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RESEARCH**

APPLICATION NUMBER:

22-393

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 16, 2009
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	022-393
Supplement#	000
Applicant	Gloucester Pharmaceuticals
Date of Submission	January 12, 2009
PDUFA Goal Date	November 13, 2009
Proprietary Name / Established (USAN) names	Istodax/Romidepsin
Dosage forms / Strength	14 mg/M ² IV days 1, 8, and 15 every 28 days
Proposed Indication(s)	Indicated for the treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy
Recommended:	Regular Approval

1. Introduction

Romidepsin is a histone deacetylase inhibitor (HDAC). HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histone and non-histone proteins. Histones bind tightly to DNA and alterations in these proteins leads to alterations in DNA configuration. This, in turn, results in a change in gene expression. Additional effects of romidepsin included a time-dependent increase in the apoptotic population, G1 and G2/M cell cycle arrest, and romidepsin-induced differentiation of tumor cell lines.

Romidepsin has been studied in a wide variety of tumors and found to have activity in cutaneous T cell lymphoma (CTCL). CTCL is a rare disease and the applicant has submitted two single arm studies, NCI 1312 and GPI-04-0001 (N = 185) in support of the following indication:

- Treatment of CTCL in patients who have received at least one prior systemic therapy.

2. Background

CTCL is a rare disease affecting 3,000 new patients in the U.S. yearly (Arch Dermatol 2007 143:854). Mycosis fungoides is the most common type of CTCL. Early stages of the disease form patches, plaques, and tumors on the skin. Advanced stages involve the lymph nodes, blood, bone marrow, and visceral organs while Sezary syndrome includes generalized erythroderma with circulating Sezary cells (large, CD4+ cells with a cerebriform nucleus).

Three agents have recently been approved for the treatment of CTCL. Methotrexate and methoxypsoralen have also been approved for this condition. In addition to these, a large number of chemotherapeutic agents are used “off-label” in this disease. The three agents recently approved for the treatment of CTCL are shown in the table below.

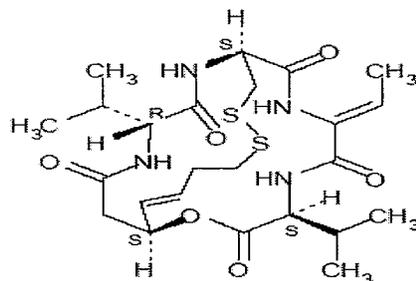
Table 1: Systemic Therapies Approved for the Treatment of Cutaneous T Cell Lymphoma					
Agent	Year Approved	Approval	Class	Indication	Basis of Approval
Vorinostat	2006	Full	HDAC inhibitor	Treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent or recurrent disease on or following 2 systemic therapies	RR 29.7% Duration of Response 148 days, RR 24.2% Duration of Response 106 days
Denileukin diftitox	1999 2008	Accelerated Full	Fusion protein	Treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor	RR 23% (9 µg), 36% (18 µg) Duration of Response 120 days PFS HR 0.27 (18 µg), 0.42 (9 µg) Median Duration 220-277 days
Bexarotene	1999	Full	Retinoid X-receptor activator	Treatment of cutaneous manifestations of CTCL in patients who are refractory to at least 1 prior systemic therapy	RR 54%, 45% Duration of Response > 107 days, 159 days

The clinical development of romidepsin was initiated in 1996 under IND 51,810 by the National Cancer Institute. The supportive study, NCI 1312, was conducted under this IND. IND 63,573 was submitted by Astellas Pharma on April 30, 2002 and subsequently transferred to Gloucester Pharmaceuticals. The pivotal study, GPI-04-0001, was conducted under this IND. Three End of Phase 2 meetings and 3 pre-NDA meetings were held with Gloucester Pharmaceuticals. Gloucester also submitted a request for Special Protocol Assessment for the pivotal study, GPI-04-0001. In these meetings, the Agency stated that a single arm study might be sufficient in patients who had failed standard therapy. Both vorinostat and bexarotene were approved on the basis of single arm studies. During review of the Special Protocol Assessment, the Agency agreed to the applicant’s primary endpoint. However, a statistical analysis plan issued just prior to analysis of the pivotal study was not agreed to by the Agency.

