CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA #	206256
Applicant Name	Spectrum Pharmaceuticals Inc.
Date of Submission	December 9, 2013
PDUFA Goal Date	August 9, 2014
Proprietary Name / Established (USAN) Name	Beleodaq/belinostat
Dosage Forms / Strength	Lyophilized powder of 500 mg belinostat in single-use vial for reconstitution at 50 mg/mL
Proposed Indications	Patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)
Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Hyon-Zu Lee, Pharm.D./Virginia Kwitkowski, BSN
Statistical Review	Erik W. Bloomquist, Ph.D./Yuan L. Shen, Dr.P.H./Thomas Gwise, Ph.D.
Pharmacology Toxicology Review	Pedro L. Del Valle, Ph.D./M. Stacey Ricci, M.Eng., Sc.D./Haleh Saber, Ph.D./John K. Leighton, Ph.D.
CMC Review	Xiao-Hong Chen, Ph.D./Janice T. Brown
Product Quality Microbiology Review	Neal J. Sweeney, Ph.D./John W. Metcalfe, Ph.D.
Clinical Pharmacology Review	Bahru A. Habtemariam, Pharm.D./Julie Bullock, Pharm.D.
OSI/DGCPC	Anthony J. Orencia, M.D./Kassa Ayelew, M.D., M.P.H.
OND/DCRP/QT-IRT	Jiang Liu, Ph.D./Norman L. Stockbridge, M.D., Ph.D.
CDTL Review	Virginia Kwitkowski, BSN, MSN
OSE/DMPP	Nathan D. Caulk, BSN, MSN/Barbara Mullen, BSN, MSN/LaShawn Griffiths, BSN, MSHS-PH
OSE/OPDP	James S. Dvorsky, Pharm.D.
OSE/OMEPRM/DRISK	Carolyn L. Yancey, M.D./Cynthia LaCivita, Pharm.D./Claudia Manzo, Pharm.D.
OSE/OMPRM/DMEPA	Tingting N. Gao, Pharm.D./Kellie A. Taylor, Pharm.D., M.P.H./Michelle K. Rutledge, Pharm.D./Yelena Maslov, Pharm.D.

OND=Office of New Drugs
OSI=Office of Scientific Investigations

DGCPC=Division of Good Practice Compliance
DCRP=Division of Cardiorenal Products
QT-IRT=QT Interdisciplinary Review Team
OSE= Office of Surveillance and Epidemiology
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion
OMEPRM=Office of Medication Error Prevention and Risk Management
DRISK=Division of Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Belinostatin (Beleodaq™), a new molecular entity, is a small molecule histone deacetylase (HDAC) inhibitor. It inhibited deacetylation of histones and some non-histone proteins in *in vitro* and/or *in vivo* studies, caused cell cycle arrest and apoptosis in cell culture studies, and had anticancer activity in animal tumor models. Clinical studies, which are described in this NDA, have shown anticancer activity in relapsed or refractory peripheral T-cell lymphomas (PTCL), a rare and heterogeneous group of disorders representing 10% to 15% of all non-Hodgkin lymphomas in North America.

There are no therapies for PTCL that have received regular approval either in first line setting or in relapsed or refractory setting. Combination therapy regimens such as CHOP are commonly used in first line setting. Two agents received accelerated approval for treatment of patients with relapsed or refractory PTCL. Pralatrexate (Folotyn™), a folate analog metabolic inhibitor, was granted accelerated approval in 2009 on the basis of a single-arm trial of 109 patients with PTCL who had a 27% ORR with a median duration of response of 9.4 months. As a post-marketing requirement, the sponsor is conducting a randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or CHOP-like regimen. Romidepsin (Istodax™), a HDAC inhibitor, was approved in 2011 on the basis of a single-arm trial of 130 patients with PTCL who had a 25% ORR with a median duration of response of 9.2 plus months. As a post-marketing requirement, the sponsor is conducting a randomized, blinded trial of previously untreated patients with PTCL randomized to treatment with CHOP or romidepsin plus CHOP with PFS as primary efficacy endpoint. Stem cell transplantation is a potentially curative option for only a subset of patients.

