CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	May 8, 2014
Reviewer:	Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm. D., DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Evaluation to determine whether a REMS is necessary to ensure that the benefits of Beleodaq outweigh the risks
Drug Name:	Beleodaq® (belinostat) for Injection
Therapeutic Class:	Histone Deacetylase (HDAC) Inhibitor
Dosage and Form:	1,000 mg/m^2 administered over 30 minutes by intravenous infusion on Days 1 to 5 of a 21-day cycle.
Indication(s):	For the treatment of patients with relapsed or refractory peripheral T-cell lymphoma
Application Type/Number:	NDA 206-256, Supplement 00, Sequence 01
PDUFA Deadline:	August 9, 2014
Applicant:	Spectrum Pharmaceuticals, Inc. (Spectrum)
OSE RCM #:	2013-2770 MASTER Record
	2014-9 DRISK Safety Review

Reference ID: 3503478

1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for the proposed new molecular entity (NME), belinostat (Beleodaq). The applicant, Spectrum, proposes belinostat for intravenous (IV) injection as a single-agent for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) who failed at least one prior systemic therapy. This original New Drug Application (NDA) 206-256, received on December 8, 2013, was submitted to the Division of Hematology Products (DHP). The applicant included a risk management plan (RMP) for belinostat in this submission without a proposed REMS.

2 BACKGROUND

Belinostat (PXD101) is a histone deacetylase (HDAC) inhibitor and a member of the hydroxamic acid class of HDAC inhibitors that catalyze removal of acetyl groups from the lysine residues of histone and non-histone proteins such as transcription factors. According to the applicant, "this, in turn, causes alterations in gene expression that result in cell cycle arrest, a decrease in cell proliferation, and apoptosis. [1]

Belinostat inhibits all three classes of zinc-dependent HDAC enzymes ((b) (4) Class I); (b) (4) (Class II); (b) (4) (Class IV) (b) (4). *In vitro*, belinostat showed preferential cytotoxicity towards tumor cells compared to normal cells and inhibited the growth of cancer cells that had developed resistance to other chemotherapeutic agents. [1]

The proposed to-be-marketed dose of belinostat is 1,000 mg/m^2 administered over 30 minutes by IV infusion on Days 1-5 of a 21 day cycle; treatment is continued until disease progression or unmanageable toxicity develops. Beleodaq is supplied in a single-use, 30 mL clear glass vial that contains 500 mg of belinostat and 1,000 mg of L-Arginine, USP.

Peripheral T-cell Lymphoma

According to the applicant, PTCL is a rare heterogeneous group of clinically aggressive hematologic malignancies that represent ~10 to 15% of all non-Hodgkin's lymphomas (NHL) in Western populations. These T-cell lymphomas are associated with a worse outcome and survival compared to B-cell lymphomas (see references in footnotes). [2, 3]

PTCL is the most prevalent type of T-cell lymphoma. The average age of onset is 61 years and the frequency of PTCL increases with increasing age. Initial symptoms of

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[1] NDA 206-256, Belinostat, Global Submit, Module 1.16 Risk Management Plan, p 6 of 42, and Module 2, Common Technical Document Summaries, Section 2.5 Clinical Overview, Subsection 2.5.1 Product Development Rationale, page 8 of 59. (b) (4)

[2] The Non-Hodgkin's Lymphoma Classification Project: A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997:89(11); 3909-3918

[3] Savage KJ, Peripheral T-cell Lymphomas. Blood Rev. 2007:21(4); 201-216

PTCL are vague, and patients often do not seek medical advice until late in the course of this cancer. The majority of patients present with advanced disease stage, Stage 3 or 4.

