

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207155Orig1s000

207155Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207155/Original-1; Original-2

SUPPL #

HFD # 161

Trade Name Evomela™ (Captisol® enabled melphalan HCl for injection)

Generic Name Melphalan HCl

Applicant Name Spectrum Pharmaceuticals, Inc.

Approval Date, If Known March 10, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant bridged the proposed product to the listed drug by means of a Phase IIa, open-label, randomized, cross-over study of CE-Melphalan HCl for injection ('test') and Alkeran for injection (reference)(CDX-001).

Bioequivalence with Alkeran was studied in CDX-001. The applicant has verified by personal communication with the investigators conducting the studies that the agent used in the key literature reports that support the high-dose conditioning treatment prior to ASCT in patients with MM indication was Alkeran. This is a bioequivalence study only.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an

already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20207 Melphalan Hydrochloride

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the

application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # YES !
! NO
! Explain:

Investigation #2
IND # YES !
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Rachel McMullen
Title: Regulatory Project Manager
Date: March 10, 2016

Name of Office/Division Director signing form: Edvardas Kaminskas, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN
03/10/2016

EDVARDAS KAMINSKAS
03/10/2016

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 207155/Original 1 Supplement Number: NA NDA Supplement Type (e.g. SE5): _____

Division Name: DHP PDUFA Goal Date: 10/23/15 Stamp Date: 12/23/2014

Proprietary Name: EVOMELA

Established/Generic Name: Melphalan HCl

Dosage Form: Powder

Applicant/Sponsor: Spectrum Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) None

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with Multiple Myeloma.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN
04/20/2015

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 207155/Original 2 Supplement Number: NA NDA Supplement Type (e.g. SE5): _____

Division Name: DHP PDUFA Goal Date: 10/23/15 Stamp Date: 12/23/2014
2015

Proprietary Name: EVOMELA

Established/Generic Name: Melphalan HCl

Dosage Form: Powder

Applicant/Sponsor: Spectrum Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) None

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- Deferred for some or all pediatric subpopulations (Complete Sections C)
- Completed for some or all pediatric subpopulations (Complete Sections D)
- Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

justification):**# Not feasible:**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

*** Not meaningful therapeutic benefit:**

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN
03/07/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207155 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection Established/Proper Name: Melphalan HCl Dosage Form: Powder		Applicant: Spectrum Pharmaceuticals, Inc. Agent for Applicant (if applicable): Anil Hiteshi
RPM: Rachel McMullen		Division: Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: Feb 17, 2016</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action: User Fee Goal Date is <u>May 9, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		Cycle 1: CR: October 22, 2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 505(b)(2)
(confirm chemical classification at time of approval)

- Fast Track
- Rolling Review
- Orphan drug designation (Original 1)
- Breakthrough Therapy designation

- Rx-to-OTC full switch
- Rx-to-OTC partial switch
- Direct-to-OTC

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified: Paragraph 1 certification <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Cycle 1: CR: October 22, 2015 Cycle 2: AP: March 10, 2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	Conditionally Acceptable letter: March 16, 2015
• Review(s) <i>(indicate date(s))</i>	DMEPA Review: March 16, 2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> PLR format review: October 22, 2015 DMEPA: <input checked="" type="checkbox"/> Cycle1: August 26, 2015 Cycle 2 (memo): February 9, 2016 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> Cycle 1: September 25, 2015 Cycle 2 (memo): February 26, 2016 OPDP: <input checked="" type="checkbox"/> Cycle 1: September 22, 2015 Cycle 2 (memo): March 1, 2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other:
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM Filing review: March 3, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	CR Action: October 22, 2015 AP Action Cleared: February 17, 2016
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>September 23, 2015</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	March 3, 2016 December 30, 2015 December 3, 2015 October 9, 2015 October 6, 2015 September 25, 2015 August 21, 2015 August 18, 2015 July 8, 2015 April 22, 2015 March 12, 2015 March 5, 2015 March 3, 2015 January 29, 2015 January 22, 2015 January 6, 2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	PeRC minutes: October 6, 2015
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	June 30, 2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	Type A: November 6, 2015 Type C: January 1, 2014 Type C CMC: April 22, 2014 Pre-NDA: June 30, 2014

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	Cycle 1: CR: October 20, 2015 Cycle 2: AP: February 24, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	Cycle 1: CR: October 16, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review _ Co-signed Cycle 2 Cycle 1: September 23, 2015 Cycle 2: Co-signed February 19, 2016
• Clinical review(s) (<i>indicate date for each review</i>)	Cycle 1: August 24, 2015 Cycle 2: February 19, 2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Page 14 of Clinical Review dated August 24, 2015.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review; Co-signed September 23, 2015
Statistical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review Cycle 1: Co-signed September 23, 2015 Cycle 2: Co-signed March 8, 2016
Statistical Review(s) (indicate date for each review)		Cycle 1: September 23, 2015 Cycle 2: March 8, 2016
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review Cycle 1: Co-signed September 18, 2015 Cycle 2: Co-signed February 29, 2016
Clinical Pharmacology review(s) (indicate date for each review)		Cycle 1: September 18, 2015 Cycle 2: February 29, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		April 7, 2015 September 4, 2015 September 28, 2015
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review Cycle 1: Co-signed August 24, 2015 Cycle 2: Co-signed February 24, 2016
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		Cycle 1: August 21, 2015 Cycle 2: February 24, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	Cycle 1: CR: September 18, 2015 Cycle 2: AP: January 25, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Page 30 of CMC review dated March 13, 2016
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable _ Cycle 2 Re-evaluation date: None <input checked="" type="checkbox"/> Withhold recommendation for Cycle 1

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN
03/14/2016

From: [McMullen, Rachel](#)
To: [Anil Hiteshi](#)
Cc: [Baird, Amy](#); [Carioti, Theresa](#); [McMullen, Rachel](#)
Subject: NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) - Please submit Pediatric Assessment ASAP
Date: Tuesday, March 03, 2015 11:03:11 AM
Importance: High

Dear Mr. Hiteshi,

In reference to your 505 (b)(2) application for your new NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection, please note that since your second proposed indication (palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate) does not have orphan status, you are therefore required to comply with PREA requirements.

Please submit your Pediatric Assessment to the NDA file no later than **10am Monday, March 9, 2015**. Please provide your response via email and follow up with an formal submission to the NDA file.

Kindly confirm receipt of this communication.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/03/2015

From: [McMullen, Rachel](#)
To: "Anil Hiteshi"
Cc: [McMullen, Rachel](#)
Subject: NDA 207155/Evomela: Final FDA Proposed Labeling: PI, PPI, Carton and Container Labels_ Please respond by COB tomorrow, March 4th
Date: Thursday, March 03, 2016 3:17:59 PM
Attachments: [m1-14-1-3-draft-ppi-fda Proposed Labeling.docx](#)
[m1-14-1-1-carton-label.pdf](#)
[m1-14-1-1-vial-label.pdf](#)
[m1-14-1-3-draft-PI-FDA proposed label.docx](#)
Importance: High

Dear Mr. Hiteshi,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 207155/Evomela. We are in agreement with Spectrum's proposed labeling. Please review and provide your concurrence to the attached FDA proposed labeling for the **PI, PPI** and **Carton Container Labels**.

Please provide Spectrum's confirmation regarding final FDA proposed labeling via email by **COB tomorrow, Friday, March 4, 2016**. Following that, please submit the information formally to your NDA file.

