CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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:	
Deputy Division Director Review	Edvardas Kaminskas, MD
RPM Review	Jessica Boehmer
Medical Officer Review	Hyon-Zu Lee, PharmD/Virginia Kwitkowski, BSN
Statistical Review	Erik W. Bloomquist, PhD/Yuan L. Shen, DrPH/Thomas Gwise, PhD
Pharmacology Toxicology Review	Pedro L. Del Valle, PhD/M Stacey Ricci, MEng, ScD/Haleh Saber, PhD/John K. Leighton, PhD
CMC Review	Xiao-Hong Chen, PhD/Janice T. Brown
Product Quality Microbiology Review	Neal J. Sweeney, PhD/John W. Metcalfe, PhD
Clinical Pharmacology Review	Bahru A. Habtemariam, PharmD/Julie Bullock, PharmD
OSI/DGCPC	Anthony J. Orencia, MD/Kassa Ayelew, MD, MPH
OND/DCRP/QT-IRT	Jiang Liu, PhD/Norman L. Stockbridge, MD, PhD
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, PharmD
OSE/OMEPRM/DRISK	Carolyn L. Yancey, MD/Cynthia LaCivita, PharmD/Claudia Manzo, PharmD
OSE/OMPRM/DMEPA	Tingting N. Gao, PharmD/Kellie A. Taylor, PharmD, MPH/Michelle K. Rutledge, PharmD/Yelena Maslov, PharmD

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

1. Introduction & Background

On December 9, 2013, Spectrum Pharmaceuticals submitted an NDA for Beleodaq (belinostat), which is a histone deacetylase (HDAC) inhibitor and new molecular entity.

The Applicant's proposed indication is for "patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)". To support the proposed indication, Spectrum conducted CLN-19, a phase 2, single-arm, open-label, multicenter trial in patients with relapsed or refractory PTCL who had received at least one prior systemic therapy.

PTCL represents a heterogeneous group of mature T and natural killer cell derived neoplasms and represents approximately 10-15% of all non-Hodgkin lymphomas in North America. At least 20 distinct histologic subtypes of PTCL have been identified. The most common types of PTCL worldwide are PTCL- not otherwise specified (NOS) at 25.9%, angioimmunoblastic T cell lymphoma (AITL) at 18.5%, and anaplastic large cell lymphoma (ALCL), which can be further subdivided by expression of the anaplastic lymphoma kinase (ALK) into ALK+ versus ALK- ALCL, representing 6.6% and 5.5% of PTCL respectively. In North America, ALK+ ALCL is more common, representing 16% of PTCL. PTCL has an aggressive clinical course with inferior outcomes compared to those of aggressive B-cell lymphomas. PTCL has an overall 5-year disease-free survival of <30% (with the exception of patients with ALK+ ALCL). PTCL is a rare malignancy with approximately 7000 cases per year in the US in 2013.

The standard first-line therapy for PTCL is anthracycline-based combination chemotherapy. These regimens provide inferior outcomes compared with those of patients with B-cell lymphomas. Consolidation therapy is often considered for patients who enter remission following chemotherapy with the exception of patients determined to be at "low risk" of relapse/recurrence. Typical first-line consolidation regimens include high-dose chemotherapy followed by stem cell transplant. Stem cell transplant is generally limited to those who are fit enough for this intensive treatment.

Two drugs have previously received accelerated approval in the second-line or later PTCL setting: pralatrexate and romidepsin. In 2009, Folotyn (pralatrexate) was granted accelerated approval for the treatment of patients with relapsed or refractory PTCL based upon a single-arm trial of 109 patients who had a 27% ORR with a median duration of response of 9.4 months. In 2011, Istodax (romidepsin) was granted accelerated approval for the treatment of PTCL in patients who have received at least one prior therapy based on a single-arm trial of 130 patients who had a 25% ORR with a median duration of response of 9.2 plus months. Both drugs have post-marketing requirements open to verify and describe the clinical benefit for each product and convert to regular approval.

2. CMC/Device

The chemistry review team recommends an overall acceptability regarding 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.

3. Nonclinical Pharmacology/Toxicology

There are no nonclinical findings that would preclude the approval of belinostat for the proposed indication. 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. Belinostat is expected to cause teratogenicity and/or embryo-fetal lethality and has been assigned a pregnancy Category D in the prescribing information. Nonclinical reviewers concluded that the submitted nonclinical 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.

4. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval. 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 the maximally tolerated dose. Belinostat undergoes extensive metabolism in the liver, primarily by UGT1A1. It is predominantly eliminated via hepatic metabolism; less than 2% of the dose is recovered unchanged in urine. Belinostat has a half-life of 1 to 2 hours.

Dosage regimen adjustments for belinostat are not recommended for any specific population:

- Renal Impairment: The sponsor did not conduct a renal impairment study. The population PK analysis, included patients with mild (n = 31) to normal (n = 217) creatinine clearance (range of 36 to 236 mL/min). There was no relationship found between creatinine clearance and belinostat PK. The sponsor will be required to evaluate the impact of renal impairment on the PK and safety of belinostat.

