

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-393

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Date	November 3, 2009
From	RICHARD PAZDUR, MD
Subject	OFFICE DIRECTOR MEMO
NDA/BLA #	22-393
Supplement #	
Applicant Name	Gloucester Pharmaceuticals Inc.
Date of Submission	January 12, 2009
PDUFA Goal Date	November 12, 2009
Proprietary Name / Established (USAN) Name	ISTODAC for injection/ Romidepsin
Dosage Forms / Strength	Single use vial containing 10 mg lyophilized powder
Proposed Indication(s)	ISTODAX is indicated for treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy.
Action/Recommended Action for NME:	<i>Approval, (regular)</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Reviews	Qin Ryan
Statistical Review	Huanyu Chen, Kun He
Pharmacology Toxicology Review	Alexander Putnam, Todd Palmby, Haleh Saber, John Leighton
CMC Review/OBP Review	Ying Wang, Hari Sarker, Sarah Miksinki
Microbiology Review	Bryan Riley
Clinical Pharmacology Review	Hua Zhang
DDMAC	JuWon Lee, Stephanie Victor
DSI	John Lee
CDTL Review and Division	Ellen Maher
Director Review	Robert Justice
OSE/ DMEPA	Cathy Miller
OSE/DDRE	N/A
OSE/ DRISK	Sharon Mills
Other: QT-IRT/SEALD/PMH	Suchitra Balakrishnan/Elektra Papadopoulos/Jeanine Best

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

SUMMARY

On November 5, 2009, the U.S. Food and Drug Administration granted approval to romidepsin for injection (Istodax[®], Gloucester Pharmaceuticals Inc.) for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

The efficacy and safety of romidepsin were evaluated in two single-arm, multicenter, open label trials. Efficacy was assessed in 167 patients with CTCL treated in the United States, Europe, and Australia. Study 1 included 96 patients with CTCL who had received at least 1 prior systemic therapy. Study 2 included 71 patients with CTCL who received a median of 2 prior systemic therapies. In both trials, patients could be treated until disease progression. Overall response was evaluated according to a composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and Sézary cells.

The primary efficacy endpoint for both trials was the overall response rate (ORR) based on the investigator assessments, and defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). The ORRs in these two trials were similar (34 and 35% in Study 1 and Study 2, respectively) and CR rates were the same (6%). The median response duration was 15 months in Study 1 and 11 months in Study 2.

Safety data was available and evaluated in 185 patients. The most common adverse reactions in Study 1 were nausea, fatigue, infections, vomiting and anorexia. The most common adverse reactions in Study 2 were nausea, fatigue, anemia, thrombocytopenia, ECG T-wave changes, neutropenia and lymphopenia. Serious adverse reactions reported in > 2% of the patients in Study 1 were infection, sepsis, and pyrexia. Serious adverse reactions reported in > 2% of the patients in Study 2 were infection, supraventricular arrhythmia, neutropenia, fatigue, edema, central line infection, ventricular arrhythmia, nausea, pyrexia, leukopenia, and thrombocytopenia.

The recommended dose and schedule of romidepsin is 14 mg/m² intravenously over 4 hours on days 1, 8 and 15 of a 28-day cycle.

REVIEW

Romidepsin is a histone deacetylase (HDAC) inhibitor which catalyzes the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. However, its mechanism of action in CTCL has not been fully characterized. The application is supported by two single-arm clinical trials in patients with previously treated CTCL. This new drug application seeks approval of ISTODAX (romidepsin) for injection for

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the indication of “treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.” The application was received on 1/12/09 and was given a standard review.