Armamentarium of Therapy for PTCL

As explained in published literature, the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the primary first-line treatment for most subtypes of PTCL. The literature cites that this combination therapy is adopted from the management of B-cell NHL. Unfortunately, most of the patients with PTCL do not respond or experience disease progression after the initial treatment and then go on to subsequently fail treatment with the available salvage therapies until they develop drug resistance or death.[4] The 5-year survival for these patients is less than 32% as cited in published literature. [5, 6]

Since the belinostat clinical development program was initiated under IND 70,789 (December 16, 2004), only Folotyn Injection (pralatrexate) and Istodax Injection (romidepsin) have been approved by the FDA for the treatment of adult patients with PTCL. Both drugs were approved under the accelerated approval regulatory pathway 21 CFR Part 314 for subpart H. However, problems with efficacy and the adverse event of thrombocytopenia with these products limits their use, particularly, in patients with pre-existing thrombocytopenia. See the **Appendix, Section A, Table 1,** "Comparator Products," for treatment of PTCL.

Risk Management Plans

The risk mitigation for the FDA approved products for PTCL is via labeling and routine pharmacovigilance. As of this review, none of the approved products for PTCL has a REMS. As cited in the **Introduction** of this review, the applicant submitted a RMP for belinostat in this NDA. The Division of Pharmacovigilance (DPV) will evaluate the proposed pharmacovigilance plan and provide comments in separate review.

Generic Products for the Treatment of PTCL

The FDA is not aware of any abbreviated NDA (ANDA) submission for the indication of treatment of PTCL and/or of any patent challenges (though a patent challenge may occur at any time) for approved drug products for PTCL.

2.1 Regulatory History

The regulatory history specific to this NME application for belinostat follows:

[4] O"Leary HM, Savage KJ. Novel therapies in peripheral T-cell lymphomas. Curr Oncol Rep. 2008; 10:404-411.

[5] Vose J, Armitage J, Weisenburger D. International T-cell Lymphoma Project International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-4130.

[6] Weisenburger D, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood. 2011;117(12):3402-3408.

Reference ID: 3503478

- May 28, 2008: The Agency granted Fast Track designation for clinical development of belinostat (PXD101) for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) who failed at least one prior systemic therapy (IND 70,789).
- September 4, 2008: The Agency issued a Special Protocol Assessment (SPA) "Granted" letter to the sponsor for the design and planned analysis of protocol PXD101-**CLIN-19**, "A Multicenter Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma."
- September 3, 2009: The Agency granted Orphan-Drug Designation for belinostat for the treatment of PTCL, as cited above.
- August 2, 2011: Type C Guidance Meeting (July 20, 2011) Minutes cite that the Agency offered guidance for reporting and handling of cardiac, hepatic impairment, and mass balance and baseline bone marrow outcomes. Postmarketing studies were briefly discussed during this meeting.
- February 8, 2013: Type C Guidance Meeting (February 7, 2013) Minutes note that the Agency discussed the proposed postmarketing Phase 1 and Phase 3 clinical development plan.
- June 5, 2013: Type B Pre-NDA Meeting (May 29, 2013) Minutes include brief comment that a RMP will be included in the NDA submission. The Agency stated that "whether additional safety related actions will be needed will be determined during review of the NDA submission."
- December 9, 2013: The applicant submitted the Original NDA 206-256 for belinostat (Beleodaq) for Injection to the Agency.
- February 5, 2014: The Filing Communication letter issued from the Agency to the applicant states that the NDA is sufficiently complete to permit a substantive review. The NDA is determined to be a **Priority**. The Agency stated that, currently, no Advisory Committee meeting to discuss this application is planned.

- February 11, 2014: (Amendment 1), the applicant submitted a revised package insert labeling in response to FDA labeling comments (Filing Letter on February 5, 2014)
- February 25, 2014: (Sequence 4), the applicant submitted a proposed proprietary Name Request to the Agency.
- March 4, 2014: The Agency communicated to the applicant that the proposed proprietary name, Beleodaq, is acceptable from a promotional and safety perspective. See review in DARRTS written by Tingting Gao, Pharm. D., dated February 28, 2014, Division of Medication Error Prevention and Analysis (DMEPA).