3. CMC/Device

The product reviewers have recommended regular approval of romidepsin. Romidepsin is a bicyclic depsipeptide. It is synthesized as a secondary metabolite by a strain of *Chromobacterium violaceum*, a naturally occurring soil bacterium that has been mutated to enhance production of romidepsin. Romidepsin is

↓ The drug substance is a white powder ↓
 ↓ The structure of romidepsin is shown below.



b(4)

The drug product contains romidepsin as a sterile lyophilized white powder in a single-use vial containing 10 mg romidepsin and 20 mg of the bulking agent, povidone. The diluent contains 80% (v/v) propylene glycol and 20% (v/v) dehydrated alcohol.

The Office of Compliance made an overall recommendation of ACCEPTABLE for all establishments in this application.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers recommend regular approval for romidepsin. Romidepsin is not genotoxic *in vitro* or *in vivo*. However, embryofetal toxicities were not adequately assessed and the applicant will be asked to complete a reproductive toxicology study as a post-marketing commitment. Given the mechanism of action of romidepsin, it has been assigned Pregnancy Category D. Romidepsin competes with β -estradiol for binding to estrogen receptors *in vitro*. Thus, romidepsin may interfere with estrogen containing contraceptives. The applicant will be asked to assess estrogenic and anti-estrogenic effects of romidepsin in post-approval studies.

In pre-clinical studies, effects on the hematopoietic system, liver, heart (irregular rhythm, QTc prolongation, cardiomyocyte injury), GI tract, and male and female reproductive systems were seen. Romidepsin and its metabolites can cross the blood-brain barrier. High doses of romidepsin can cause an increased heart and respiratory rate, effects on equilibrium and gait, and CNS excitation (convulsion, tremor).

⌈ used in the drug product manufacturing and is largely removed during the lyophilization process. This : — is not included in the ICH list of : — and there are no animal toxicology studies using intravenous administration. Based on clinical data, the pharmacology/toxicology reviewer recommended a product specification of : — /10 mg vial of romidepsin. Note that in clinical studies, maximum administered ⌈

b(4)

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers recommend regular approval for romidepsin. Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0-24.9 mg/m² administered intravenously over a 4 hour period in patients with advanced cancers. Romidepsin is highly protein bound in plasma (92-94%). In patients with T cell lymphomas who received 14 mg/m² of romidepsin intravenously over a 4 hour period on days 1, 8 and 15 of a 28-day cycle, geometric mean values of the maximum plasma concentration (C_{max}) and the area under the plasma concentration versus time curve (AUC_{0-∞}) were 377 ng/mL and 1549 ng*hr/mL, respectively. The terminal half-life is approximately 3 hours. After repeated administration using the proposed dosing regimen, romidepsin pharmacokinetics did not change appreciably and no accumulation was observed. The population pharmacokinetic

analysis of romidepsin showed that age, gender, or race did not appear to influence the pharmacokinetics of romidepsin.

Romidepsin undergoes extensive metabolism in vitro primarily by CYP3A4 with minor contribution from CYP3A5, CYP1A1, CYP2B6, and CYP2C19. Co-administration of romidepsin with potent CYP3A4 inhibitors and inducers is expected to alter its pharmacokinetics. The population pharmacokinetic analysis indicates that mild and moderate hepatic impairment and mild, moderate, or severe renal impairment had no significant influence on romidepsin pharmacokinetics. The effect of severe hepatic impairment on the pharmacokinetics of romidepsin is unknown.

6. Clinical Microbiology

There were no clinical microbiology issues with romidepsin. Vials are filled using _____ techniques and the container closure is sterile.

