CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-393

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 2, 2009
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-393
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:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	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	Ellen Maher
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

Division Director Summary Review

1. Introduction

This new drug application seeks approval of ISTODAX (romidepsin) for injection for 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. This review will summarize the designs of the submitted clinical trials, the efficacy and safety results, and the recommendations of each review discipline.

2. Background

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.

3. CMC/Device

The Chemistry Review of 10/21/09 made the following recommendation and conclusion on approvability:

> From the chemistry, manufacturing, and control perspective, this NDA is recommended for approval, pending receipt of final and acceptable container/carton labels for the drug product.
>
> Please insert the following language into the action letter: "The approved expiration dating period is 36-months based on the submitted stability data for this drug product, as co-packaged in two separate single-use vials and when stored at 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F)."

The ONDQA Division Director's Memo stated that "ONDQA recommends approval (AP)."

The Product Quality Microbiology Review of 8/6/09 recommended approval.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections

were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation of 10/19/09 recommended approval of romidepsin for the proposed indication. The review recommended the following post-marketing study requirements:

1) The reproductive toxicology studies conducted in rats did not result in significant maternal or embryo-fetal toxicity, and are therefore deemed inadequate to assess potential risk to a developing embryo or fetus associated with romidepsin treatment. Adequate embryo-fetal risk assessment should be provided. Embryo-fetal toxicology studies are typically conducted in two species. If romidepsin causes embryo-fetal lethality or is teratogenic in one species, a study in the second species may not be warranted. Provide dates for protocol submission, study completion, and submission of the final study report.
2) Romidepsin was shown to bind to estrogen receptors *in vitro*. Toxicology studies suggested romidepsin modulation of estrogen signaling as evidenced by female-specific findings (e.g. atrophy of mammary gland, uterus, ovary and vagina; pituitary hyperplasia; elevated cholesterol and triglycerides). Therefore, romidepsin may increase the risk of estrogen-agonist-like serious risks, such as uterine cancer, clotting, and cardiovascular disease, or the risk of estrogen-antagonist-like serious risks, such as osteoporosis and fracture. In addition, romidepsin may interfere with hormonal contraceptives, resulting in high-risk pregnancies. Please assess estrogenic and anti-estrogenic effects of romidepsin. The assessment could be based on clinical or non-clinical data. Provide dates for protocol submission, study completion, and submission of the final study report.
3) The final ISTODAX drug product contains the [ ] This —— is not currently listed in ICH Q3C, and the safety of I.V. administered —————— has not been adequately established. The amount of —————— delivered to patients in clinical trials was — of the dose of your drug product, and may have contributed to toxicities seen in clinical trials. Please characterize toxicities associated with I.V. administered —————— in at least one non-clinical toxicology study, using an appropriate animal species, and propose a safe clinical dose based on your data. Provide dates for protocol submission, study completion, and submission of the final study report.

b(4)

The Pharmacology/Toxicology Acting Team Leader and Associate Director for Pharmacology/Toxicology memorandums concurred with the recommendations for approval and the PMRs.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval and with the post-marketing study requirements.

5. Clinical Pharmacology

The Clinical Pharmacology Review of 9/1/09 provided the following recommendations:

1.1 RECOMMENDATIONS

This NDA is considered acceptable from a clinical pharmacology perspective provided that the Applicant agrees to the post-marketing studies:

1.2 PHASE 4 REQUIREMENTS

1. Conduct a drug interaction study to evaluate the effect of CYP3A4 inhibitor (e.g. ketoconazole) on the pharmacokinetics of romidepsin.
2. Conduct a drug interaction study to evaluate the effect of CYP3A4 inducer (e.g. rifampin) on the pharmacokinetics of romidepsin.
3. Conduct a study to determine the pharmacokinetics of romidepsin in patients with moderate and severe hepatic impairment.
4. Perform a study to determine the potential of ISTODAX to prolong QT.

1.3 PHASE 4 COMMITMENT

Conduct an *in vitro* study to determine whether romidepsin is an inducer of CYP enzymes including CYP3A4.

The QT-IRT consultation provided the following summary of QT effects:

- There are several limitations to the ECG data collected in these studies which limit the interpretation of results. The limitations include:
    1. In study GPI-04-001, triplicate ECGs were collected at screening, at baseline, and within 2 hours after completion of administration of romidepsin. An ECG was not acquired at maximum plasma concentrations. ECGs were not collected at later time points to rule out any delayed drug effects on QT prolongation. Blood draws for PK were not obtained; therefore, exposure-response analysis cannot be performed. There were no controls (positive or negative).