- March 10, 2014: (Sequence 11), the applicant submitted a meeting request to discuss Postmarketing Requirements or Commitments.
- April 3, 2014: (Amendment 14), the applicant submitted the 4-Month Safety Update Report (SUR).

FDA Resources

- *Guidance for Industry, "Labeling for Human Prescription Drug and Biological Products Approve under the Accelerated Approval Regulatory Pathway"(March 2014)*

2.2 Materials Reviewed

- December 9, 2013: Original NDA 206-256 Belinostat (PXD101) proposed for the treatment of relapsed or refractory PTCL including the module 1.16 Risk Management Plan
- April 3, 2014: 120-Day SUR of all safety data collected from the time of the NDA data cut-off (August 31, 2012) to date of NDA submission (December 9, 2013).
- April 4, 2014: *Draft Sections,* Clinical Review, NDA 206-256 Belinostat (PXD101) written by Hyun Joo Lee, Pharm. D., DHP (*Note, only as FYI, MO review was cited*)

3 Overview of the Clinical Development Program

The pivotal study, CLN-19, is a Phase 2, multicenter, single-treatment arm, open-label study in which adult patients with relapsed or refractory PTCL were enrolled to receive belinostat as IV monotherapy. The supportive data is from study, CLN-6, a Phase 2, multicenter, open-label, 2-treatment arm study that enrolled a mixed NHL population (PTCL, n= 24; CTLC, n=29) who had failed prior systemic therapy.

Study Population and Demographics

A total of 129 patients were enrolled in CLN-19 across 62 sites in 16 countries. Twenty-eight percent (28%) and 71% of patients were enrolled in US study sites in CLN-19 and CLN-6, respectively. The majority of patients were male (54%) and Caucasian (86%) with a median age of 63 years (range 29 to 81 years).

Efficacy Analysis Datasets

The efficacy analysis datasets consisted of 120 patients who received at least 1 dose of belinostat and had a confirmed diagnosis of PTCL on central pathology review. Nine (9) of 129 enrolled patients (CLN-19) were considered non-evaluable for efficacy due to either inadequate specimens or non-eligible PTCL histopathology.

Most patients in CLN-19 (85%) and CLN-6 (75%) were Stage 3 or 4 at study entry and received pre-treated prior to enrollment. In CLN-19, the median number of prior systemic therapies was 2 (range 1 - 8) and 37% of patients received $\geq$ 3 prior systemic therapies.

In CLN-6, the median number of prior systemic therapies was 3 (range 1 - 9) and 54% of patients received $\geq$ 3 prior systemic therapies. The same proportion of patients, 21%,

Reference ID: 3503478

received a prior stem cell transplant in CLN-19 and CLN-6. Patients were treated with repeat cycles of belinostat until disease progression or unacceptable toxicity.

Efficacy Results

For complete review of the efficacy analysis of belinostat (under NDA 206-256), refer to the Clinical Review written by Hyun Joo Lee, Pharm. D., DHP

In study CLN-19 and CLN-6, the primary efficacy endpoint was the objective response rate (ORR) as assessed by the independent review committee using the International Working Group (IWG) criteria.[7] Secondary efficacy endpoints included Time to Response (TTR), Duration of Response, Time to Progression (TTP), Progression-free Survival (PFS), 1-year Progression-free Rate, 1-year Survival Rate, and Overall Survival (OS).

Primary Efficacy Results: CLN-19 and CLN-6

The primary efficacy results from CLN-19 demonstrated a clinically meaningful and durable ORR rate (Complete Response + Partial Response) of 25.8% (CI 95% CI 18.3 - 34.6) with a median duration of response of 13.6 months. Thirteen patients (10.8%) achieved a complete response and 18 patients (15%) achieved a partial response. A total of 12 patients were subsequently able to receive a stem cell transplant.