- Hepatic Impairment: The sponsor did not submit a study in subjects with impaired hepatic function, but a hepatic impairment trial is currently ongoing. The sponsor also did not conduct a human ADME study. The population PK analysis, which included 59 patients with mild hepatic impairment, showed that mild hepatic impairment does not influence the PK of belinostat.

Impact of Belinostat on CYP Enzymes:
In vitro studies suggest that belinostat and three of its metabolites were shown to inhibit human CYP2C8 and CYP2C9. The pending clinical drug-drug interaction study using warfarin as a substrate of CYP2C9 will provide definitive information on the effect of belinostat and its metabolites on the metabolic activity of CYP2C9. Belinostat is a weak inducer of CYP1A2.

Impact of Belinostat on the QTc:
The review division consulted the QT-Interdisciplinary Review Team, and their review concludes that "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."

The sponsor will be asked to evaluate the influence of UGT1A1 inhibitors, UGT1A1 polymorphism, and renal impairment on the PK and safety of belinostat in patients with cancer.

5. Clinical Microbiology

N/A.

6. Clinical Efficacy and Safety

This application is supported by the results of a multi-center, single-arm trial of 120 evaluable patients with PTCL that was refractory or had relapsed after prior treatment and included patients with baseline platelets <100,000/µL. The median age of the efficacy patient population was 64 years (range, 29-81), 52% of patients were male, and the median number of prior treatments was 2 (range, 1-8). Belinostat was administered by intravenous infusion at a dose of 1,000 mg/m2 once daily on days 1-5 of a 21-day cycle.

The primary trial endpoint was overall response rate (ORR) as assessed by an independent review committee. The ORR was 25.8% (95% CI: 18.3, 34.6). The overall complete and partial response rates were 10.8% and 15.0%, respectively. The median response duration (first date of response to disease progression or death) was 8.4 months (95% CI: 4.5-29.4). See results in Table 1 below.

Table 1 CLN-19 Summary Efficacy Results

	Efficacy Analysis Set (n=120)
Primary endpoint	
ORR by IRC	31 (25.8%)
95% CI	18.3-34.6
Complete response	13 (10.8%)
Partial response	18 (15.0%)
Secondary endpoints	
Median duration of response (by SAP)	8.4 months
95% CI	4.5-29.4
Median time to response	5.6 weeks
Range	4.3-50.4
Median time to progression	2 months
95% CI	1.5-2.8
Median PFS	1.6 months
95% CI	1.4-2.7
Median OS	7.9 months
95% CI	6.1-13.9

The most common adverse reactions (>25%) in the safety population (N=129) were nausea, fatigue, pyrexia, anemia, and vomiting. Thrombocytopenia was reported in 16% of patients with grade 3 or 4 thrombocytopenia in 7% of patients. Serious adverse reactions were reported in 47% of patients. The most common serious adverse reactions (>2%) were pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and multi-organ failure. One treatment-related death due to hepatic failure was reported.

7. Advisory Committee Meeting

This application was not presented to the Oncologic Drugs Advisory Committee because belinostat is not first in its class and there were no controversial issues that would benefit from committee discussion.

8. Pediatrics

Belinostat has been granted Orphan Drug designation for PTCL and is therefore exempt from PREA requirements.

9. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated approval.

- Risk Benefit Assessment
  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%. There is no consensus on standard treatment for PTCL in the first-line and second-line settings and the approved therapies are not optimal. In the treatment of 129 patients with belinostat in patients with relapsed or refractory PTCL who had received at least one prior systemic therapy, a 26% overall response rate was reported. This included an 10.8% complete response rate and a 15% partial response rate. The median duration of response was 8.4 months.

  In the CLN-19 trial, the most common treatment-emergent adverse events (TEAEs) of belinostat (>25%) included nausea, fatigue, pyrexia, anemia and vomiting. Grade 3/4 TEAEs (>5.0%) were anemia (10.9%),

thrombocytopenia (7.0%), dyspnea (6.2%), neutropenia (6.2%), fatigue (5.4%), pneumonia (5.4%) and hypokalemia (5.4%). Though inter-trial comparisons are not reliable, the incidences of grade 3/4 treatment-emergent hematologic toxicities occurred less often in the CLN-19 trial than in the pivotal trials of romidepsin and pralatrexate.

The risk-benefit profile was deemed favorable by Drs. Kaminskas, Kwitkowski and Lee, and I concur with their assessment. Furthermore, all review team members recommend approval. The benefit/risk assessment is positive for belinostat in the treatment of patients with relapsed/refractory PTCL, and I recommend accelerated approval for this application.

- Recommendation for Postmarketing Risk Management Activities
  The Division and OSE agree that a REMS is not necessary, and I concur.

- Recommendation for other Postmarketing Study Commitments:
  See action letter.

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/s/

TAMY E KIM
07/02/2014

RICHARD PAZDUR
07/02/2014