2. Background

The IND for belinostat (referred to as PXD101) was originally filed by the CuraGen Corporation on November 15, 2004. It was transferred to Topotarget A/S in April, 2008 and then to Spectrum Pharmaceuticals on March 18, 2010. There were a number of meetings with the Agency regarding the sizes of clinical trials, safety issues, post-marketing confirmatory trial, phase 3 clinical development plans, and proposed structure and content of the NDA (11/29/2007, 7/25/2008, 9/4/2008, 7/20/2011, 2/7/2013, and 5/29/2013). A SPA for trial CLN-19 was granted on September 4, 2008. Orphan drug status was granted for the PTCL indication on September 3, 2009.

The sponsor describes belinostat as a "pan-HDAC inhibitor" in that it inhibits the enzymatic activity of histone deacetylases (b) (4)

(b) (4). It can alter acetylation levels of histone and non-histone proteins, (b) (4) resulting in cell cycle arrest and apoptosis. Belinostat activity has been explored in various advanced solid tumors and in hematologic malignancies in Phase 2 trials. A phase 2, open-label, single-arm study in patients with recurrent or refractory PTCL or cutaneous T-cell lymphoma (CTCL) showed promising results (Trial CLN-6) that were confirmed in the Phase 2, open-label, single-arm trial in 129 patients with relapsed or refractory PTCL (Trial CLN-19), the pivotal trial in this NDA.

PTCL are a rare and heterogeneous group of disorders. The most common subtypes, according to the International T-Cell Lymphoma Project data (1314 cases from 22 countries worldwide), are: PTCL-NOS (not otherwise specified) (26%), angioimmunoblastic T-cell lymphoma (19%), natural killer cell lymphoma (10%), adult T-cell lymphoma/leukemia (10%), and anaplastic large cell lymphoma (ALK-positive [7%] and ALK-negative [5%]). Patients with PTCL have a poor prognosis. The overall 5-year disease-free survival is less than 30%. Patients typically relapse after treatment with available therapies.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F to 86°F). No microbiology deficiencies were identified by the Product Microbiology reviewers. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in *in vitro* systems and/or in animal species. Belinostat-related toxicities in rats and dogs included cardiomyopathy, anemia, neutropenia, lymphopenia, lymphoid atrophy, vomiting, liquid feces, reduced weight of testes, and injection site reactions. Belinostat was genotoxic and targeted rapidly dividing cells. The pharmacology/toxicology reviewers concluded that the submitted pharmacology and toxicology studies support the safety of belinostat in patients with relapsed or refractory PTCL. No additional nonclinical studies using belinostat are necessary for the proposed indication. I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The proposed dose of belinostat is 1000 mg/m^2 given on days 1 - 5 of a 21-day cycle. This dose was determined to be maximally tolerated dose. At this dose the levels of acetylation (PD marker for HDAC activity) appeared to plateau at 900 mg/m^2 and above, providing supporting

evidence for the adequacy of the 1000 mg/m^2 dose. Belinostat undergoes extensive metabolism in the liver, primarily by UGT1A1. Belinostat is predominantly eliminated via hepatic metabolism; less than 2% of the dose is recovered unchanged in urine. The sponsor will be asked to evaluate the influence of UGT1A1 inhibitors, UGT1A1 polymorphism, and renal impairment on the pharmacokinetics and safety of belinostat in patients with cancer. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