In CLN-6, belinostat-treated patients with PTCL demonstrated an ORR of 25% (CI 95% 9.75 - 42.6), similar to the ORR for belinostat in CLN-19. Both study results exceeded the 20% ORR that was pre-defined with FDA in the Special Protocol Analysis as clinically meaningful in patients with relapsed or refractory PTCL.

Supportive Efficacy Results: CLN-19

A total of 19 patients (61.3% of responders) responded at the 1st scheduled tumor assessment (within 30 - 45 days of their 1st dose) with a median TTR of 5.6 weeks (39.2 days). The median duration of response was 13.6 months and ranged from 4.5 to 29.4 months. Belinostat-treated patients showed a 63.5% probability of experiencing duration of response greater than 6 months. A total of 12 patients were subsequently able to receive a stem cell transplant.

The median TTP in belinostat-treated patients was 2 months, median PFS estimated by the Kaplan-Meier method was 1.6 months, and the median OS was 7.9 months (95% CI 6.1 to 13.9).

Supportive Efficacy Results: CLN-6

In CLN-6, there were too few patients in the PTCL treatment-arm to estimate the TTR. The median duration of response was 3.6 months and ranged from 0.2 to 15.3 months.

3.1 Clinical Safety

The safety profile for belinostat is derived from 14 clinical studies that include 662 patients and 542 exposures to IV belinostat, which included monotherapy or

[7] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht, Horning SJ et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-586.

Reference ID: 3503478

combination therapy (IV or oral), across study designs (controlled or uncontrolled). See the **Appendix**, **Section B., Table 2,** "Clinical Safety Data for Analysis", to this review, that shows the patient groups used for safety analysis in this application.

The primary safety data (Group 1) includes 129 patients (CLN-19) in which belinostat IV monotherapy was employed using 1,000 mg/m^2 on Days 1 - 5 of a 21 day cycle in patients with PTCL.[8] Guidelines for adjusting belinostat dosing to mitigate hematologic and non-hematologic toxicities were included in each study protocol and based on platelet and neutrophil nadir counts in the preceding cycle of therapy. Dose adjustments for non-hematologic toxicities were permitted based on development of Grade 3 or 4 adverse events (AEs).

Exposure

The duration of exposure was dependent on the efficacy of treatment in individual patients. A total of 1 to 165 doses of belinostat (median: 10 doses in Group 1 and Group 2) were administered in 1 to 33 cycles of treatment (median: 2 cycles in both Groups) over 3 to 135 weeks of treatment (median: Group 1, 7.0 weeks; Group 2, 6.1 weeks).

A total of 46 patients (35.7%) received belinostat for $\geq$ 3 months, 23 patients (17.8%) for $\geq$ 6 months, and 13 patients (10.1%) for > 12 months. In Group 1, 87.6% of patients tolerated belinostat without dose reduction.

Discontinuations

The number of patients discontinuing from CLN-19 (94.2%) or CLN-6 (83.3%) secondary to progressive disease, death, or other causes was similar. See **Table 3** for a brief summary of reasons for discontinuations.

[8] As agreed with the FDA under the SPA (September 4, 2008), the design and planned analyses of the pivotal open-label study CLN-19 were adequate to address the safety and efficacy objectives to support this NDA for belinostat for the proposed treatment of relapsed or refractory PTCL. All reported symptoms and adverse events (AEs) were graded for intensity using the National Cancer Institute/NCI-Common Terminology Criteria for AE (CTCAE) and mapped to body System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

Reference ID: 3503478

Table 3. Reason for Discontinuations from Study CLN-19 and CLN-6	**# Patients, N (%) ***	
Study and Patients, N (%)	**CLN-19,** 120 patients (100%)	**CLN-6,** 24 patients (100%)
Progressive Disease	76 (63.3)	NA
Lack of Efficacy	NA	6 (25.0)
Deaths	13 (10.8), Disease Progression	4 (0.17) Disease Progression
	9 (0.08) Adverse Event	3 (12.5) Adverse Event
Adverse Event	8 (6.7)	3 (12.5)
Stem Cell Transplant	3 (2.5)	0 (0)
Withdrew Consent	10 (8.3)	1 (4.2)
Physician Decision	1 (0.8)	7 (29.2)
Lost to Follow-Up	1 (0.8)	0 (0)