Please ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/03/2016

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Wednesday, December 30, 2015 7:38 PM
To: 'Anil Hiteshi'
Cc: McMullen, Rachel
Subject: Evomela FDA Information Request

Importance: High

Hello Anil,

The CMC team has the following information request:

1. In the IR response dated July 27, 2015 Spectrum committed to include a (b) (4) as part of the (b) (4). The current process flow diagram lists (b) (4); however, it does not appear in the updated master batch record for the proposed (b) (4) L commercial batches. Please confirm a test for (b) (4) solution and update your master batch record accordingly.

Please respond at your earliest convenience in order to continue review of this re-submission.

Thanks & Happy New Year,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov





NDA 207155 /Original 1
NDA 207155 /Original 2

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

We acknowledge receipt on November 9, 2015, of your November 7, 2015, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for or EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection; 50 mg (free base)/vial.

We consider this a complete, class 2 response to our October 22, 2015 action letter. Therefore, the user fee goal date is May 9, 2016.

Please note this acknowledgement communication replaces the previous correspondence, dated November 23, 2015.

If you have any questions, call me at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RACHEL S MCMULLEN
12/03/2015



NDA 207155

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irving, CA 92618

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evomela® (Melphalan).

We also refer to the telecon between representatives of your firm and the FDA on November 6, 2015. The purpose of the meeting was to discuss and resolve the Product Quality and Facility Inspections comments included in FDA's *Complete Response Letter* dated October 22, 2015, and facilitate the EVOMELA NDA approval.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rabiya Laiq, Pharm.D, Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: CMC

Meeting Date and Time: November 6, 2015 12:00PM to 1:00 PM
Meeting Location: Teleconference

Application Number: 207155
Product Name: Evomela® (Melphalan)
Indication: High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

Applicant Name: Spectrum Pharmaceuticals, Inc.

Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Rabiya Laiq, Pharm.D.

FDA ATTENDEES

Janice Brown, Quality Assessment Lead
Olen Stephens, Quality Assessment Branch Chief
Donald Obenhuber, Facility Reviewer, OPF
Amit Mitra, Quality Drug Product Reviewer
Zhihao Peter Qiu, Facility Branch Chief, OPF
Haripada Sarker, API Reviewer
Rachel McMullen, Project Manager OND
Rabiya Laiq, CMC Regulatory Business Process Manager, OPQ

SPONSOR ATTENDEES

Rajesh C. Shrotriya, MD, Chairman and Chief Executive Officer
Joseph Turgeon, President and Chief Operating Officer
Lee F. Allen, MD, PhD, Chief Medical Officer
Pramod K. Gupta, PhD, Vice President, Pharmaceutical Operations
Pramod K. Gupta, PhD, Vice President, Quality
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs

1.0 BACKGROUND

The purpose of meeting was to discuss and resolve the Product Quality and Facility Inspections comments included in FDA's *Complete Response Letter* dated October 22, 2015, and facilitate the EVOMELA NDA approval.

FDA sent Preliminary Comments to Spectrum on November 5, 2015.

2. DISCUSSION

Question 1:

Does the Agency agree that no additional review comments are pending on the Drug Substance Section after removal of (b) (4) as a proposed supplier in our pending NDA for Evomela?

FDA Response to Question 1:

Revise the drug substance section and justify the CMC information based on the only drug substance supplier, (b) (4) (DMF (b) (4)). The determination of additional review comments will be made when the NDA is resubmitted for review.

Sponsor's Response to Question 1:

As proposed, the Drug Substance sections of the Melphalan NDA will be revised to list (b) (4) (DMF (b) (4)) as the only Drug Substance supplier; all references to (b) (4) will be deleted. Therefore, the only changes to the Melphalan NDA resubmission are administrative in nature with the deletion of all CMC references to (b) (4).

As shown in **Table 1**, the original Melphalan NDA submission included complete information and the required data supporting (b) (4) as a Drug Substance supplier for Melphalan API, and therefore, no new information will be included in the Melphalan NDA resubmission for (b) (4). As discussed with FDA at the Type C meeting on 16APR2014, we agreed to use a single harmonized set of specifications for API from both Drug Substance suppliers.

Table 1 Detailed List of NDA Section Updates for Drug Substance

SECT.	SECTION NAME	INCLUDED IN ORIGINAL NDA	ADDITIONAL INFORMATION IN NDA RESUBMISSION
3.2.S DRUG SUBSTANCE			
3.2.S.1	General Information	Yes	None
3.2.S.2	Manufacturer	Yes	None
3.2.S.3	Characterization	Yes	None
3.2.S.4	Control of Drug Substance	Yes	None
3.2.S.5	Reference Standards or Material	Yes	None
3.2.S.6	Container Closure System	Yes	None
3.2.S.7	Stability	Yes	None

As proposed, the Drug Substance sections of the NDA will be revised to list (b) (4) Corporation (DMF (b) (4)) as the only Drug Substance supplier; all references to (b) (4) will be deleted. The information already provided in the Melphalan NDA justifies (b) (4) as the Drug Substance supplier.

Does the Agency agree?

Meeting Discussion:

The plan to remove the (b) (4) site from the NDA is reasonable. When the NDA is formally resubmitted, the reviewer will confirm references to the (b) (4) site have been removed.

Question 2:

Does the Agency accept the previously made agreement to allow Spectrum to submit the toxicological risk assessment for (b) (4) in a supplemental application to the NDA within twelve months post approval?

FDA Response to Question 2:

Yes

Sponsor's Response to Question 2:

We acknowledge the Agency's agreement.

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 3:

Does the Agency agree that removing (b) (4) as the proposed Drug Product manufacturer and replacing it with (b) (4), would eliminate the need to satisfactorily resolve the (b) (4) facility deficiencies before approval of our NDA for Evomela?

Does the Agency agree that a review of this change in the pending NDA is sufficiently minor and would not unduly extend the review timeline?

Does the Agency agree to expeditiously review our proposed amendment to the pending NDA in which we replace (b) (4) with (b) (4) as the Drug Product manufacturer?

FDA Response to Question 3:

Any data submitted from the (b) (4) site in the original NDA would need to be resubmitted by data generated from the (b) (4) site.

All facilities proposed for commercial manufacturing operations will be evaluated as part of the second review cycle. An acceptable facility compliance evaluation is required before a new drug application can be approved. Given that facility deficiencies were noted in the Complete Response, your application would be classified as a Class 2 Resubmission.

Sponsor's Response to Question 3:

As shown in **Table 2**, Spectrum confirms that the original Melphalan NDA contained all data required for (b) (4) as a Drug Product manufacturer that was also submitted for (b) (4), with the exception of the following three items:

- **3.2.P.3.1 Manufacturer(s) – GMP Certification**
- **3.2.P.3.3 Description of Manufacturing Process and Process Control – Master Batch Record**
- **3.2.P.3.5 Process Validation and/or Evaluation – (b) (4) Type V Facility DMF**

Therefore, only the GMP certification for (b) (4), Master Batch Record, and reference to (b) (4) Type V facility DMF will be included as additional information in the Melphalan NDA resubmission.