A total of 14 clinical oncology trials were submitted with this NDA. The pivotal trial (CLN-19) enrolled 129 patients (mainly from US and Europe) with relapsed or refractory PTCL. Most of the patients (97%) had received prior CHOP chemotherapy, 33% of patients had received platinum-containing regiments, 37% of patients other multi-agent therapies, 21% of patients prior stem cell transplant, and 8% of patients had been treated previously with pralatrexate. The median number of prior therapies was 2 (range, 1 – 8). The primary efficacy endpoint was overall response rate (ORR), based on central radiology and clinical review by an Independent Review Committee. A Central Pathology Review Group confirmed the histopathology. The majority of patients had PTCL-NOS (64%), followed by angioimmunoblastic T-cell lymphoma (18%), and ALCL (ALK-negative 11% and ALK-positive 2%).The diagnosis of PTCL could not be confirmed in 9 patients, thus the number of evaluable patients was 120. The IRC-assessed ORR was 25.8% (31/120 patients, 95% CI: 18.3-34.2). The CR rate was 10.8% (13/120 patients, 95% CI: 5.9-17.8) and the PR rate was 15.0% (18/120 patients, 95% CI: 9.1 – 22.7). The median duration of response was 8.4 months (95% CI: 4.5 – 29.4). The median time to response was 5.6 weeks, range 4.3 – 50.4. Median time to progression was 2.0 months, as estimated by Kaplan-Meier method. The median overall survival was 7.9 months (95% CI: 6.1 – 13.9). Seventy-four patients (62%) had died. The one-year OS (the probability of being alive at one year) was 40.9%. Clinical and statistical reviewers concluded that ORR results by disease subgroups should not be included in the labeling, as the numbers of patients in each subgroup were small.

The supportive trial (CLN-6) enrolled 24 patients with PTCL (in US, Thailand, Israel, France and Germany). The investigator-assessed ORR was 25.0% (6/24 patients, 95% CI: 9.8 – 46.7), with 2 CRs and 4 PRs.

The above efficacy results for belinostat are similar to those of pralatrexate and romidepsin trials in the relapsed or refractory PTCL population.

I concur with the conclusions reached by the clinical and statistical reviewers.

8. Safety

Safety evaluation of belinostat is limited by the single-arm design of all the trials. The evaluation was primarily based on the 129 patients enrolled in the CLN-19 trial, but also evaluated were data from CLN-6 and CLN-20 trials (n=80) and cardiac safety data from TT-20, TT-30, 301-G trials. In the CLN-19 trial, the median duration of treatment was 7 weeks (range, 3 – 135), the median number of treatment cycles was 2 (range, 1 – 33), and the median number of doses received by patients was 10 (range 1 – 165). The most common TEAEs of belinostat (>25%) were nausea, fatigue, pyrexia, anemia, and vomiting. The most frequent grade 3/4 TEAEs were anemia (11%), thrombocytopenia (7%), dyspnea (6%), neutropenia (6%), fatigue (5%), pneumonia (5%), and hypokalemia (5%). Nine patients (7%) died as a result of adverse events during the trial or within 30 days of the last dose of belinostat. Causes were multi-organ failure (2), cardiac failure (2), hepatic failure (1), lung infection (1), GI hemorrhage (1), euthanasia (1), and shock (1). A total of 55 (43%) patients had myelosuppression, 13 (10%) had cardiac AEs, 13 (10%) had QT prolongation (2 patients had confirmed grade 3 QT prolongation). Tumor lysis syndrome occurred in 4 patients (3.1%). In the pooled analysis of TT-20, TT-30, CLN-6, CLN-20, and 301-G, 35 patients (21%) experienced cardiac AEs, 3 patients had grade 3 AEs. One patient died due to ventricular fibrillation (in the setting of pneumonia and sepsis). QT/QTc prolongation occurred in 4 patients (2.4%), with one case of grade 3 QTc prolongation.

Most of the abnormal laboratory values were of NCI CTCAE grades 1 or 2. Most common were hematological abnormalities (anemia in 92% of patients, lymphopenia in 84%, thrombocytopenia 70%, neutropenia in 36%). Grade 3/4 lymphopenia occurred in 48% of patients; grade 3/4 anemia, neutropenia or thrombocytopenia, in 12% - 15%. Grades 1 or 2 hepatic and renal function abnormalities occurred in 40% to 50% of patients, but grade 3/4 abnormalities were rare.