Source: NDA 206-256 Belinostat, Module 2.7.3 Summary of Clinical Efficacy, Table 8, p 27 of 45.
* Study CLN-20: 150 to 1,200 mg/m^2 IV belinostat monotherapy included 4 deaths (attributed to disease progression).

Common Adverse Events

The most common AE in the primary safety data (Group 1, all Grades) were nausea (41.9%) and fatigue (37.2%), followed by pyrexia (34.9%), anemia (31.8%), vomiting (28.7%), constipation (23.3%), and diarrhea (22.5%). Thrombocytopenia was reported in 16.3%, the majority of this AE was Grade 1 or 2. The most common AEs in the supportive safety data (Group 2, CLN-6) were nausea and fatigue, the same as reported in Group 1.

Adverse Events (All causality and treatment-related)

Among the AEs in ≥ 10% of all patients from CLN-19 (Group 1, n = 129), by PT and severity (NCI-CTC Grade 1 to 4), a total of 125 patients (96.9%) experienced at least one AE: 124 patients (96.1%) experienced Grade 1 or 2, and 79 patients (61.2%) experienced Grade 3 to 4.

The Grade 3 or 4 AEs were reported as: anemia (14, 10.9%), thrombocytopenia (9, 7%), dyspnea (8, 6.2%), fatigue (7, 5.4%), hypokalemia (5, 3.9%), ECG QT prolongation (5, 3.9%), pruritus (4, 3.1%), hypotension (4, 3.1%), pyrexia (3, 2.3%), ↓ appetite (3, 2.3%), diarrhea (2, 1.6%), ↑ LDH (2, 1.6%), and nausea, vomiting, constipation, rash, vomiting, rash, and phlebitis (each AE in one patient, 1, 0.8%).

In Group 2, Grade 3 or 4, the most frequently occurring adverse events were reported as: fatigue (6.0%), dyspnea (3.6%), and anemia (3.6%).

Deaths

CLN-19
There were a total of 22 (17.1%) deaths during the studies or within 30 days after the last dose of belinostat. Per the DHP Clinical Reviewer, there were 13 patients (10.1%) attributed to disease progression and 9 deaths (7%) attributed to an adverse event. There was one death secondary to hepatic failure (day of death, Day 25, post last dose) that is causally attributed to belinostat treatment.

The most common cause of death was multi-organ failure (2 cases, both day of death, Day 10, relative to the last dose) and cardiac failure (2 cases, one on Day 26, and one on Day 29, relative to the last dose). The additional deaths occurred in one patient, each: lung infection (death on Day 2, post last dose), gastrointestinal hemorrhage (death on Day 5, post last dose), euthanasia (death on Day 14, post last dose), and shock (death on Day 2, post last dose).

CLN-6
In CLN-6, there were 5 deaths: 2 patient deaths were attributed to disease progression and 3 patient deaths attributed as follows: 62 year-old male/ventricular fibrillation; 74 year-old male/pneumonia; 40 year-old female; sepsis.

CLN-20
In CLN-20, there were 4 deaths attributed to disease progression.

Other Serious Concerns with Belinostat Monotherapy

Hematological
A total of 55 (42.6%) of patients in CLN-19 experienced myelosuppression with the most frequently reported adverse events, by PT, as decreased hemoglobin/ anemia 43 (33.3%), anemia 41 (31.8%), and decreased platelet count/thrombocytopenia 30 (23.2%). The Grade 3 and 4 hematological toxicities included decreased hemoglobin/ anemia 15 (11.7%), anemia 14 (10.9%), and decreased platelet count/thrombocytopenia 13 (10.1%), followed by decreased neutrophil count 9 (7.0%).