The Sponsor confirms that three process validation batches will be manufactured by (b) (4) before commercial distribution of the product. All CMC commitments made to the Agency during the NDA review will be implemented for the commercial manufacturing at (b) (4)

The Sponsor also confirms that the description of the manufacturing process and process controls for (b) (4) in the NDA are identical to what (b) (4) will use for the manufacturing of commercial supply. There will be no change in manufacturing scale, process, testing and/or container closure system between the batch data submitted from (b) (4) in the original Melphalan NDA, and that which will be used for commercial manufacturing.

Table 2 Detailed List of Updated NDA Sections for Drug Product

SECT.	SECTION NAME	INCLUDED IN ORIGINAL NDA*	ADDITIONAL INFORMATION INCLUDED IN NDA RESUBMISSION
3.2.P DRUG PRODUCT			
3.2.P.1	Description and Composition of the Drug Product	Yes	None
3.2.P.2	Pharmaceutical Development	Yes	None
3.2.P.3	Manufacturers	Yes	Yes <ul style="list-style-type: none"> • Provide GMP certification for (b) (4) • Provide blank master batch record • Provide reference to (b) (4) Type V Facility

SECT.	SECTION NAME	INCLUDED IN ORIGINAL NDA*	ADDITIONAL INFORMATION INCLUDED IN NDA RESUBMISSION
			DMF
3.2.P.4	Control of Excipients	Yes	None
3.2.P.5	Control of Drug Product	Yes	None
3.2.P.6	Reference Standards or Material	Yes	None
3.2.P.7	Container Closure System	Yes	None
3.2.P.8	Stability	Yes	None
3.2.R	Regional Information	Yes	None
3.3	Literature References	Yes	N/A

**resubmission to include only administrative changes*

The Melphalan NDA resubmission will only include the GMP certification for (b) (4), Master Batch Record, and reference to (b) (4) Type V facility DMF as additional information to support the approval of (b) (4) as the commercial Drug Product manufacturer. Therefore, Spectrum believes that the Melphalan NDA resubmission should be classified as a Class 1 Resubmission, since it includes only minor clarifying information.

Does the Agency agree?

Meeting Discussion:

Until the NDA is formally resubmitted, FDA cannot determine whether it would be a Class 1 or Class 2 resubmission. If no facilities inspections are required, and the status of the sites have not changed from the first review cycle, it is likely the resubmission will be a Class 1 resubmission.

For the two sites removed from the application, please also remove these sites from the 356h form.

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/s/

RABIYA LAIQ
11/06/2015

OLEN M STEPHENS
11/06/2015



NDA 207155

MEETING PRELIMINARY COMMENTS

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irving, CA 92618

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evomela® (Melphalan).

We also refer to your October 23, 2015, correspondence, received October 26, 2015, requesting a meeting to discuss and resolve the Product Quality and Facility Inspections comments included in FDA's *Complete Response Letter* dated October 22, 2015, and facilitate the EVOMELA NDA approval.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to Rabiya Laiq, Regulatory Business Process Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Rabiya Laiq, Pharm.D., at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: A
Meeting Category: CMC

Meeting Date and Time: November 6, 2015 12:00PM to 1:00 PM
Meeting Location: Teleconference

Application Number: 207155
Product Name: Evomela® (Melphalan)
Indication: High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

Applicant Name: Spectrum Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 6, 2015 from 12:00 PM to 1:00 PM, with the FDA as a teleconference between Spectrum and the Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory business process manager (RBPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact Rabiya Laiq, if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Purpose of meeting is to discuss and resolve the Product Quality and Facility Inspections comments included in FDA's *Complete Response Letter* dated October 22, 2015, and facilitate the EVOMELA NDA approval. Preliminary comments are being sent to the sponsor November 4, 2015.

2.0 DISCUSSION

Question 1:

Does the Agency agree that no additional review comments are pending on the Drug Substance Section after removal (b) (4) as a proposed supplier in our pending NDA for Evomela?

FDA Response to Question 1:

Revise the drug substance section and justify the CMC information based on the only drug substance supplier, (b) (4) Corporation (DMF (b) (4)). The determination of additional review comments will be made when the NDA is resubmitted for review.

Question 2:

Does the Agency accept the previously made agreement to allow Spectrum to submit the toxicological risk assessment for (b) (4) in a supplemental application to the NDA within twelve months post approval?

FDA Response to Question 2:

Yes

Question 3:

Does the Agency agree that removing (b) (4) as the proposed Drug Product manufacturer and replacing it with (b) (4), would eliminate the need to satisfactorily resolve the (b) (4) facility deficiencies before approval of our NDA for Evomela?

Does the Agency agree that a review of this change in the pending NDA is sufficiently minor and would not unduly extend the review timeline?

Does the Agency agree to expeditiously review our proposed amendment to the pending NDA in which we replace (b) (4) with (b) (4) as the Drug Product manufacturer?

FDA Response to Question 3:

Any data submitted from the (b) (4) site in the original NDA would need to be resubmitted by data generated from the (b) (4) site.

All facilities proposed for commercial manufacturing operations will be evaluated as part of the second review cycle. An acceptable facility compliance evaluation is required before a new drug application can be approved. Given that facility deficiencies were noted in the Complete Response, your application would be classified as a Class 2 Resubmission.

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/s/

RABIYA LAIQ
11/04/2015

JANICE T BROWN
11/04/2015

From: [McMullen, Rachel](#)
To: "Anil Hiteshi"
Cc: [McMullen, Rachel](#)
Subject: NDA 207155/Evomela: FDA Proposed Labeling (PI and PPI) _ Response Due: October 13th
Date: Friday, October 09, 2015 5:28:10 PM
Attachments: [m1-14-1-3-draft-ppi-sppi-FDA Proposed Edits_10-9-15.docx](#)
[m1-14-1-3-draft-pi.docx-sppi-FDA proposed Edits_10-9-15.docx](#)
Importance: High

Good evening Mr. Hiteshi,

Please refer to your New Drug Application, NDA 207155 for EVOMELA™ (Captisol® -enabled melphalan HCl) for Injection). FDA's current edits/comments on the **PI** and **PPI** are attached.

Please review and provide revisions to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please submit your revised labeling response via email by **2pm on Tuesday, October 13, 2015**, followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please confirm receipt of this email.

Kind Regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
10/09/2015

**PeRC Meeting Minutes
September 23, 2015**

PeRC Members Attending:

Lynne Yao

Wiley Chambers – Acting Chair for the following: (Completion of [REDACTED] NON-RESPONSIVE [REDACTED])

Gettie Audain

Meshaun Payne

Hari Cheryl Sachs

Lily Mulugeta

Belinda Hayes

Deanna Greene

Davia Shetty

George Greeley

Shrikant Pagay

Thomas Smith

Michelle Roth-Kline

Melissa Tassinari

Freda Cooner

Adrienne Homatko-Munoz ([REDACTED] NON-RESPONSIVE [REDACTED] reviews only)

Barb Buch ([REDACTED] NON-RESPONSIVE [REDACTED] reviews only)

Lisa Faulcon

Maura O’Leary – [REDACTED] NON-RESPONSIVE [REDACTED] reviews only)

Agenda

NON-RESPONSIVE					
9:00					
9:15					
9:35	NDA 207155	Evomela (captisol enabled melphalan HCl) Full Waiver	DHP	Rachel McMullen	1) A high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma (orphan designated) and, 2) Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate