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7. Clinical/Statistical- Efficacy

Two studies supported the efficacy and safety of romidepsin in CTCL. These are shown in the table below. The top and bottom numbers (under N) represent the number of patients available at the efficacy and safety cutoffs. Safety data was also provided for an additional 685 patients from 33 studies involving a number of tumor types.

Table 2: Primary Studies Supporting the Efficacy and Safety of Romidepsin			
Study ID	Title	N	Data Cutoff
GPI-04-0001	A Single Agent Phase II Study of Depsipeptide in the Treatment of Cutaneous T Cell Lymphoma	96	Efficacy: 5-2008
		102	Safety: 10-2007
NCI 1312	Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma	71	Efficacy: 3-2007
		83	Safety: 12-2007

Study Design

The design of GPI-04-0001 and NCI1312 is discussed very briefly in this review. Please see Dr. Ryan's primary clinical review for additional details on the study design. On the surface, the two studies appear very similar. However, there are a number of differences in the eligibility criteria and in the assessment of response. GPI-04-0001 (GPI study) is considered the pivotal study. It enrolled patients with Stage IB (patients with patches and plaques over \geq 10% of their body surface area) to Stage IVA (nodal involvement and erythroderma) disease. All patients received skin directed therapy as well as at least one course of systemic therapy prior to entry. Patients received romidepsin 14 mg/M² IV on days 1, 8, and 15 every 28 days. The primary endpoint was a composite score of skin and lymph node involvement. To be considered a partial response, patients could have a partial response in the skin and stable disease elsewhere. Disease status was evaluated at baseline and every other cycle.

NCI 1312 is considered the supportive study. It enrolled patients with Stage IA (patches and plaques over < 10% of their body surface area) to IVB (visceral involvement) disease. The extent of prior therapy varied by disease stage, but most patients had received prior systemic therapy. The first 3 patients received romidepsin 18 mg/M². This proved toxic and the protocol was amended to administer romidepsin 14 mg/M². The primary endpoint involved a retrospective physician’s global assessment of complete response, partial response (> 50% improvement), etc. To be considered a partial response, patients could have a partial response in the skin and stable disease elsewhere. Disease status was assessed at baseline and periodically throughout the treatment period.

In both studies, patients with significant cardiac disease, a prolonged QTc interval, or those who were on medications that prolong the QTc interval were excluded. Although response was assessed differently on the two studies, the primary endpoint on both was response rate defined as the percentage of patients with a clinical complete response (CCR) or a partial response (PR). Secondary endpoints included the duration of response.

Baseline Characteristics

Patient demographics were similar between the two studies. Both the GPI and the NCI study had a male predominance with a median age of 56.9 and 56 years, respectively. In the U.S., CTCL occurs more commonly in blacks. Despite this, most patients, on both studies, were Caucasian. The table below presents information on the baseline disease characteristics in both studies.

Table 3: Baseline Disease Characteristics		
Parameter	GPI-04-0001 N = 96	NCI 1312 N = 71
Duration of Disease		
Median (Range)	3.03 years (0.06, 25.5)	3.0 years (1, 23.7)
Disease Stage at Study Entry		
IA	0	1 (1%)
IB	15 (16%)	6 (9%)
IIA	13 (14%)	2 (3%)
IIB	21 (22%)	14 (20%)
IIIA or B	23 (24%)	8 (11%)
IV/IVA	24 (25%)	27 (38%)
IVB	0	12 (17%)
Performance Status		
0	49 (51%)	16 (23%)
1	47 (49%)	41 (58%)
≥2	0	10 (14%)
Missing	0	4 (6%)

The following table presents information on prior therapy. Most patients received prior systemic therapy. The median number of prior systemic therapies and the median number of prior skin directed therapies was the same on both studies. The number of patients receiving individual therapies (e.g., the number of patients who received prior bexarotene) is too small to draw any conclusions. Note that N = 70 rather than 71 in NCI 1312. Data is missing for one patient.