Cardiac Disorders/QT Prolongation
Cardiac disorders were reported in 10.1% of patients, most frequently atrial fibrillation (2.3%) of patients. Additional cardiac disorders reported in ≥ 2% of patients (1.6%) included cardiac failure, sinus tachycardia, and tachycardia. The applicant reports that a total of 14 patients (10.9%) had AEs of ECG QT prolongation and 3.9% were Grade 3; no patients were reported with Grade 4 or 5 ECG QT prolongation.

The pharmacokinetic-pharmacodynamic model does not show a relationship between change in QTcF and belinostat plasma concentration. Analysis of clinical ECG and belinostat plasma concentration data demonstrated no signal or meaningful effect of Beleodaq on cardiac repolarization per the Division of Cardiovascular and Renal Products, QT Consult.

Clinical Laboratory Evaluations
The majority of patients in Group 1 had ≥ 1 abnormal biochemistry value during the study with most being Grade 1 or 2 severity. The most common Grade 3 AEs were: ↓phosphate (7.8%), ↑glucose (7%), and ↓potassium (6.2%). There were shifts of ≥ 2 Grades in ≥ 2 patients for ALT, albumin, alkaline phosphate, AST, bilirubin, calcium, creatinine, glucose, magnesium, phosphate, potassium, sodium, and urate.

The most common Grade 4 AE was ↑ urate in 3.1% of patients. One patient with baseline hyperuricemia and bulky disease experienced Grade 4, tumor lysis syndrome during the first cycle of treatment and died due to multi-organ failure (as cited in the proposed substantially complete labeling).

120-Day Safety Update Report

There were no new safety signals or changes in the frequency of reported AEs in the 120-Day SUR as reported in the Integrated Safety Summary.

Two additional deaths were reported in CLN-19 with causality attributed to pulmonary hemorrhage and disease progression, each in one patient.

3.2 Discussion

The pharmacologic class of HDAC inhibitors, vorinostat and romidepsin, appear to have a class-effect in the treatment of PTCL. Pralatrexate, a folate analog inhibitor, is also approved for the treatment of PTCL. However, each of these approved drug products has limitations with regard to safety and efficacy.

As cited in published literature, the primary efficacy results for belinostat in pivotal study, CLN-19 (ORR 28.5%) and supportive CLN-6 (ORR 25%) appear comparable to the efficacy results of approved products, the ORR for pralatrexate (27%) and romidepsin (25.4%) in relapsed or refractory PTCL patients.[9, 10]

The proposed belinostat dosing regimen and IV administration, similar to romidepsin and pralatrexate, appears to be tolerated and achieved clinical efficacy in the treatment cycles repeated over 21 days until there was disease progression or unacceptable toxicity. Vorinostat, a 2nd HDAC inhibitor (oral capsule), is indicated for CTCL, a milder disease than PTCL, though serious and life threatening.

The adverse events and serious adverse events reported in the belinostat IV monotherapy clinical trials include gastrointestinal events (nausea, vomiting and diarrhea); hemato-logic events [thrombocytopenia, leucopenia (neutropenia and lymphopenia)]; serious infections including pneumonia and sepsis; and hepatic toxicity and liver function test abnormalities including one fatal case of hepatic failure causally attributed to belinostat treatment. Based on the mechanism of action, belinostat may cause embro-fetal toxicity if administered to a pregnant woman.

Many of the reported adverse events reported for belinostat pose serious risks; however, they are not new or unexpected events in patients with PTCL and are associated with the class of HDAC inhibitors as well as with pralatrexate, a folate analog inhibitor.

As cited in the **Introduction** of this review, the applicant submitted a RMP for belinostat in PTCL. The DHP did not require that the applicant to submit a proposed REMS for belinostat in this NDA application. The sponsor proposes to manage the risks with routine post marketing pharmacovigilance and with labeling including Prescriber Patient Information that focuses on the key serious risks reported with use of belinostat.