NON-RESPONSIVE

NON-RESPONSIVE

NON-RESPONSIVE

Evomela (captisol enabled melphalan HCl) Full Waiver

- Proposed Indications: 1) A high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma (orphan designated) and 2) Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
- The division clarified that this formulation of melphalan will likely provide a considerable advantage in the administration. The currently approved formulation of melphalan requires careful mixing and administration instructions that are cumbersome to follow. This new formulation increases the ease of administration. Therefore, the division believes that this new formulation will likely completely replace the currently approved formulation. The division also noted that this application does not include any new clinical studies (only bioequivalence studies in adults).
- The approved EMA PIP includes studies to be used as part of a preparative regimen prior to autologous bone marrow (rescue) therapy that could be used for non-hematologic pediatric malignancies in which bone marrow ablation is required (e.g., neuroblastoma). Therefore, the PeRC agreed with the division that the sponsor could submit a PPSR to evaluate the efficacy of this product for this indication.
- The division also noted that melphalan is not approved for neuroblastoma in adults and could potentially require the sponsor to conduct clinical trials in pediatrics. The PeRC recommended that the division consider other potential indications that could be considered (e.g., as part of a preparative regimen prior to autologous bone marrow transplant) if this allows for pediatric extrapolation from efficacy already established in adult patients.
- PeRC Recommendations:
 - The PeRC concurred with the divisions comments.
 - The PeRC agreed with the division's granting of a full waiver for multiple myeloma for whom oral therapy is not appropriate.
 - The PeRC recommended that the division communicate with the sponsor that a Written Request could also be considered and encourage the sponsor to submit a PPSR.

NON-RESPONSIVE

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/s/

GETTIE AUDAIN
10/06/2015

From: [McMullen, Rachel](#)
To: ["Anil Hiteshi"](#)
Cc: [McMullen, Rachel](#)
Subject: NDA 207155/Evomela: FDA Proposed Labeling_ (PI, PPI and Carton Container Labels) _ Labeling response Due Thursday, October 8
Date: Tuesday, October 06, 2015 3:27:16 PM
Attachments: [m1-14-1-3-draft-pi.docx](#) [NDA 207155 Evomela PI with FDA proposed edits 10-6-15.docx](#)
[DMPP recommendation to Applicant response-PPI 5 OCT 2015.docx](#)
[NDA 207155 Revised Carton Container Recommendations Oct 6.doc](#)
Importance: High

Dear Mr. Hiteshi,

Please refer to your New Drug Application, NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection). The FDA review team's current edits/comments on the **PI, PPI** and **Carton Container Labels** are attached.

Please review and provide revisions to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response via email by **5pm EST on Thursday, October 8, 2015**, followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please confirm receipt of this email.

Kind Regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RACHEL S MCMULLEN
10/06/2015

From: [McMullen, Rachel](#)
To: "Anil Hiteshi"
Cc: [McMullen, Rachel](#)
Subject: NDA 207155/Evomela: FDA Proposed Labeling (PI, PPI and Carton Container Labels)
Date: Friday, September 25, 2015 5:16:13 PM
Attachments: [melphalan hydrochloride \(EVOMELA\) NDA 207155 DMPP-OPDP PPI Sep-2015 marked.docx](#)
[m1-14-1-3-melphalan-package-insert-FDA Proposed Edits 9-25-15.doc](#)
[NDA 207155 Carton Container Labeling Recommendations Sept25.doc](#)
Importance: High

Good afternoon Mr. Hiteshi,

Please refer to your New Drug Application, NDA 207155 for EVOMELA™ (Captisol® -enabled melphalan HCl) for Injection).

FDA's current edits/comments on the **PI, PPI** and **Carton Container Labels** are attached.

Please review and provide revisions to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please submit your revised labeling response via email by **COB Tuesday, September 29, 2015**, followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please **confirm** receipt of this email.

Kind Regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RACHEL S MCMULLEN
09/25/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Friday, August 21, 2015 11:32 AM
To: 'anil.hiteshi@sppirx.com'
Cc: McMullen, Rachel
Subject: FDA NDA 207155 Information Request 2_ Please respond by COB August 27, 2015

Dear Mr. Hiteshi:

Please refer to your New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evomela™ (Melphalan HCl).

We also refer to your December 23, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your proposal to use (b) (4) melphalan, related substances and Captisol assay is not acceptable because of lack of experience in commercial scale variability. Revise your sampling plan for potency of melphalan, related substances, and Captisol assay method to include (b) (4) vial composite. After gaining sufficient commercial scale variability information you may submit a statistically sound reduced sampling plan via a supplement.
2. We acknowledge your commitment to provide a toxicological risk assessment for presence of (b) (4) based on PDE calculation in the first annual report post approval. Since a safety evaluation may be necessary with the proposed information, commit to submit the proposed information via a supplement within twelve months post approval.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by **August 27, 2015**.

Kindly confirm receipt of this email.

Thanks,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

From: [McMullen, Rachel](#)
To: "Anil Hiteshi"
Cc: [McMullen, Rachel](#)
Subject: NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) - Information Request _ Please respond by 1pm on Wednesday, Sept 2, 2015
Date: Tuesday, August 18, 2015 4:26:00 PM
Attachments: [NDA 207155_Evomela_ClinPharm_IR.doc](#)

Good afternoon Mr. Hiteshi,

In reference to your 505 (b)(2) application for your new NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection, please note the attached information request from the team.

Please respond to me via email by **1pm on Wednesday, September 2, 2015** and kindly follow up with an formal submission to the NDA file.

Kindly confirm receipt of this communication.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
08/18/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Wednesday, July 08, 2015 7:08 PM
To: 'anil.hiteshi@sppirx.com'
Subject: FDA NDA 207155 Information Request- Please Respond by July 27, 2015.

Dear Mr. Hiteshi:

Please refer to your New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evomela™(Melphalan HCl).

We also refer to your December 23, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1) Adopt a control strategy assuring that the reconstituted solution is free of visible particles.
- 2) Adopt a seal integrity test in the drug product specification.
- 3) Include justified acceptance criteria for resolution factor as a part of system suitability of the following analytical methods: a) HPLC assay and related substances for melphalan hydrochloride for injection; b) Determination of Captisol content.
- 4) You have identified a (b) (4) as an extractable (b) (4). Identify the (b) (4) by chemical name and add a control strategy to limit its presence in the drug product.
- 5) The established name “(b) (4)” is not acceptable. Change the established name to “Melphalan (b) (4) for injection” in PI/PPI/Carton and container label.
- 6) We recommended that you include the following statement in the carton and container labels: “Keep out of reach of children”.
- 7) Include the quantity of the inactive ingredient Captisol on the container and carton label.
- 8) The current sampling plan for the chromatographic methods for melphalan assay, related substances, and Captisol assay calls for three samples with duplicate injections. Revise sampling plan for melphalan assay and related substances, and Captisol assay method to include (b) (4) vial composite for sampling; otherwise justify your current sampling plan.
- 9) Provide limit of detection (LOD) for the related substances (b) (4) as a part of Methods Validation for related substances assay.
- 10) The current method for related substances does not use reference standards for the (b) (4) (b) (4) impurities. Justify the absence of reference standards for (b) (4) (b) (4)

(b) (4) in the impurities and related substances method of the drug product. If there is no justification, include these reference standards instead of using melphalan as an external standard in the related substances assay method and or incorporate the relative response factors for in the calculation of these known impurities concentration related to melphalan.