Table 4: Prior Therapies		
	GPI-04-0001 N = 96	NCI 1312 N = 70
Number of Patients with Any Prior CTCL Therapy	96 (100.0%)	68 (97.1%)
Number of Prior CTCL Therapies		
N	96	68
Median (Range)	4 (1, 11)	3 (1, 10)
Number of Prior Systemic CTCL Therapies		
N	96	63
Median (Range)	2 (1, 8)	2 (1, 7)
Number of Prior Skin Directed Therapies		
N	90	43
Median (Range)	2 (1, 6)	2 (1, 3)

Primary Endpoint

The table below provides the confirmed overall response rate (CR + PR) as assessed by the investigator in both studies. The Agency considers this to be the primary endpoint. The applicant presented both the investigator assessed and the Independent Review Committee (IRC) assessed response rate. Since skin disease is difficult to assess with photographs, the investigator assessments are considered primary and the IRC assessments (which used patient photographs) to provide corroboration of the investigator assessment. It should also be noted that IRC review was not part of the original protocol, but was added post hoc.

Table 5: Investigator-Assessed Response Rate in All Enrolled Patients		
Response Rates	GPI-04-0001 N = 96	NCI 1312 N = 71
Confirmed Response Rate [95%CI]	33 (34.4%) [25.0, 44.8]	25 (35.2%) [25.4, 49.3]
Complete Response [95%CI]	6 (6.3%) [2.3, 13.1]	4 (5.6%) [1.6, 14.4]
Partial Response [95%CI]	27 (28.1%) [19.4, 38.2]	21 (29.6%) [20.2, 43.3]

Despite the differences in the patient population and in the assessment of response, the response rate is almost identical in these two studies. The median time to response was approximately 2 cycles (first patient assessment occurred after 2 cycles) on both studies. However, the time to complete response was much longer, 131 days on the GPI study and 196 days on NCI 1312. While it is interesting to speculate that a partial response may gradually evolve into a complete response, the number of patients with a complete response is too small to draw this conclusion.

Secondary Endpoint

The table below provides the median duration of response in both studies. The duration of response cannot be directly compared between studies since patients were assessed at different intervals. Further, confirmation of disease progression was required in patients on GPI-04-0001, but not on NCI 1312.

Table 6: Duration of Response		
	GPI-04-0001	NCI 1312
	N = 33	N = 25
Median Response Duration [95% CI]	454 Days [454, NE]	336 Days [148, NE]

NE: not evaluable

Pruritus was also assessed as a secondary endpoint in the GPI study using a VAS. This was an open-labeled single arm study and was not able to provide an unbiased estimate of changes in pruritus. Therefore, an examination of this data is not included in the review.

Sensitivity and Subset Analyses

Antibiotic use was widespread in both the GPI study and NCI 1312 with half of the GPI and on-quarter of the NCI patients receiving systemic antibiotics. Since it is often difficult to distinguish a skin response from a clearing of infection, the effect of antibiotic use on response rate was examined in both studies. Response rates in those that did NOT receive antibiotics were substantially lower than the response rates in patient who DID receive concomitant antibiotics.

Note that the response rate for patients who did NOT receive concomitant systemic antibiotics in the GPI study was 27% and that the lower limit of the 95% confidence interval was 15%. This is identical to the response rate in the placebo arm of the denileukin difitox registration study.

Table 7: Response with and without Anti-Infectives				
Concomitant Anti-infective Therapy	GPI-04-0001 N = 96		NCI 1312 N = 71	
	Response Rate		Response Rate	
	Use	No Use	Use	No Use
Systemic [95%CI]	42% [28, 57]	27% [15, 42]	44% [20, 70]	33% [21, 47]
Antibacterial [95%CI]	44% [30, 59]	25% [14, 40]	40% [19, 64]	33% [21, 48]
Topical [95%CI]	30% [12, 54]	36% [25, 47]	50% [25, 75]	31% [19, 45]
Antiviral [95%CI]	11% [0.3, 48]	37% [27, 48]	43% [10, 82]	34% [23, 47]
Antifungal [95%CI]	27% [10.7,50.2]	37% [25.6,48.5]	40% [5.3,85.3]	35% [23.5,47.6]

The following table provides information on discrepancies between the investigator and IRC response. On the GPI study, 4 investigator-assessed responders were considered, by the IRC, non-responders while on the NCI study, 6 investigator-assessed responders were considered, by the IRC, non-responders.