At this time, the DRISK and DHP do not believe that belinostat, proposed for the treatment of PTCL, is associated with serious risks that exceed the benefits. If belinostat is approved for PTCL, the DRISK and DHP agree that a REMS is not necessary if belinostat is approved. The rationale for this conclusion follows:

[9] Folotyn US Prescribing Information, Allos Therapeutics Westminster, CO; 2012.

[10] Istodax US Prescribing Information, Celgene Corporation, Summit NJ; 2013.

- The most likely prescribers for belinostat will be hematologists who are familiar with the other treatment options for PTCL, experienced in the management of adverse events associated with chemotherapeutic agents in oncology patients, and the management of the reported serious risks with use of belinostat in this application.
- The DRISK and the DHP acknowledge that this NDA has limited clinical duration in the Phase 2, open label safety data. Under accelerated approval for subpart H, the DHP is requiring the applicant to submit a proposal for a trial to evaluate belinostat, as a single active-control treatment, compared with 3-treatment arms with CHOP, CHOP + belinostat, and CHOP + pralatrexate, respectively.

The class of HDAC inhibitors in the treatment of PTCL has a well characterized safety profile that includes the risks of myelosuppression, cardiac risk of QT prolongation, gastrointestinal events (i.e., bleeding, elevation of AST/ALT), Tumor Lysis Syndrome, and the potential to cause embryo-fetal toxicity. The adverse events reported for belinostat are comparable to those seen with the approved HDAC inhibitors. The labeling for vorinostat and romidepsin does not include a Box Warning or a Medication Guide and neither product has a REMS.

The pending regulatory action for belinostat will be under the accelerated approval for subpart H, 21 CFR 314.560, and labeling will follow the *Guidance for Industry "Labeling for Human Prescription Drug and Biological Products Approve under the Accelerated Approval Regulatory Pathway" (dated March 2014).*

4 CONCLUSION

The DRISK and the DHP concur that the benefit risk profile of belinostat for the treatment of adult patients with relapsed or refractory PTCL is acceptable and, based on the reported data, a REMS is not necessary to ensure that the benefits outweigh the risks, at this time. The DHP should consult the DRISK if additional safety information is identified that warrants reevaluation of risk mitigation measures for belinostat.

APPENDIX:

Section A. Brief Comments on Approved Products for PTCL and/or CTCL

- Pralatrexate (Folotyn) is a folate analog inhibitor associated with bone marrow suppression, mucositis, and thrombocytopenia which can prompt dose reductions and/or withdrawal from treatment. Many patients with PTCL not otherwise specified (NOS) (20 to 40%) and most patients with angioimmunoblastic T-cell lymphoma (AITL) (70 to 90%) have bone marrow involvement making it difficult to use pralatrexate which can lead to worsening thrombocytopenia. Note, both abbreviation definitions were already in the sentence, see above.
- Romidepsin (Istodax) is a bi-cyclic selective HDAC inhibitor of the Class I- HDAC enzymes contrasted with belinostat that inhibits all three classes of zinc-dependent HDAC enzymes. Romidepsin is approved for the treatment of two different indications, CTCL and PTCL in adult patients who have received at least one prior systemic therapy. Romidepsin is associated with the clinical safety risks of QT interval prolongation, serious infections, decreased platelets, leucopenia, and anemia.
- Vorinostat (Zolina) represents a different class of HDAC inhibitor and is approved for the treatment of adult patients with CTCL. The clinical safety risks associated with vorinostat include pulmonary embolism and deep vein thrombosis; dose related thrombocytopenia and anemia; nausea, vomiting and diarrhea; hyperglycemia; and the need for careful monitoring of blood cell counts and chemistry tests.

Table 1.