11) Clarify whether the primary stability data were generated under upright or inverted conditions. If long term and accelerated stability data were generated only under upright conditions, provide the stability data under inverted conditions. Otherwise, justify with supportive data that direct contact between the rubber stopper and the powder for Injection does have any impact on drug product stability.

12) Revise your post-approval stability commitment to place the first three production batches under long term and accelerated stability as recommended in "Guidance for Industry, ICH Q1 (R2) Stability Testing of New Drug Substances and Products" under inverted conditions.

13) Provide correlation, if any, between decrease of pH and the increase of total degradation products to justify your lower end of the pH acceptance criterion during batch release. We recommend you adopt (b) (4) to prevent potential batch failure during stability.

14) The lyophilization cycle for the (b) (4)
[Redacted]

15) Provide a list comparing equipment and equipment capacity to be used for commercial scale and registration batch manufacturing.

16) Degradation seems to be a potential concern during manufacturing and yet there is no mention made for (b) (4).

17) We note that photostability studies demonstrated increase impurities, (b) (4). Please comment on what controls, if any, have been put into place to limit light induced instability during the manufacturing process.

18) In Table 3.2.P.3-2, the proposed in-process (b) (4)
[Redacted]

19) The fill time is about (b) (4)
[Redacted]

20) It is noted that the registration batches were manufactured in (b) (4) and (b) (4) and the registration batch sizes were comparable (b) (4). It is observed that more vials were rejected after lyophilization from the (b) (4) registration batches (See Table 3.2.P.3-6 and Table 3.2.P.3-7 of the process validation reports). Please specify the rejection criteria of the 100% visual test.

Other comment for the team: A (b) (4) was observed with the decreased assay and increased total impurities in the (b) (4) in Report: MEL-R-002.00.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by **July 27, 2015**.

Kindly confirm receipt of this email.

Thanks,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov



From: [McMullen, Rachel](#)
To: [Anil Hiteshi](#)
Cc: [McMullen, Rachel](#)
Subject: NDA 207155: Please provide updated Carton and Container Labels by 5/6/15
Date: Wednesday, April 22, 2015 3:46:17 PM
Importance: High

Dear Mr. Hiteshi,

In reference to your 505 (b)(2) application, please submit updated carton labeling and container labels containing the proprietary name, Evomela, NDA 207155 (*Melphalan Hydrochloride*) by **Wednesday, May 6, 2015**

Please provide a response via email by the date requested. Following that, please also submit this information formally to the NDA.

Kindly **confirm** receipt of this email.

Thank you,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
04/22/2015



NDA 207155

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618

ATTENTION: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) dated and received December 23, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Captisol[®]-enabled Melphalan Hydrochloride for Injection, 50 mg per vial.

We also refer to your correspondence, dated and received December 23, 2014, requesting review of your proposed proprietary name, Evomela.

We have completed our review of the proposed proprietary name, Evomela and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Rachel McMullen, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/16/2015

From: McMullen, Rachel
To: ["Anil Hiteshi"](#)
Subject: NDA 207155: Information Request - EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection
Date: Thursday, March 12, 2015 3:49:00 PM

Dear Mr. Hiteshi,

In reference to your 505 (b)(2) application for your new NDA 207155 for EVOMELA™ (Captisol® - enabled melphalan HCl) for Injection, the team is requesting the following information:

Please submit analysis datasets (ADAM files) and the corresponding SAS programs that were used to derive myeloablation rate, time to myeloablation, neutrophil engraftment rate, time to neutrophil engraftment, platelet engraftment rate and time to platelet engraftment (i.e. variables used for tables 21, 22.a, 22.b, 23, 24, 25, 26, 27, 28) in the Clinical Study Report (CSR).

Please provide a response via email **by 2pm EST, on Friday, March 20, 2015**. Following that, please also submit this information formally to the NDA.

Kindly ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/12/2015



NDA 207155/Original 1
NDA 207155/Original 2

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received December 23, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection; 50 mg (free base)/vial.

We have administratively split your application into Original 1 and Original 2 which provides for the following indications:

Original 1: High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with Multiple Myeloma.

Original 2: Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 23, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If

major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 25, 2015.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing and Control:

1. We recommend that elemental impurities be included in the drug product specification. Please follow the recommendations of USP <232>, <233>, and ICH Q3D for setting specification for elemental impurities in the drug product.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

- Submit the analytical method used to test elemental impurities along with its validation.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable).

Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement for NDA 207155/Original 2. Within 30 days of the date of this letter, please submit one of the following: a full waiver request, a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this application/supplemental application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
03/05/2015

From: [Kallungal, Beatrice](#)
To: anil.hiteshi@sppirx.com
Cc: [Kallungal, Beatrice](#); [McMullen, Rachel](#)
Subject: NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) - Information Request - 01/29/2015
Date: Thursday, January 29, 2015 10:38:37 AM

Dear Mr. Hiteshi,

In reference to your 505 (b)(2) application for your new NDA 207155 for EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection, the team is requesting the following information:

The reviewer cannot find any documentation for how the baseline characteristics and efficacy results were calculated. There is no analysis dataset (ADAM files) submitted for baseline characteristics and efficacy variables. Please submit SAS programs for creating Tables 11, 12, 13, 14, 15, 16 in the Clinical Study Report (CSR).

Please provide a response via email **by 3 pm EST, February 3, 2015**. Following that, please also submit this information formally to the NDA.

Please acknowledge receipt of this request.

Regards,

Beatrice (for Rachel McMullen)

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
01/29/2015

From: [McMullen, Rachel](#)
To: [Anil Hiteshi](#)
Cc: [McMullen, Rachel](#)
Subject: New NDA 207155: Information Request
Date: Thursday, January 22, 2015 3:24:38 PM
Importance: High

Dear Mr. Hiteshi,

In reference to your 505 (b)(2) application for your new NDA 207155 for EVOMELA™ (Captisol® - enabled melphalan HCl) for Injection, the team is requesting the following information:

1. In the pre NDA meeting held 6/23/14, FDA advised Spectrum that it was Spectrum's responsibility to confirm the drug used in the reference studies, (Vesole, 1999 and Barlogie, 1999) was the reference drug for this application, Alkeran. Please advise the FDA reviewer where to locate the information that provides this confirmation in the application.
2. Please advise the FDA where to locate the risk benefit analysis for the 2 indications in the application.
3. Please advise the FDA where to locate the "coding dictionary" listing all investigator verbatim terms and the preferred terms to which they were mapped.

Please provide a response via email **by 12pm EST, tomorrow Friday, January 23, 2015**. Following that, please also submit this information formally to the NDA.

Kindly ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/22/2015



NDA 207155

NDA ACKNOWLEDGMENT

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection;
50 mg (free base)/vial

Date of Application: December 23, 2014

Date of Receipt: December 23, 2014

Our Reference Number: NDA 207155

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2015 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RACHEL S MCMULLEN
01/06/2015



IND 104925

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Captisol Enabled (CE)-Melphalan HCl for Injection (Propylene-Glycol Free).

We also refer to the meeting between representatives of your firm and the FDA on June 23, 2014. The purpose of the meeting was to the format and content of the clinical sections of the 505(b)(2) New Drug Application for the product.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Patricia Garvey, Senior Regulatory Project Manager, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA (505(b)(2))

Meeting Date and Time: June 23, 2014 at 9:00 AM to 10:00 AM (EDT)
Meeting Location: FDA White Oak Campus
10903 New Hampshire Avenue
White Oak Building 22, Room 1315
Silver Spring, MD 20903

Application Number: IND 104925
Product Name: Captisol Enabled (CE)-Melphalan HCl for Injection (b) (4)

Indication: For use as a high-dose conditioning treatment prior to autologous stem cell transplantation in patients with multiple myeloma

Sponsor/Applicant Name: Spectrum Pharmaceuticals, Inc.