Table 8: Discrepancies between Investigator and Independent Review Response			
	Independent Review Committee		
GPI-04-0001			
Investigator	CR	PR	Total-INV
CR	6	0	6
PR	1	22	27
Total-IRC	7	22	
NCI 1312			
Investigator	CR	PR	Total-INV
CR	4	0	4
PR	0	15	21
Total-IRC	4	15	

Subset analyses included response by disease stage and prior therapy. The table below provides information on response by disease stage. This analysis suggests that response was not strongly affected by disease stage.

Table 9: Response Rate by Disease Stage		
	GPI-04-0001 N = 96	NCI 1312 N = 71
Disease Stage	Number of Responders / N	Number of Responders / N
IA	0	1/1
IB	0/15	3/6
IIA	3/13	1/2
IIB	9/21	6/14
III A or B	9/23	4/8
IVA	8/24	4/27
IVB	0	6/12

This next table examines the response rate by the extent of prior therapy. Again, response does not seem to be affected by the number of prior therapies, skin directed or systemic. However, while it can be concluded that response is not confined to patients with 1 prior therapy, the number of patients is too small to state that prior therapy is unrelated to response.

Table 10: Response Rate by Prior Therapy		
Prior Treatments	GPI-04-0001 N = 96	NCI 1312 N = 71
No. of Prior Therapies	Number of Responders / N	Number of Responders / N
1	0/2	7/19
2	8/19	6/10
≥ 3	25/75	11/39
No. of Skin Directed Therapies		
1	12/36	8/19
2	9/28	4/14
≥ 3	11/26	3/10
No. of Systemic Therapies		
1	11/30	7/20
2	9/22	9/20
≥ 3	13/44	6/23

8. Safety

Safety Database

The table below provides an overview of the safety database submitted with NDA 22-393. The safety update presented information on 185 patients with CTCL. It also provided data on an additional 685 patients with other tumor types who received romidepsin. This included 428 patients treated at 14 mg/M².

Indication	Safety Update n (%)	Treated at 14 mg/M ² Safety Update n (%)
CTCL		
GPI-04-0001	102 (12)	102 (17)
NCI 1312	83 (10)	80 (13)
PTCL and Other T Cell Lymphomas	91 (10)	89 (15)
Hematologic Malignancies	82 (9)	67 (11)
Solid Tumors	512 (59)	272 (45)
Overall Total	870	610

The cutoff date for the safety update for GPI-04-0001 was study completion while the cutoff for NCI 1312 was April 2009. On the remaining studies data cutoff varied from November 2008 to March 2009.

Most of the safety review will focus on GPI-04-001 and NCI 1312 since these studies were conducted in the indicated population. The remainder of the data will be used to further explore adverse events of concern or to provide an overview of adverse events.

Safety Assessments

The schedule of safety assessments differed markedly between the two studies. On the GPI study, adverse events, CBCs, chemistries, and multiple EKGs were collected on the day of dosing and at the end of study. A CBC was collected on Day 22. On NCI 1312, the schedule of safety assessments differed by site. Patients at the NCI Clinical Center were hospitalized for dosing and adverse events, CBCs, chemistries, multiple EKGs, troponin, and CPK were collected on Days 1 and 2, 8 and 9, and 15 and 16. In addition, at the NCI Clinical Center, an echocardiogram was done on Day 16 and a Holter monitor placed on Day 1 of each cycle. Patients on NCI 1312 at extramural sites were seen on the day of dosing and adverse events, CBCs, chemistries, and multiple EKGs were collected at that time. Further, on the NCI study, each abnormal laboratory was reported as an AE while on the GPI study, investigators were instructed to record only clinically significant laboratory values.