Comparator Products				
PRODUCT	**BELINOSTAT** Beleodaq	**ZOLINZA** Vorinostat	**ISTODAX** Romidepsin	**FOLOTYN** Pralatrexate
Administr	Injection	Oral Capsule	Injection	Injection
NME	Yes	Yes	Yes	Yes
NDA	NDA 206-256 *Pre-approval* received 8-Dec-13	NDA 021-991 Approved (Subpart H) 6-Oct-06	NDA 022-393 Approved (Subpart H) 5-Nov-09 (CTCL) May-2011 (PTCL)	NDA 022-468 Approved (Subpart H) 24-Sep-09
Class	HDAC Inh bitor	HDAC Inhibitor	HDAC Inhibitor	Folate Analog Inhibitor
Indication	*Proposed Indication:* Tx of patients w/ relapsed/refractory peripheral T-cell lymphoma (PTCL)	Tx of cutaneous sx/sy in pts w cutaneous T-cell lymphoma (CTCL) w/progressive, persistent or recurrent disease on or p 2 systemic tx.	1. Tx of CTCL in pts who received at least 1 prior systemic tx 2. Tx of PTCL in pts. who have had tx w at least 1 prior therapy	Tx of pts w/relapsed or refractory PTCL
Risks in Labeling, *Warnings* and *Precautions*	Gastrointestinal; Hematologic; Infection; Use in Pregnancy; Hepatic Impairment; Renal Impairment	Pulmonary embolism; DVT; ↓ Platelets, anemia; Gastrointestinal disturbances; Caution w/hepatic impairment; Hyperglycemia; Monitor electrolytes, blood ct, Severe thrombocytopenia, and gastrointestinal bleeding; Fetal harm can occur when rx to a pregnant woman.	↓Plts, leukopenia, anemia; Serious/fatal infections; ECG changes, caution w/ congenital long QT syndr; Tumor Lysis Syndr; Fetal harm when tx'ing pregnant woman	Bone Marrow Suppression; Mucositis; Dermatologic Reactions; Tumor Lysis Syndr; Hepatic Toxicity; Renal: ↑Toxicity w/ Impaired Renal Function Embryo-Fetal Toxicity
REMS	None proposed	No	No	No

Additional abbreviations cited in Table 1 (above):

Adminstr: Administration

Ct: count

Pts: patients

Plts: platelets

p: post

rx: prescribing

Sx/Sy: signs and symptoms

Syndr: syndrome

Tx: treatment

Tx'ing: treating

Reference ID: 3503478

Section B. Clinical Safety Data for Analysis

Table 2. Summary of Clinical Studies of Belinostat			
Group	**Classification**	**# of Patients (pts.)**	**Route of Administration**
Primary Safety Data			
Group 1	Uncontrolled, Phase 2 study in pts. w/relapsed or refractory PTCl (CLN-19)	129	IV monotherapy
Supportive Safety Data (in Multiple Indications)			
Group 2	Uncontrolled, 3 Phase 1 and Phase 2 studies in pts w/lymphoma (CLN-6) and other advanced malignancies (CLN-20, TT20, TT30, and 301-G)	167	IV monotherapy
Group 3	Controlled, 1 Phase 2 controlled study in carcinoma of unknown primary (CLN-17)	42 (belinostat + carboplatin/ paclitaxel)	IV/oral combination therapy
Group 4	Uncontrolled 1 Phase 1, 4 Phase 1b/2, and 1 Phase 2 uncontrolled studies of IV belinostat in advanced malignancies (CLN-4, CLN-5, CLN-8, CLN-14, CLN-15, and CLN-16)	204	IV, combination therapy
Group 5	Uncontrolled, 1 Phase 1 study in advanced malignancies (CLN-9)	120	Oral monotherapy
Ref. NDA 206-256, Belinostat, Section 2.5 Clinical Overview, applicant Table 5, p 37 of 59.			

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/s/

CAROLYN L YANCEY
05/08/2014
REMS Review for NDA 206256 BELEODAQ (belinostat) for PTCL