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Patricia Garvey, RPh

FDA ATTENDEES

OHOP/DIVISION OF HEMATOLOGY PRODUCTS

Edvardas Kaminskas, MD – Deputy Director
Albert Deisseroth, MD, PhD – Clinical Team Leader
Patricia Garvey, RPh – Senior Regulatory Project Manager

OHOP/DIVISION OF HEMATOLOGY, ONCOLOGY, TOXICOLOGY

Brenda Gehrke, PhD – Nonclinical Reviewer

OFFICE OF CLINICAL PHARMACOLOGY/DIVISION OF CLINICAL PHARMACOLOGY V

Gene Williams, PhD – Clinical Pharmacology Team Leader

SPONSOR ATTENDEES

Rajesh C. Shrotriya, MD – Chairman and Chief Executive Officer
Lee F. Allen, MD, PhD – Chief Medical Officer
Gajanan Bhat, PhD – Executive Director, Biostatistics and Data Management
Guru Reddy, PhD – Vice President, Preclinical Research and Development
Anil K. Hiteshi, RAC – Vice President, Global Regulatory Affairs

1.0 BACKGROUND

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcosylsin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent of the bischloroethylamine type that is active against selected human neoplastic diseases.

The innovator product, Alkeran, is currently approved in the United States and marketed by (b) (4) as a single-use vial containing melphalan HCl equivalent to 50mg melphalan and 20 mg povidone together with a diluent vial consisting of sodium citrate, propylene glycol, ethanol, and water for injection. Alkeran for Injection is approved for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

On March 2013, Spectrum Pharmaceuticals acquired development and commercialization rights for Ligand Pharmaceuticals' Melphalan HCl for Injection (b) (4) formulation.

Melphalan HCl for Injection is a new injectable formulation without propylene glycol, (b) (4) Captisol® in the (b) (4) drug product. This new formulation does not need a propylene glycol diluent vial but uses a normal saline diluent. In addition, the Sponsor states that reconstituted Melphalan HCl for Injection (b) (4) is stable at room temperature for at least 4 hours, which increases the use time to 60 minutes for Melphalan HCl for Injection compared to the immediate use of Alkeran.

On January 3, 2014, FDA provided preliminary meeting comments regarding the adequacy of the bridging pharmacokinetic and/or toxicology studies to support the Agency review of a 505(b)(2) NDA for this product.

On April 16, 2014, the Agency met with the Sponsor for a Pre-NDA CMC only meeting to discuss various CMC studies which will be used to support the 505(b)(2) NDA for this product. The purpose of this Pre-NDA meeting is to discuss the format and content of the clinical sections of the 505(b)(2) New Drug Application for the product.

2.0 DISCUSSION

2.1. Clinical

Question 1 Integrated Summary of Safety:

The clinical data from Sponsor-conducted trials come from two studies in patients with MM receiving myeloablative treatment for autologous stem cell transplantation (CDX-353-001; CDX-353-002) and published data with melphalan. The two studies are different in design, treatment allocation and the timing of assessments with the first study involving a cross-over of two drug treatments and the second study involving a single-arm study drug treatment. The safety data from these two studies will be comprehensively summarized individually, but cannot be pooled to provide an integrated summary of safety. Therefore, Spectrum plans to provide a summary of the individual study safety data in the Clinical Summary of Safety in

Module 2.7.4, and not prepare a separate Integrated Summary of Safety (ISS) as part of the CE-Melphalan HCl NDA submission. Does the Agency agree?

FDA Response to Question 1: Yes.

Discussion: There was no discussion required.

Question 2 Integrated Summary of Efficacy:

The clinical study data that serves as the primary basis of efficacy for the CE-Melphalan HCl NDA is available from CDX-353-002, a multicenter, open-label study of high-dose CE-Melphalan HCl for Injection [REDACTED] ^{(b) (4)} in patients with MM undergoing autologous transplantation, and the published data with melphalan. Therefore, Spectrum does not plan to prepare a separate Integrated Summary of Efficacy (ISE) as part of the NDA submission. In addition to the clinical study report for CDX-353-002, Spectrum will provide a summary of the efficacy data in the Clinical Summary of Efficacy in Module 2.7.3 of the NDA submission and reference the published data with melphalan. Does the Agency agree?

FDA Response to Question 2: Yes.

Discussion: There was no discussion required.

Question 3 Published Clinical Trials:

A comprehensive review and summary of clinical trial data with high-dose melphalan that have been published in peer reviewed publications will be submitted in Section 5.3.5.4 and discussed in the Summary of Clinical Safety (Module 2.7.4) in the NDA. Spectrum plans to also include a complete list and copies of the full publications in Literature References (Section 5.4) in the NDA.

Given that generic Melphalan HCl for Injection was not on the market before 9 Jun 2009, it is logical to conclude that Alkeran was the specific drug product used in the clinical studies reported in the two key papers to be referenced in the 505(b)(2) for high-dose melphalan in the treatment of MM patients undergoing stem cell transplantation (Vesole, 1999 and Barlogie, 1999). Does the Agency agree?

FDA Response to Question 3: This is a review issue. It is ultimately your responsibility to verify the source (e.g., USA, Non USA, compounded) and formulation of melphalan products used in your referenced trials if you are planning to propose to bridge their results to CE-Melphalan HCl. We note that the authors of the papers you cite above appear to still be in clinical practice and can be contacted and asked to confirm the source of products used in their respective trials.

Sponsor Response provided in presentation slides: Spectrum acknowledges the Agency's comments and would like to further discuss our strategy for trying to identify the source/type

of products used in the cited papers. We plan to present our strategy at the meeting and are open to discussing additional recommendations from the Agency.

Discussion: FDA stated that it is standard for all 505(b)(2) applications to have the primary source document. FDA recommended that the Sponsor contact the collaborators (i.e. research institution and/or academic institutions) involved with Dr. Barlogie's bridging studies. FDA also recommended that literature review should include pediatric use.

2.2 Operational/Procedural Questions

Question 4 Submission Datasets for Integrated Summaries:

As discussed in Question 1 and Question 2, Spectrum proposes that safety and efficacy data from the two Sponsor-conducted clinical studies (CDX-353-001; CDX-353-002) will be presented individually and not be pooled in an ISS or ISE. Therefore, the Sponsor plans to provide only the individual study datasets and not integrated datasets in the Melphalan NDA submission. Does the Agency agree?

FDA Response to Question 4: Yes.

Discussion: There was no discussion required.

Question 5 Submission Datasets for Individual Studies:

Spectrum proposes to submit SDTM datasets for both Sponsor-conducted clinical studies (CDX-353-001 and CDX-353-002) with corresponding define.xml and define.pdf files. All supporting datasets, such as input data for population PK and ECG analysis, will also be submitted in SAS transport file format (.XPT) in the original data structure along with DEFINE.PDF documentation. Does the Agency agree?*

FDA Response to Question 5: Yes. See additional clinical pharmacology comments below.

Discussion: There was no discussion required.