Exposure

The table below presents information on romidepsin exposure in the two trials. The median number of cycles and the median dose of romidepsin were similar in the two trials. However, differences in dose modification criteria can be seen in the number of patients with dose delay or dose reduction. Dose delay occurred in 41% of patients on the GPI and only 18% of patients

on the NCI study. Criteria for dose delay on the GPI study included grade 2-4 non-hematologic and grade 3-4 hematologic toxicity. Criteria for dose delay on NCI 1312 included grade 3-4 non-hematologic and grade 4 hematologic toxicity. Given these more stringent criteria, the percentage of patients with dose delay was greater on the GPI study.

Alternatively, the frequency of dose reduction was lower on the GPI study than on NCI 1312. On the GPI study, 25% of patients underwent dose reduction while on NCI 1312, 63.4% of patients were dose reduced. This is again due to differences in dose modification criteria. The GPI study permitted only one dose reduction while the NCI study allowed up to four dose reductions prior to discontinuation. These differences in the dose modification criteria may have led to the differences in the adverse event profile, particularly in the number of SAEs, between studies. Note that the differences in the dose modification criteria did not lead to a difference in the response rate (although response assessment differed in these two studies).

Table 12: Patient Exposure		
Exposure to Romidepsin	GPI-04-00011 N = 96	NCI 1312 N = 71
Number of Cycles		
Median (Range)	4 (1, 23)	4 (1, 72)
Total Romidepsin Dose (mg)		
Median (Range)	278.8 (24.0, 1764.0)	306.0 (42.8, 5681.0)
Dose Delay		
Percentage with Dose Delay	39 (40.6%)	13 (18.3%)
Dose Reduction		
Percentage with Dose Reduction	24 (25.0%)	45 (63.4%)

Deaths and Discontinuations

There were 6 deaths (6%) on the GPI study and 7 deaths (8%) on NCI 1312 during the study period. This included one death due to cardiopulmonary failure, one due to acute MI, and one due to infection. In the safety database, there were four additional cardiogenic deaths.

Discontinuation due to an adverse event occurred in 24 patients on the GPI study and 10 patients on NCI 1312. Causes of discontinuation included infection, fatigue, QT prolongation, fever, and dyspnea. Three patients discontinued due to allergic dermatitis.

Serious Adverse Events

Serious adverse events were reported in 23% of patients on the GPI study and 59% of patients on NCI 1312. This difference may have been due to a different threshold for hospitalization at the NCI Clinical Center (since hospitalization is by definition in a SAE). This may also be due to differences in performance status, disease stage, safety assessments, and dose modification criteria. To further explore this, the number of SAEs on NCI 1312 at the Clinical Center and at the extramural sites was examined. The percentage of patients with SAEs was very similar in the two groups. This suggests that a difference in the threshold for hospitalization at the Clinical Center is an unlikely cause of the discrepancy, in the number of SAEs, between GPI-04-0001 and NCI 1312.

Serious adverse events in the GPI study ($\geq 2\%$) included pyrexia, infection, sepsis, tumor lysis syndrome and hypotension. Serious adverse events in the NCI study ($\geq 5\%$) included supraventricular arrhythmia, fatigue, pyrexia, edema, infection, line sepsis, neutropenia, hyperuricemia, and hypotension. While both studies report infection and hypotension, central venous access was required in the initial patients on NCI 1312. This may have led to differences in the number of patients with line sepsis or with infection and, in part, to the difference in the number of SAEs between studies.

Common Adverse Events

The table below provides the grade 1-4 adverse events ($\geq 25\%$) in patients on either study along with the incidence of the corresponding grade 3-4 events. Adverse events include gastrointestinal disturbances, hematologic toxicities, fatigue, infections, electrolyte abnormalities, and ST-T wave changes.