I concur with the conclusions reached by the clinical safety reviewer.

9. Advisory Committee Meeting

This application was not presented to Oncologic Drugs Advisory Committee because the protocol for trial CLN-19 was under Special Protocol Assessment agreement, the Division is familiar with the trial design and endpoints, and an agreement on the Post-Marketing Requirement was reached before the application review was completed.

10. Pediatrics

N/A. Belinostat has been granted Orphan Drug status for PTCL.

11. Other Relevant Regulatory Issues

OSI/DGCPC inspected the sponsor in accordance with Compliance Program 7348.810. It was concluded that the sponsor generally maintained adequate oversight of the clinical trial CLN-19, and that sponsor monitoring appeared reliable. The preliminary classification of the sponsor is NAI (No Action Indicated). Clinical inspections were carried out at two clinical sites that enrolled relatively high numbers of patients in CLN-19 trial. The final regulatory classifications were NAI at one site and VAI (Voluntary Action Indicated) at the other. OSI reviewer concluded "The study data collected from these clinical sites and the sponsor appear generally reliable in support of the requested indication."

CDER DCRP QT Interdisciplinary Review Team concluded "Based on information available, QT prolongation with belinostat cannot be confirmed or excluded. However, large QT prolongation (e.g., > 20 ms) with belinostat seems unlikely."

OSE/DRISK concluded that "…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 management measures for belinostat."

There are no other unresolved relevant regulatory issues.

12. Labeling

- OSE/DMEPA approved the proprietary name request
- OSE/OMEPRM assisted in revisions of Prescribing Information
- OSE/OMEPRM assisted in review of the carton and immediate container labels
- OSE/OMEPRM assisted Patient labeling/Medication guide
- The Product Label is in the process of being finalized.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that Belinostat be granted accelerated approval for treatment of patients with relapsed or refractory T-cell lymphoma with the labeling recommended by the review team.

- Risk Benefit Assessment

Analysis of Condition: PTCL is a serious and life-threatening disease, characterized by an aggressive clinical course with the overall 5-year disease-free survival of less than 30%.
Unmet Medical Need: There is no consensus on standard treatment for PTCL in the first-line and second-line settings and the approved therapies are not optimal. NCCN guidelines recommend enrollment in a clinical trial as the preferred first-

line and second-line treatment. The two approved therapies (pralatrexate and romidepsin) received accelerated approval, hence do not constitute available therapies as defined by CFR 21 part 314, subpart H.
Clinical Benefit: The key efficacy results of the CLN-19 trial (ORR and DOR) for Belinostat are similar to those of Folotyn (pralatrexate) and Istodax (romidepsin) that resulted in granting of accelerated approval. A confirmatory randomized trial is required to further characterize and verify the clinical benefit of belinostat for the treatment of patients with relapsed or refractory PTCL.
Risk: The safety profile of blinostat appears to be similar to that of romidepsin, another HDAC inhibitor approved for the same indication. The safety profile of belinostat will be further evaluated in the post-marketing confirmatory randomized trial.
Risk Management: The sponsor proposes to manage risks with routine post-marketing pharmacovigilance and with labeling including Prescriber Patient Information that focuses on the key serious risks reported with the use of belinostat. The Division of Hematology Drug Products and the OSE/Division of Risk Management agree that a REMS is not necessary if belinostat is approved.
Final Benefit-Risk Summary and Assessment: Benefit-risk profile of Belinostat for the treatment of patients with relapsed or refractory PTCL is acceptable.

- Recommendation for Postmarketing Risk Management Activities

Standard.