Question 6 eCTD Table of Contents:

A draft high level eCTD Table of Contents of the proposed 505(b)(2) NDA for CE-Melphalan HCl for Injection [REDACTED]^{(b)(4)} is provided in Appendix 1 of this Briefing Package. Does the Agency have any additional suggestion regarding the proposed organization of the 505(b)(2) NDA submission?

FDA Response to Question 6: Yes. See additional clinical pharmacology comments below.

Discussion: There was no discussion required.

Additional Clinical Pharmacology Comments:

In the appropriate clinical pharmacology sections of the eCTD include the following:

- An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of CE-Melphalan HCl.
- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADRs), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.
- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate.
- Provide a table listing of patients with renal or hepatic impairment, if enrolled, who have received CE-Melphalan HCl, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.
- We encourage you to refer to the Guidance for Industry [Population Pharmacokinetics](#). For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

GENERAL DISCUSSION:

- The Sponsor wanted to discuss the possibility of Breakthrough Therapy Designation for this product. FDA discouraged the submission of a Breakthrough Designation Request.
- FDA also discussed that the Sponsor's supporting information may be based on the label

of the listed drug, published articles, or studies they have conducted. The Sponsor's information cannot rely on the summary basis of approval (SBA).

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

- Spectrum Pharmaceuticals’ presentation slides, which also includes their responses to FDA meeting preliminary comments.

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/s/

ALBERT B DEISSEROTH
06/30/2014



IND 104925

MEETING MINUTES

Spectrum Pharmaceutical Inc.
Attention: Anil Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Melphalan HCl for injection.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2014. The purpose of the meeting was to discuss various CMC studies which will be used to support the 505(b)(2) NDA for Melphalan HCl for Injection [REDACTED] ^{(b)(4)} planned for submission in 2014.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teicher Agosto, Regulatory Project Manager at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance Meeting

Meeting Date and Time: Wednesday, April 16, 2014, 10:00 – 11:00 am EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 104925
Product Name: Melphalan HCl (b) (4)
Indication: High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation for multiple myeloma.
Sponsor/Applicant Name: Spectrum Pharmaceutical Inc.

Meeting Chair: Ali Al Hakim, Branch Chief
Meeting Recorder: Teicher Agosto, Regulatory Project Manager

FDA ATTENDEES

Ali Al Hakim, PhD, Branch Chief, ONDQA
Banu Zolnik, Ph.D., Biopharmaceutics Reviewer, ONDQA
Haleh Saber, Pharmacology/Toxicology Supervisor, OHOP/DHOT
Brenda Gehrke, Pharmacology/Toxicology Reviewer, OHOP/DHOT
Teicher Agosto, PharmD, RPh, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES

Lee F. Allen, MD, PhD, Chief Medical Officer
Pramod K. Gupta, PhD, Vice President, Pharmaceutical Operations
Guru Reddy, PhD, Vice President, Preclinical R&D
Teresa Miller, PhD, Director, Analytical Development, Manufacturing
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs
(b) (4) Spectrum Consultant

1.0 BACKGROUND

Melphalan HCl for injection (b) (4) is intended as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation for patients with multiple myeloma.

Spectrum Pharmaceutical, Inc. submitted a Type C meeting request to the FDA on February 21, 2014. The purpose of this meeting is to discuss various CMC studies which will be used to support the 505(b) (2) NDA for Melphalan HCl for Injection (b) (4) planned for submission in 2014. A Meeting Granted letter was mailed on March 11, 2014 to Spectrum Pharmaceutical Inc. Meeting Briefing Packages was received on March 19, 2014. Meeting comments were sent to Spectrum on April 11, 2014. The sponsor sent additional questions to be discussed during the meeting on April 16, 2014.

2.0 DISCUSSION

Question 1:

The Sponsor plans to provide reference in the NDA to the Drug Master Files (DMFs) from the two Melphalan HCl API suppliers ((b) (4) and (b) (4) . In addition, batch analysis and stability data from both vendors will be compared in the NDA to demonstrate equivalent quality characteristics. The Sponsor believes these data are sufficient to support the Agency's review of the Melphalan HCl 505(b) (2) NDA submission for the qualification of (b) (4) and (b) (4) API suppliers.

Does the Agency agree?

FDA Response to Question 1:

Your approach to qualify the (b) (4) and (b) (4) API suppliers appear reasonable, however, a final determination will be made based on the data submitted in your NDA. Your comparability proposal to perform API batch and characterization analysis is acceptable, provided that the drug substance batches produced at (b) (4) and (b) (4) meet a single drug substance specification as described in the response to question 2. Comparative 3 month accelerated and long term stability data on drug product batches manufactured at (b) (4) (b) (4) using the API from (b) (4) and (b) (4) is also acceptable provided that 36 months of long-term and 6 months of accelerated stability data for 3 batches of DP manufactured at (b) (4) is included in the NDA submission.

Meeting Discussion:

No further discussion required.

Question 2:

Sponsor plans to test and control the quality of API per the USP monograph.

Does the Agency agree?

FDA Response to Question 2:

Testing melphalan following USP monograph does not fully cover all characteristics of API manufactured by different suppliers using different manufacturing process. For example, the USP monograph for melphalan does not include method to test impurities, residual solvents or heavy metals. To fully address the purity aspect of your API, these methods need to be included in drug substance specification. We recommend that you follow ICH Q6A for establishing a specification for melphalan drug substance.

Additional question after receiving the preliminary comments:

Two vendors have been selected to supply CE-Melphalan API, (b) (4) in their manufacturing processes. The Sponsor plans to use a single harmonized set of specifications for API from both vendors, except for the testing of samples for residual solvents, which will be specific to the relevant vendor. Does the Agency agree?

Meeting Discussion:

The Agency agrees with the Sponsor's proposal regarding using a single harmonized set of specifications for API from both vendors (two DMFs), (b) (4) testing of samples for residual solvents, which will be specific to the relevant vendor.

Question 3:

The Sponsor plans to provide detailed chemistry information in the NDA from the two DP manufacturers ((b) (4)) that are typical of Module 3. In addition, manufacturing process and in-process control data for batches from both vendors will be compared in the NDA to demonstrate their equivalent quality characteristics. The Sponsor believes this is sufficient data to support the Agency's review of the Melphalan HCl 505(b) (2) NDA submission for the qualification of (b) (4) DP manufacturing vendors. Does the Agency agree?

FDA Response to Question 3:

Your approach to qualify the two drug product manufacturers appears to be reasonable. Full determination of the acceptability will be a review issue.

Meeting Discussion:

No further discussion required.

Question 4:

The Sponsor believes that the comparability data described under Questions 1 and 3 are adequate to support the Agency's review of the Melphalan HCl 505(b)(2) NDA submission for the interchangeable use of the proposed DS vendors ((b) (4) and (b) (4)) to manufacture commercial product at either DP manufacturing site ((b) (4)).

Does the Agency agree?

FDA Response to Question 4:

Your proposal seems to be reasonable. However, we are not able to provide a definitive response to your question about the interchangeable use of the proposed drug substance manufacturers ((b) (4) and (b) (4) and drug product manufacturers ((b) (4)) without full evaluation of the impurity profiles and stability data for drug substances from the two suppliers and associated drug products manufactured by separate sites. See FDA responses to Questions # 1 and #3.

Meeting Discussion:

No further discussion required.

