CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA #	207155
Applicant Name	Spectrum Pharmaceuticals, Inc.
Date of Submission	November 9, 2015
PDUFA Goal Date	May 9, 2016
Proprietary Name / Established (USAN) Name	Evomela™ Captisol®-enabled Melphalan Hydrochloride
Dosage Forms / Strength	Powder for Injection, 50 mg per vial [5 mg/mL when reconstituted]
Proposed Indications	• High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma • Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CMC Review/OBP Review	Haripada Sarker, Ph.D., Kasturi Srinivasachar, Ph.D. (Drug Substance)/Olen Stephens, Ph.D., Anamitro Banerjee, Ph.D. (Drug Product)/Steve Rhieu, Ph.D., L Christensen, Ph.D. (Process)/ Vinayak B. Pawar, Ph.D., John Arigo, Ph.D. (Microbiology)/ Donald Oberhuber, Ph.D., Zhihao Peter Qiu, Ph.D. (Facilities Inspection)/ Bapu Gaddam, Ph.D. and Ying Lin, Ph.D. (DMF)/ Maziar Kakhi, Ph.D., Okpo Eradiri, Ph.D. (Biopharmaceutics)/Amit Mitra, Ph.D. (Environmental Assessment)/Olen Stephens, Ph.D.(Application Technical Lead)
OSE/OMERM/DMEPA	Nicole Garrison, Pharm.D./Yelena Maslov, Pharm.D.

OND=Office of New Drugs
OBP=Office of Biotechnology Products
OSE=Office of Surveillance and Epidemiology
OMEPRM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis

Signatory Authority Review Template

1. Introduction

Melphalan, also known as L-phenylalanine mustard, is a phenylalanine derivative of nitrogen mustard, an alkylating agent. The current melphalan product for parenteral use, Alkeran® (melphalan hydrochloride) for Injection, is approved for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. Evomela™ (Captisol®-enabled melphalan hydrochloride) for Injection is a new melphalan hydrochloride product that contains Captisol as excipient instead of propylene glycol. NDA 207155 has been submitted as a 505(b)(2) application for Evomela with Alkeran (melphalan hydrochloride) for Injection as the listed drug.

The Applicant is pursuing two indications for Evomela, the current palliative treatment indication for Alkeran and a new indication of high-dose conditioning prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. Autologous stem cell transplantation (ASCT) is often recommended for medically fit patients as first line standard of care after initial induction therapy because of long sustained remissions and low transplant-related mortality. High-dose melphalan is used as conditioning agent in ASCT. Total body irradiation regimens have been largely superseded by 200 mg/m^2 melphalan divided in two 100 mg/m^2 doses and administered on Days -3 and -2 prior to autologous stem cell transplant.

2. Background

This NDA was initially submitted on December 23, 2014. It was not approved because one of the two Drug Master Files (DMF (b) (4)) was found inadequate to support the submission, and one of the drug product manufacturing facilities (b) (4) failed facility inspection by the FDA field investigator, who conveyed deficiencies to the representative of the facility (Official Action Indicated recommendation). The Sponsor was sent a Complete Response letter on October 22, 2015.

The Sponsor and FDA CMC staff met on November 6, 2015 to discuss and resolve the Product Quality and Facilities Inspections comments in the Complete Response letter and to facilitate the Evomela NDA approval. The Sponsor proposed 1) to revise the Drug Substance sections to list only (b) (4) (holder of DMF (b) (4)) as the Drug Substance supplier; all references to (b) (4) (holder of DMF (b) (4)) are be deleted, 2) to remove (b) (4) as the proposed Drug Product manufacturer and replace it with (b) (4), and 3) to submit the toxicological risk assessment for (b) (4). FDA Staff was in agreement.

Please see the Division Director review of the original application for reviews of disciplines other than CMC/OBP.