There was a marked difference in adverse event reporting in the two studies. This may be due to increased reporting on one study, decreased reporting on the other study, or due to a real difference in the number of AEs. In NCI 1312, all laboratory abnormalities were reported as adverse events while on GPI-04-0001, only clinically significant laboratory abnormalities were reported as adverse events. Thus, the difference in the number of adverse events between studies may be due to increased reporting. Alternatively, there is a marked difference in the number of patients with grade 3-4 neutropenia (a clinically significant laboratory event) on the two studies; 4% on the GPI study and 27% on NCI 1312. Thus, the difference in the number of adverse events between studies may be due to decreased reporting. Finally, there may be a real increase in the number of adverse events on NCI 1312 due to the more stringent dose modification criteria on the GPI study. One weakness of single arm trials is the inability to distinguish the true cause of these differences in adverse event reporting.

Table 13: Grade 1-4 Adverse Events in > 25% of Patients in Either Study				
Adverse Reactions n (%)	Study GPI-04-0001 N= 102		Study NCI 1312 N = 83	
	Grade 1-4	Grade 3 or 4	Grade 1-4	Grade 3 or 4
Any	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)

Cardiac Events

QT Prolongation and Arrhythmia

Drugs in this class, including romidepsin are associated with prolongation in the QTc interval. A prolonged QTc interval was reported in 59 patients with CTCL. Among these 59 patients, there was one ventricular arrhythmia, 1 nodal rhythm, and 2 supraventricular arrhythmias. Among the 685 patients with other tumor types who have received romidepsin, there were three reports of grade 3-4 ventricular arrhythmias and 1 report of wide complex tachycardia.

Torsades de pointes was not reported in the CTCL (N = 185) or in the complete safety database (N = 870).

ST-T Changes, Troponin, and CPK

ST-T wave segment changes, T wave flattening and non-specific ST changes, were reported in 63% of patients on the NCI study. Troponins were not collected in patients with these EKG abnormalities. CPK were collected routinely on the days of dosing in the NCI study and were included in the initial laboratory dataset. Twenty patients on the NCI study had a grade 1-2 increase in CPK. Fractionation was not provided and troponins were not included in the laboratory dataset. Echocardiograms were collected routinely on day 16 on the NCI study. Among the 65 patients with a normal baseline echocardiogram, three were abnormal at some point in the treatment period. In two patients, the ejection fraction (EF) returned to baseline at the next cycle. In one patient, the EF decreased from 59% to 40% and subsequent levels varied between 45 and 55%.

Skin and Systemic Infections

Patients with CTCL are immunocompromised and do not have an intact skin barrier. Romidepsin can cause hematologic toxicity, further exposing these patients to the risk of infection. Grade 3-4 infections on the GPI study included skin infections, sepsis, oral candidiasis, tonsillitis, and perineal abscess. Grade 3-4 infections in the NCI study included urinary infections, infection not otherwise specified, febrile neutropenia, sepsis, catheter infection, and endocarditis. These differences may be related to skin care and to the use of central lines.

Laboratories

In the laboratory dataset (does not include data from the safety update), grade 3-4 neutropenia was seen in 2% of patients on the GPI study and 25% of patients on the NCI trial. Grade 3-4 thrombocytopenia was reported in no patients on the GPI and in 16% of patients on the NCI study. Abnormal chemistries included hypomagnesemia, hypocalcemia, and hypokalemia. Given the prolonged QTc interval seen with romidepsin, electrolyte monitoring is recommended.

9. Advisory Committee Meeting

An advisory committee meeting was held on September 2, 2009. The committee was asked to vote on the following question: Do the results of the two romidepsin single arm studies represent a favorable risk-benefit profile for patients with previously treated CTCL? Ten committee members stated that romidepsin had a favorable risk-benefit profile and one abstained.

10. Pediatrics

Romidepsin has been granted orphan drug status and a pediatric waiver is not required.