The efficacy results from the clinical studies submitted in support of this application are provided in the following excerpt from the agreed-upon package insert:

ISTODAX was evaluated in 2 multicenter, single-arm clinical studies in patients with CTCL. Overall, 167 patients with CTCL were treated in the US, Europe, and Australia. Study 1 included 96 patients with confirmed CTCL after failure of at least 1 prior systemic therapy. Study 2 included 71 patients with a primary diagnosis of CTCL who received at least 2 prior skin directed therapies or one or more systemic therapies. Patients were treated with ISTODAX at a starting dose of 14 mg/m² infused over 4 hours on days 1, 8, and 15 every 28 days.

In both studies, patients could be treated until disease progression at the discretion of the investigator and local regulators. Objective disease response was evaluated according to a composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and abnormal circulating T-cells (“Sézary cells.”).

The primary efficacy endpoint for both studies was overall objective disease response rate (ORR) based on the investigator assessments, and defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). CR was defined as no evidence of disease and PR as $\geq 50\%$ improvement in disease. Secondary endpoints in both studies included duration of response and time to response...

Demographic and disease characteristics of the patients in Study 1 and Study 2 are provided in Table 2.

Table 2. Baseline Patient Characteristics

Characteristic	Study 1 (N=96)	Study 2 (N=71)
Age		
N	96	71
Mean (SD)	57 (12)	56 (13)
Median (Range)	57 (21, 89)	57 (28, 84)
Sex, n (%)		
Men	59 (61)	48 (68)
Women	37 (39)	23 (32)
Race, n (%)		
White	90 (94)	55 (77)
Black	5 (5)	15 (21)
Other/Not Reported	1 (1)	1 (1)
Stage of Disease at Study Entry, n (%)		
IA	0 (0)	1 (1)
IB	15 (16)	6 (9)
IIA	13 (14)	2 (3)
IIB	21 (22)	14 (20)
III	23 (24)	9 (13)
IVA	24 (25)	27 (38)
IVB	0 (0)	12 (17)
Number of Prior Skin-Directed Therapies		
Median (Range)	2 (0,6)	1 (0,3)
Number of Prior Systemic Therapies		
Median (Range)	2 (1, 8)	2 (0, 7)

Table 3. Clinical Results

Response Rate	Study 1 (N=96)	Study 2 (N=71)
ORR (CR + PR), n (%)	33 (34)	25 (35)
[95% Confidence Interval]	[25, 45]	[25, 49]
CR, n (%)		
[95% Confidence Interval]	6 (6) [2, 13]	4 (6) [2, 14]
PR, n (%)		
[95% Confidence Interval]	27 (28) [19, 38]	21 (30) [20, 43]
Duration of Response (months)		
N	33	25
Median (range)	15 (1, 20*)	11 (1, 66*)
*denotes censored value		

The safety data from the two clinical trials is summarized in the following excerpt from the Adverse Reactions section of the agreed-upon package insert:

Common Adverse Reactions

Table 1 summarizes the most frequent adverse reactions (> 20%) regardless of causality using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0). Due to methodological differences between the studies, the AE data are presented separately for Study 1 and Study 2. Adverse reactions are ranked by their incidence in Study 1. Laboratory abnormalities commonly reported (>20%) as adverse reactions are included in Table 1.

