. A limited audit of the study data from two clinical sites (Sites 48 and 02 linked with this sponsor inspection, Study GPI-04-0001) revealed no discrepancies among source data, case report forms, and data submitted under the NDA. The regulatory files for the two linked clinical sites supported the inspectional findings at those clinical sites. b(4)

c. Assessment of data integrity: The inspectional findings indicate that the data reported by the sponsor in the NDA accurately reflect the data reported by the clinical sites.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five inspections (4 clinical sites and sponsor) were conducted between April 27, 2009 and June 19, 2009 in support of NDA 22-393. No major deficiencies were observed at the five inspections. The minor deficiencies were apparently isolated, did not suggest bias in study conduct, and were not expected to importantly affect data integrity. The data generated from the four clinical sites as reported by the sponsor under NDA 22-393 are considered acceptable in support of the proposed indication.

{See appended electronic signature page}

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/s/

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