

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-393

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022-393

NDA APPROVAL

Gloucester Pharmaceuticals, Inc.
Attention: Jean Nichols, Ph.D.
President & Chief Operating Officer
One Broadway, 14th Floor
Cambridge, MA 02142

Dear Dr. Nichols:

Please refer to your new drug application (NDA) dated January 12, 2009, received January 12, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ISTODAX[®] (romidepsin) for injection 10 mg per single-use vial.

We acknowledge receipt of your submissions dated February 4, 11, and 18, 2009; April 9; May 7 and 15; July 31; August 20, 26, and 31; September 17, October 20, 22 and 29; and November 4 (electronic), 2009.

This new drug application provides for the use of ISTODAX[®] (romidepsin) for injection 10 mg per single-use vial for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of toxicity from a solvent, and to assess a signal of a serious risk of embryo-fetal toxicity, estrogenic/anti-estrogenic effects, hepatic impairment, Q-T prolongation and drug-drug interaction with ISTODAX[®].

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1556-1 Conduct a GLP embryo-fetal developmental reproductive toxicology study in rats to assess the embryo-fetal toxicity of romidepsin. The results from the rat study will determine if a study in a second species is warranted.

The timetable you submitted on October 14, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission: July 31, 2010
Study Completion Date: November 30, 2010
Final Report Submission: June 30, 2011

- 1556-2 Conduct an animal study(ies) to determine the estrogenic/anti-estrogenic effects of romidepsin.

The timetable you submitted on October 22, 2009, states that you will conduct the study(ies) according to the following timetable:

Final Protocol Submission: April 30, 2010
Study Completion Date: July 31, 2010
Final Report Submission: October 31, 2010

- 1556-3 Conduct a GLP toxicology study in an appropriate animal species to characterize the toxicity profile of _____ The data from this study will be used in the justification of the acceptance criterion for _____ in romidepsin drug product administered IV on Days 1, 8 and 15 of a 28-day cycle.

The timetable you submitted on October 14, 2009, states that you will conduct this study according to the following timetable:

b(4)

Final Protocol Submission: June 30, 2010
Study Completion Date: September 30, 2010
Final Report Submission: February 28, 2011

1556-4 Conduct an in vitro induction study using cryopreserved human hepatocytes to evaluate the effects of romidepsin on the 3 inducible forms of cytochrome P450 (CYP1A2, CYP3B6 and CYP3A4).

The timetable you submitted on October 14, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission: April 30, 2010
Study Completion Date: July 31, 2010
Final Report Submission: October 31, 2010

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of hepatic impairment, Q-T prolongation and drug-drug interaction.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1556-5 Conduct a drug interaction clinical trial with a CYP3A4 inhibitor, ketoconazole, in patients with advanced cancer. This trial will be a crossover design to evaluate the effects of ketoconazole on the pharmacokinetic disposition of romidepsin.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission: July 31, 2010
Trial Completion Date: July 31, 2012
Final Report Submission: December 31, 2012

1556-6 Conduct a drug interaction clinical trial with a CYP3A4 inducer, rifampin, in patients with advanced cancer. This trial will be a crossover design to evaluate the effects of induction of CYP3A4 by rifampin on the pharmacokinetic disposition of romidepsin.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission: July 31, 2010
Trial Completion Date: July 31, 2012
Final Report Submission: December 31, 2012

1556-7 Conduct a clinical trial to determine the pharmacokinetics of romidepsin in advanced cancer patients with moderate and severe hepatic impairment. Submit the protocol for agency review prior to commencing the trial.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission: August 31, 2010

Trial Completion Date: August 31, 2014

Final Report Submission: August 31, 2015

1556-8 Perform trial GPI-06-0005 with adequate number of subjects to determine the potential of ISTODAX to prolong QT. The final analysis plan for the previously submitted protocol GPI-06-0005 will be provided. Exposure-response, central tendency and outlier analyses will be included in the final report.

The timetable you submitted on October 27, 2009, states that you will conduct this trial according to the following timetable:

Final Analysis Plan Submission: February 28, 2010

Trial Completion Date: August 31, 2010

Final Report Submission: March 31, 2011

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 022393.**”

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022393.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure
Labeling and Patient Labeling