**Table 1. Adverse Reactions
Occurring in >20% of Patients in Either CTCL Study (N=185)**

Adverse Reactions n (%)	Study 1 (n=102)		Study 2 (n=83)	
	All	Grade 3 or 4	All	Grade 3 or 4
<i>Any adverse reaction</i>	99 (97)	36 (35)	83 (100)	68 (82)
Nausea	57 (56)	3 (3)	71 (86)	5 (6)
Asthenia/fatigue	54 (53)	8 (8)	64 (77)	12 (14)
Infections	47 (46)	11 (11)	45 (54)	27 (33)
Vomiting	35 (34)	1 (<1)	43 (52)	8 (10)
Anorexia	23 (23)	1 (<1)	45 (54)	3 (4)
Hypomagnesemia	22 (22)	1 (<1)	23 (28)	0
Diarrhea	20 (20)	1 (<1)	22 (7)	1 (1)
Pyrexia	20 (20)	4 (4)	19 (23)	1 (1)
Anemia	19 (19)	3 (3)	60 (72)	13 (16)
Thrombocytopenia	17 (17)	0	54 (65)	12 (14)
Dysgeusia	15 (15)	0	33 (40)	0
Constipation	12 (12)	2 (2)	32 (39)	1 (1)
Neutropenia	11 (11)	4 (4)	47 (57)	22 (27)
Hypotension	7 (7)	3 (3)	19 (23)	3 (4)
Pruritus	7 (7)	0	26 (31)	5 (6)
Hypokalemia	6 (6)	0	17 (20)	2 (2)
Dermatitis/Exfoliative dermatitis	4 (4)	1 (<1)	22 (27)	7 (8)
Hypocalcemia	4 (4)	0	43 (52)	5 (6)
Leukopenia	4 (4)	0	38 (46)	18 (22)
Lymphopenia	4 (4)	0	47 (57)	31 (37)
Alanine aminotransferase increased	3 (3)	0	18 (22)	2 (2)
Aspartate aminotransferase increased	3 (3)	0	23 (28)	3 (4)
Hypoalbuminemia	3 (3)	1 (<1)	40 (48)	3 (4)
Electrocardiogram ST-T wave changes	2 (2)	0	52 (63)	0
Hyperglycemia	2 (2)	2 (2)	42 (51)	1 (1)
Hyponatremia	1 (<1)	1 (<1)	17 (20)	2 (2)
Hypermagnesemia	0	0	22 (27)	7 (8)
Hypophosphatemia	0	0	22 (27)	8 (10)
Hyperuricemia	0	0	27 (33)	7 (8)

Serious Adverse Reactions

Serious adverse reactions reported in > 2% of patients in Study 1 were infection, sepsis, and pyrexia. In Study 2, serious adverse reactions in > 2% of patients were

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infection, supraventricular arrhythmia, neutropenia, fatigue, edema, central line infection, ventricular arrhythmia, nausea, pyrexia, leukopenia, and thrombocytopenia.

Most deaths were due to disease progression. In Study 1, there were two deaths due to cardiopulmonary failure and acute renal failure. In Study 2, there were six deaths due to infection (4), myocardial ischemia, and acute respiratory distress syndrome.

Discontinuations

Discontinuation due to an adverse event occurred in 21% of patients in Study 1 and 11% in Study 2. Discontinuations occurring in at least 2% of patients in either study included infection, fatigue, QT prolongation, and dyspnea.

The Warnings and Precautions section addresses the need to monitor potassium, magnesium, and blood counts. It also describes the potential for T-wave and ST-segment changes and QT prolongation, the potential for fetal harm if used during pregnancy, and the potential for reducing the effectiveness of estrogen-containing contraceptives.

This application was discussed at the September 2, 2009 meeting of the Oncologic Drugs Advisory Committee. The committee was asked the following two questions:

- “Do the results of the two romidepsin single arm studies represent a favorable risk-benefit profile for patients with previously treated CTCL?” The vote was 10 Yes, 0 No, and 1 Abstain.
- “FDA has approved drugs in CTCL on the basis of single-arm trials. Should randomized studies be required for future approvals?” The vote was 7 Yes, 3 No, and 1 Abstain.

- Risk Benefit Assessment

Favorable risk/benefit assessment. Recommendation for regular approval.

- There were no recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing studies and trials are required to identify an unexpected serious risk of toxicity from a _____ 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 interactions with ISTODAX:

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1. 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.
2. An animal study(ies) to determine the estrogenic/ anti-estrogenic effects of romidepsin.
3. 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.
4. 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).
5. 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.
6. 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.
7. 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.
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.

b(4)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22393

ORIG-1

GLOUCESTER
PHARMACEUTICA
LS INC

ROMIDEPSIN FOR INFUSION

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

/s/

RICHARD PAZDUR
11/05/2009