11. Other Relevant Regulatory Issues

- The Division of Drug marketing, Advertising, and Communications has reviewed both the package insert and patient package insert and has made recommendations for improvements in both.
- The Division of Medication Error Prevention and Analysis (DMEPA) has reviewed the package insert and the carton and container labels and provided feedback to the Division and to the applicant. The proprietary name was also reviewed by DMEPA and was found acceptable.
- The Division of Scientific Integrity has inspected four clinical sites and has also inspected the applicant. The conclusion for two of the clinical sites was voluntary action indicated while the other three sites were no action indicated. The applicant's production facilities were also inspected and they were found acceptable.
- The Division of Risk Management has reviewed the package insert and the patient package insert and has made recommendations for their improvement.
- The Study Endpoints and Label Development (SEALD) team has reviewed the data regarding pruritus that was collected on GPI-04-0001. Their recommendation is that the data are insufficient to support product labeling for this claim. The formatting of the package insert has also been reviewed by SEALD.
- The prolongation in the QTc interval has been assessed by the Interdisciplinary Review Team for QT Studies and they have recommended that the applicant provide additional data.
- The Pediatrics and Maternal Health team has reviewed the package insert and has recommended labeling as Pregnancy Category D. Further, they have recommended that the package insert inform women that romidepsin may interfere with estrogen-containing contraceptives.
- Financial disclosure information was provided and there were no conflicts of interest.

12. Labeling

Please see the final package insert and the patient package insert.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: **Regular Approval**
- Risk Benefit Assessment:

- Benefit: The efficacy of romidepsin in cutaneous T cell lymphoma has been established in two single arm trials. These trials demonstrated response rate of 34 and 35% with median response durations of 15 and 11 months.
- Risk: Labeled warnings include QT prolongation, hematologic toxicity, fetal harm, and possible interference with estrogen containing contraceptives. Physicians are instructed to monitor serum electrolyte levels and the complete blood count. Physicians should consider cardiovascular monitoring in patients with congenital long QT syndrome, a history of significant cardiovascular disease, and in patients taking medications that can prolong the QT interval. Common adverse events associated with romidepsin include nausea, fatigue, infections, vomiting, anorexia, anemia, thrombocytopenia, EKG T wave changes, neutropenia, and lymphopenia.
- Recommendation for Post-marketing Risk Management Activities: Please see comments to applicant.
- Recommendation for other Postmarketing Study Commitments: Please see comments to applicant.
- Recommended Comments to Applicant: The draft post-marketing requirements are below. There were no post-marketing commitments. Please see the approval letter for the final post-marketing requirements/commitments.

- 1556-1 Conduct a GLP Segment II 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.
- 1556-2 Conduct animal study(ies) to determine the estrogenic/ anti-estrogenic effects of romidepsin.
- 1556-3 Conduct a GLP toxicology study in rats 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.
- 1556-4 Conduct a drug interaction clinical trial with the CYP3A4 inhibitor ketoconazole in patients with advanced cancer. This study will be a crossover design to evaluate the effects of a single dose of ketoconazole on the pharmacokinetic disposition of romidepsin. Pharmacokinetic parameters of exposure will be used to assess the effects of CYP3A4 inhibition on the disposition of romidepsin.
- 1556-5 Conduct a drug interaction clinical trial with the CYP3A4 inducer rifampin in patients with advanced cancer. This study will be a crossover design to evaluate the effects of induction of CYP3A4 by rifampin on the pharmacokinetic

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Cross Discipline Team Leader Review

disposition of romidepsin. Pharmacokinetic parameters of exposure will be used to assess the effects of CYP3A4 induction on the disposition of romidepsin.

- 1556-6 Conduct a clinical trial to determine the pharmacokinetics of romidepsin in advanced cancer patients with moderate and severe hepatic impairment.
- 1556-7 Conduct an examination of the potential of ISTODAX to prolong the QT interval in an expanded dataset of EKG matched pharmacokinetic data from Study GPI-06-0005. Exposure-response, central tendency and outlier analyses will be included in the evaluation.
- 1556-8 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).

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/

VIRGINIA E MAHER
11/02/2009