- Recommendation for other Postmarketing Study Commitments

PMR #1 Description
Establish the optimal safe dose of belinostat in combination with the cyclophosphamide/ vincristine/doxorubicin/prednisone (CHOP) regimen. Perform a Phase 1 dose finding trial of belinostat plus CHOP for the treatment of patients with peripheral T-cell lymphoma (PTCL). Enroll a sufficient number of patients to characterize the safety of the combination of belinostat in combination with the CHOP regimen. Submit a complete study report with all supporting datasets.

PMR #1 Schedule Milestones

Final Protocol Submission:	Completed
Trial Completion:	June 2015
Final Report Submission:	April 2016

PMR #2 Description
Characterize the comparative efficacy and safety of Beleodaq when used in combination with a treatment regimen such as CHOP versus CHOP alone or pralatrexate plus CHOP versus CHOP alone for the initial therapy of patients with PTCL.Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, with progression free survival (PFS) as the primary efficacy endpoint. Enroll a sufficient number of patients to characterize the efficacy and safety of each drug added to CHOP, versus CHOP alone. The PFS endpoint should be determined by a blinded independent review committee. PFS analysis should be performed when the trial has experienced the planned number of events necessary

for trial completion. Using the same data cutoff date as the PFS analysis, perform an interim analysis of overall survival. Submit a complete study report with all supporting datasets.

PMR #2 Schedule Milestones

Preliminary Protocol Submission:	July 2014
Final Protocol Submission:	December 2015
Accrual of 25% of Subjects:	April 2017
Accrual of 50% of Subjects:	April 2018
Accrual of 75% of Subjects:	April 2019
Trial Completion:	January 2020
Final Report Submission:	January 2021

PMR #3 Description

Characterize the mass balance information for Beleodaq. Submit the final clinical trial report for the ongoing human mass balance trial (Protocol SPI-BEL-12-103) designed to evaluate the excretion route of belinostat in humans. Submit a complete study report with all supporting datasets.

PMR #3 Schedule Milestones

Final Protocol Submission:	completed
Trial Completion:	December 2014
Final Report Submission:	March 2015

PMR #4 Description

Characterize the PK and safety of belinostat in the presence of hepatic impairment. Submit the final clinical trial report for the ongoing hepatic impairment trial (Protocol CTEP #8846) that is designed to evaluate the influence of hepatic impairment on the PK and safety of belinostat. Submit a complete study report with all supporting datasets.

PMR #4 Schedule Milestones

Final Protocol Submission:	completed
Trial Completion:	December 2015
Final Report Submission:	March 2016

PMR #5 Description

Characterize the PK and safety of belinostat in the presence of renal impairment. Conduct a clinical trial in patients with varying degrees of renal impairment to evaluate the pharmacokinetic and safety of belinostat patients with impaired renal function. The trial should be conducted for sufficient duration in order to evaluate safety following multiple dose administration. Submit a complete study report with all supporting datasets.

PMR #5 Schedule Milestones

Final Protocol Submission:	December 2014
Trial Completion:	December 2015
Final Report Submission:	March 2016

PMR #6 Description

Characterize the PK of belinostat in the presence of strong UGT1A1 inhibitors. Conduct a clinical trial evaluating the influence of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat in patients with cancer. Submit a complete study report with all supporting datasets.

PMR #6 Schedule Milestones

Final Protocol Submission: December 2014
Trial Completion: December 2015
Final Report Submission: March 2016

PMR #7 Description

Evaluate the safety and pharmacokinetics of belinostat in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration and in a sufficient number of subjects in order to evaluate safety following multiple dose administration. Submit a complete study report with all supporting datasets.

PMR #7 Schedule Milestones

Final Protocol Submission: December 2014
Trial Completion: December 2015
Final Report Submission: March 2016

PMR #8 Description

Conduct an *in vitro* study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat. Submit a complete study report with all supporting datasets.

PMR #8 Schedule Milestones

Final Protocol Submission: December 2014
Study Completion: July 2015
Final Report Submission: September 2015

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/s/

EDVARDAS KAMINSKAS
06/12/2014