2. In study NCI 1312, single ECGs were collected at baseline, within 2 hours after completion of administration of romidepsin and at 24 and 48 hours post-dose.
3. In study GPI-06-0005, triplicate ECGs and PK samples were collected prior to infusion and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-infusion. There are only 7 patients with available data. The number of patients to be evaluated may be too low to obtain any meaningful results from the exposure-response analysis.
4. Waveforms were not submitted to the ECG warehouse for review.

The consult recommended that "The sponsor should perform a dedicated QT assessment in a sufficient number of patients, with triplicate ECGs and PK samples similar to GPI-06-0005 to adequately characterize the QT effect…"

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval and with the recommended post-marketing study requirements. However, the PMC should be a PMR.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

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/m^2 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 ≥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)

Efficacy outcomes are provided in Table 3. Median time to first response was 2 months (range 1 to 6) in both studies. Median time to CR was 6 months in Study 1 and 4 months in Study 2 (range 2 to 9).

Table 3. Clinical Results

Response Rate	Study 1 (N=96)	Study 2 (N=71)
ORR (CR + PR), n (%) [95% Confidence Interval]	33 (34) [25, 45]	25 (35) [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 Clinical Review of 10/22/09 made the following recommendation on regulatory action.

> This reviewer recommends Istodax (romidepsin) administered at 14 mg/m^2 intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

The CDTL Review of 10/21/09 recommended regular approval.

The Statistical Review and Evaluation stated the following:

> The data and analyses from the submission indicated that the response rate in patients with CTCL treated with romidepsin was 34% and 35% in the GPI-04-0001 and NCI 1312 studies, respectively. The median duration of response was 454 and 336 days in the GPI-04-0001 and NCI 1312 studies, respectively. Whether the data and analyses from the current submission demonstrate a favorable risk-benefit profile is deferred to the clinical team reviewing this submission.

The Acting Statistical Team Leader's of 9/22/09 concurred with the statistical review.

8. Safety

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:

> The safety of ISTODAX was evaluated in 185 patients with CTCL in 2 single arm clinical studies in which patents received a starting dose of 14 mg/m^2. The mean duration of treatment in these studies was 5.6 months (range: <1 to 83.4 months).
>
> *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)

	Study 1 (n=102)		Study 2 (n=83)	
Adverse Reactions n (%)	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**
Any adverse reaction	*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

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.

9. Advisory Committee Meeting

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.

10. Pediatrics

Romidepsin has orphan drug exclusivity and PREA does not apply.

11. Other Relevant Regulatory Issues

- DSI Audits

The Clinical Inspection Summary provided the following 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.

- Financial Disclosure

  As noted in the Clinical Review, no financial conflicts of interest were reported.

- DDMAC provided comments on the PI and PPI. DRISK provided revisions to the PPI. SEALD provided comments on the PI. Pediatric and Maternal Health Staff provided recommendations regarding revisions to the Use in Pregnancy and Use in Women of Childbearing Potential subsections in the PI. Recommendations from all consultants were discussed during the labeling meetings and incorporated as indicated.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: DMEPA found the proprietary name to be acceptable.
- Physician labeling: Agreement was reached with the applicant on the physician labeling.
- Carton and immediate container labels: Deficiencies identified by DMEPA were corrected by the applicant.
- Patient labeling: The applicant agreed to the revisions to the patient labeling recommended by DRISK.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: approval
- Risk Benefit Assessment

  The risk benefit assessment for romidepsin is favorable. The objective response rates (CR+PR) in the two submitted studies were 34% and 35% and the complete response rates were 6% in both studies. The responses were durable with a median duration of response of 15 months in one study and 11 months in the other. The most common adverse reactions were nausea, fatigue, infections, vomiting, and anorexia in Study 1

and nausea, fatigue, anemia, thrombocytopenia, ECG T-wave changes, neutropenia and lymphopenia in Study 2. Serious adverse reactions reported in Study 1 included infection, sepsis, and pyrexia. In Study 2, serious adverse reactions included infection, supraventricular arrhythmia, neutropenia, fatigue, edema, central line infection, ventricular arrhythmia, nausea, pyrexia, leukopenia, and thrombocytopenia. Most deaths were due to disease progression. The Oncologic Drugs Advisory Committee voted 10 to 0 with one abstention that the risk-benefit profile was favorable.

- Recommendation 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: b(4)

  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. b(4)

  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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS 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/

ROBERT L JUSTICE
11/02/2009