3. CMC/Device

- DMF [redacted] was reviewed (Bappu Gadam, Ph.D.) during the original submission and found to be adequate to support NDA 207155. DMF [redacted], which was found inadequate in the first cycle review, was removed from the current application.
- Drug Substance Reviewer (Haripada Sarker, Ph.D.) found the application acceptable from the Drug Substance perspective. Drug Substance from the only DS supplier, [redacted], is used to manufacture Drug Product by [redacted], the only commercial DP manufacturer. Three DP batches from [redacted] are utilized to support the DP expiration dating. [redacted] drug substance manufacturing site was removed from the current application.
- Drug Product Reviewer (Olen Stephens, Ph.D.) states that there is sufficient data from the [redacted] drug substance manufacturing site and [redacted] drug product manufacturing site to support the NDA. Removal of the [redacted] drug substance manufacturing site and [redacted] drug product manufacturing site is acceptable. The proposed drug product is a new formulation of melphalan that incorporates sulfobutylether-β-cyclodextrin (Captisol) as an excipient, improving the solubility and stability of melphalan. Captisol allows the use of an aqueous diluent (normal saline) for reconstituting the drug product instead of the propylene-glycol containing diluent necessary for the reconstitution of the LD, Alkeran for Injection. [redacted]
  According to the nonclinical review of the proposed dose of 100 mg/m^2/day melphalan for the high-dose conditioning treatment, the daily exposure to Captisol is approximately [redacted] for a 70 kg human. This exposure is similar to the daily exposures with other approved products (Nexterone, Noxafil, VFend I.V.). The non-clinical reviewer found the levels of Caprisol in the proposed drug product acceptable. Review of DMF [redacted] for Captisol was deemed adequate (Amit Mitra, Ph.D.).
- Assessment of Manufacturing Process was found to be adequate (Steve Rhieu, Ph.D.). The proposed manufacturing process for the commercial batches will remain unchanged from the manufacturing process previously used for the clinical/registration batches at [redacted]. The review of critical process parameters considered during manufacturing process development had been performed during the review of the original application. The primary container is a 20 mL USP type I glass vial with a [redacted] rubber stopper and crimp vial. The DMFs for the container/ closure systems are adequate to support the NDA. To minimize the risk of light-induced degradation, the drug product should be used in the carton until use (so stated in the label).

- Assessment of the Facilities concluded that "There are no significant, outstanding manufacturing risks that prevent approval of this application". Facilities assessed included the following:
  - [redacted], the manufacturer of melphalan hydrochloride drug substance (most recently inspected in [redacted] and classified as VAI),
  - [redacted], an independent contract testing laboratory to be utilised for quality control testing of Drug Substance used to manufacture commercial Drug Product (underwent routine surveillance cGMP inspection in [redacted] and classified as NAI),
  - [redacted] (manufacture, testing, labeling and packaging of CE-Melphalan HCl for Injection), last inspection [redacted], approved based on District recommendation,
  - [redacted] (labeling and packaging only), last inspection on [redacted], approved based on District recommendation,
  - [redacted] (control testing laboratory), last inspection on [redacted], approved based on Profile.
- Biopharmaceutics reviewers had reviewed and recommended approval of the original NDA submission. The Applicant's resubmission does not contain any new Biopharmaceutics information.
- Microbiology reviewers concluded that the tests and proposed acceptance criteria for microbial burden are adequate for assuring the microbial quality of the drug product. This conclusion indicates "No change from the review of the original NDA".
- Assessment of Environmental Analysis: "The applicant's claim of categorical exclusion from the requirement to submit an Environmental Assessment or Environmental Impact Statement has not changed from the original NDA submission."

Table from OBP review:

"10. Final Discipline Recommendations

DISCIPLINE	REVIEWER	Final Recommendation
DMF 20544	Bapu Gaddam	Adequate
Drug Substance	Haripada Sarker	Approval
Drug Product	Olen Stephens	Approval
Process	Lin Qi	Approval
Microbiology	Vinayak Pawar	Approval
Facility	Donald Obenhuber	Approval
Biopharmaceutics	Maziar Kakhi	Approval (from last cycle)
Application Technical Lead	Olen Stephens	Approval

"Office of Pharmaceutical Quality recommends approval of NDA 207155".

I concur with the conclusions reached by the Office of Pharmaceutical Quality reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36

months, when stored at 25°C (77°F);excursions permitted between 15°C and 30°C (59°F and 86°F), protected from light. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

This NDA resubmission did not contain any new nonclinical data. The review the original submission concluded, "The nonclinical studies submitted to this NDA and the previous findings of safety and efficacy for the listed drug Alkeran provide sufficient information to support the use of Evomela (Captisol®-enabled melphalan hydrochloride) for the proposed indications."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

This NDA resubmission did not contain any new clinical pharmacology/biopharmaceutics data.
From the review of the original submission:
In the original NDA submission, the Sponsor submitted the results of two studies. Study CDX-353-001 was a comparative bioavailability and bioequivalence, Phase 2a single-center, open-label, randomized, cross-over study (N=24) of high dose (100 mg/m^2) CE-Melphalan HCl and Melphalan HCl (Alkeran for Injection, FDA approved drug). The applicant demonstrated that the new formulation was equivalent (80 – 125% for AUC and C_{max}) to Alkeran.

Study CDX-353-002 was a Phase 2b, Multi-center, Open-Label, Safety and Efficacy Study of High-Dose Melphalan HCl for Injection (Propylene Glycol-free) for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation. The dose of CE-Melphalan HCl used in this trial was 100mg/m^2 on Days -3 and -2 [Adjusted Ideal Body Weight for patients with > 130% ideal body weight]. CE-Melphalan produced clinically meaningful increases in overall multiple myeloma response rates: 95% versus 79% response rate post-treatment versus pre-treatment, respectively. Myeloablation was achieved in all 24 patients on CE-Melphalan between Days 0 and 5. Mean myeloablation time was 2.9 days. Similarly, all 24 subjects met criteria for engraftment between Day 9 and Day 13. The mean time to engraftment was 11 days.

PK data was pooled from the two studies to build population PK models. Simulations based on the final model indicated that it was not necessary to adjust CE-Melphalan dose for patients with renal impairment. The Clinical Pharmacology review team concluded that NDA 207155 is acceptable for approval from a clinical pharmacology perspective.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

The Applicant did not submit any new clinical efficacy data in this NDA resubmission.

From the clinical/statistical review of the original NDA:
"The applicant is relying on consensus treatment recommendations and published literature to support the proposed ASCT indication and the proposed dose. NCCN evidence-based guidelines for treatment of multiple myeloma (2014), the British Society of Hematology Guidelines, and the European Myeloma network all recommend ASCT following induction therapy as the first-line standard of care in medically fit patients, and high-dose melphalan 200 mg/m^2 as standard conditioning medium prior to ASCT. In addition the applicant conducted a comprehensive literature review of high-dose melphalan followed by ASCT. The median PFS/EFS were significantly higher with high-dose melphalan followed by ASCT in 4 of the 7 studies. In 2 other studies the median PFS was higher but did not achieve significant difference. Overall Survival was significantly longer in 3 of the 7 studies.

The applicant uses the bioequivalence study (described above in Clinical Pharmacology) to support palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate."

8. Safety

The Applicant did not submit any new safety data in this NDA resubmission.

9. Advisory Committee Meeting

This NDA was not presented at an Advisory Committee meeting.

10. Pediatrics

As noted in the review of the original submission, the application was presented to the Pediatric Research Committee (PeRC) on September 23, 2015. The Applicant has received Orphan Drug designation for Evomela for the indication of high-dose conditioning treatment for HSCT in patients with multiple myeloma. Full waiver was granted for the second indication of palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

11. Other Relevant Regulatory Issues

The Office of Study Integrity and Surveillance inspected the clinical portion of Study CDX-353-001. The inspector concluded "I recommend that the clinical data for study CDX-353-001 be accepted for Agency review if the unreported adverse events and use of concomitant medication (Zometa) did not impact the study outcome." The final classification was VAI.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name of Evomela concurrence with OSE/DMETS recommendation.
- Physician labeling. This was a PLR conversion largely based on the Alkeran label. Prescribing Information was reviewed by Division of Medication Error Prevention and Analysis. An error-prone abbreviation (IV) was identified.
- Carton and immediate container labels were reviewed by Division of Medication Error Prevention and Analysis.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment

The risk:benefit analysis supports approval of Evomela (CE-Melphalan HCl) for the proposed indications. The CE-Mephalan HCL has superior characteristics of solubility, stability and avoids propylene glycol. The formulation simplifies the logistics of administration, provides flexibility of infusion duration, and avoids propylene glycol toxicity. No new safety signals were identified.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None.

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/s/

EDVARDAS KAMINSKAS
02/24/2016