Question 5:

Sponsor plans to include detailed justification of Captisol content in the 3.2.P.2 Pharmaceutical Development section of the 505(b) (2) NDA. In addition, data will be provided demonstrating that monitoring of the Captisol-melphalan complex is not possible in the finished DP. The Sponsor believes this is sufficient data to support the Agency's review of the Melphalan 505(b) (2)NDA submission for (1) the proposed Captisol content levels in the finished dosage form and (2) rationale for not establishing a test method and acceptance criteria to monitor the Captisol melphalan complex in the finished dosage form.

Does the Agency agree?

FDA Response to Question 5:

We agree with your plan of including a detailed justification of Captisol content in the finished dosage form in the Module 3.2, P.2 Pharmaceutical Development of the 505(b) (2)NDA. Acceptability of your justification will be evaluated and determined during the NDA review process.

Regarding your justification for not establishing a test method and acceptance criteria to monitor the Captisol-melphalan (b) (4) in the finished dosage form (lyophilizate), we agree overall with your explanation and approach from CMC perspective. However, final determination of your proposal will be made during NDA review.

Meeting Discussion:

No further discussion required.

Question 6:

There are three impurities in the DP above the ICH Q3B qualification threshold,

(b) (4)
Because (b) (4) are inactive metabolites and the (b) (4) is structurally related to melphalan, and because the product is intended for use in patients with advanced cancer, Sponsor believes that the qualification of these impurities is not required, as per the ICH S9 guidance.

Does the Agency agree?

FDA Response to Question 6:

We do not agree. For a 505(b) (2) NDA application, impurity levels in the drug product should be below the ICH Q3B qualification threshold or may be at or below the level present in the listed drug in a side-by-side comparison. Degradation products that are also significant metabolites present in animals and/or humans may be considered qualified; however, information on the plasma levels should be provided. This information may be based on the label of the listed drug, published articles, or studies you have conducted; information in the summary basis of approval (SBA) cannot be used for this purpose. References including published articles or data demonstrating that [REDACTED] (b) (4) [REDACTED] are significant metabolites of melphalan need to be submitted in the NDA. A decision on the acceptable levels of the impurities will be made after review of the data.

Additional question after receiving the preliminary comments:

The RLD package insert allows the use of Drug Product in concentrations not to exceed 0.45 mg/ml. Therefore, the Sponsor plans to use the impurity profiles of admixture solutions of RLD over the range of approved concentration. Does the Agency agree?

Meeting Discussion:

The Agency clarified that the amount of the impurities that the patient receives from the new formulation of melphalan (CE-melphalan) needs to be the same or less than the impurities patients receive from the listed drug. The Sponsor clarified that they will compare the admixture of their product to the admixture of the listed drug.

The Agency reminded the Sponsor that any impurities that are above the threshold described in ICH Q3 A/B and not in the listed drug will need to be qualified. The Sponsor stated that while the NDA is a 505 (b)(2) application, there is a clinical study with their product, and the Agency confirmed that the clinical study with CE-melphalan could be used to qualify the impurities at the levels present in the clinical batch.

Additional question after receiving the preliminary comments:

As proposed by the Agency, the recommended specifications for impurity levels for CE-melphalan will be based on levels in RLD. In addition to ICH Q3B and RLD, the Sponsor plans to also reference the impurity limits listed in the EP and BP monographs for melphalan. Does the Agency agree?

Meeting Discussion:

As the Agency could not access the sites, the Agency asked what additional information could be used from the Eu Pharmacopoeia (EP) and British Pharmacopoeia (BP) monographs. The Sponsor stated that they would like to use these monographs to support the impurity specifications since this is public information. The Agency stated that the use of EP and BP will need further internal discussions. The Sponsor could provide the information in the NDA and a decision will be made during the NDA review.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 ATTACHMENTS AND HANDOUTS

There are no handouts

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALI H AL HAKIM
04/22/2014



IND 104925

MEETING PRELIMINARY COMMENTS

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Melphalan HCl for Injection (b)(4)

We also refer to your October 25, 2013, correspondence, received October 28, 2013, requesting a meeting to discuss the adequacy of the bridging pharmacokinetic and/or toxicology studies to support the Agency review of a 505(b)(2) New Drug Application (NDA) for Melphalan HCl for Injection (b)(4)

Our preliminary responses to your meeting questions are enclosed.

You should provide to me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please contact me at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Patricia Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: January 8, 2014, 9:00 AM to 10:00 AM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Room 1309
Silver Spring, MD 20903

Application Number: IND 104925
Product Name: Melphalan HCl for Injection (b) (4)
Indication: For use as a high-dose conditioning treatment prior to autologous hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.
Sponsor/Applicant Name: Spectrum Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 8, 2014, 9:00 AM to 10:00 AM (EST), 10903 New Hampshire Avenue, White Oak Building 22, Silver Spring, MD between Spectrum Pharmaceuticals, Inc. and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional

alkylating agent of the bischloroethylamine type that is active against selected human neoplastic diseases.

The innovator product, Alkeran, is currently approved in the United States and marketed by (b) (4) as a single-use vial containing melphalan HCl equivalent to 50mg melphalan and 20 mg povidone together with a diluent vial consisting of sodium citrate, propylene glycol, ethanol, and water for injection. Alkeran for Injection is approved for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

On May 27, 2009, a pre-IND teleconference was held to discuss between CyDex Pharmaceuticals, a wholly-owned subsidiary of Ligand Pharmaceuticals, to discuss their proposed development plans (preclinical, clinical and CMC) and regulatory strategy for the submission, and approval of Melphalan HCl for Injection (b) (4). On March 2013, Spectrum Pharmaceuticals acquired development and commercialization rights for Ligand Pharmaceuticals' Melphalan HCl for Injection (b) (4) formulation.

Melphalan HCl for Injection is a new injectable formulation without propylene glycol, but with (b) (4) Captisol® in the (b) (4) drug product. This new formulation does not need a propylene glycol diluent vial but uses a normal saline diluent. In addition, the Sponsor states that reconstituted Melphalan HCl for Injection (b) (4) is stable at room temperature for at least 4 hours, which increases the use time to 60 minutes for Melphalan HCl for Injection compared to the immediate use of Alkeran.

On August 13, 2009, following the May 2009 pre-IND teleconference, the FDA issued a advice/information request letter regarding CMC, nonclinical and clinical issues. In the letter, the FDA requested that the Sponsor discuss the requirement for additional bridging nonclinical pharmacokinetics and toxicology studies to adequately demonstrate safety of Melphalan for Injection (b) (4) before the proposed 505(b)(2) NDA submission.

The purpose of this Type C meeting is to discuss the adequacy of the bridging pharmacokinetic and/or toxicology studies to support the Agency review of a 505(b)(2) NDA for Melphalan HCl for Injection (b) (4)

2.0 DISCUSSION

Nonclinical

Question 1: *Based on previous discussion with the Agency and the available pharmacokinetic and safety data from nonclinical and clinical studies on melphalan, the Sponsor believes the completed bridging pharmacokinetic and toxicology studies are adequate to demonstrate safety and efficacy of Melphalan for Injection (b) (4) to support the Agency's review of a 505(b)(2) NDA submission for the proposed indications, i.e., its use as a high-dose (100 mg/m² on 2 consecutive days) conditioning treatment prior to autologous hematopoietic progenitor (stem) cell transplantation for multiple myeloma. Does the FDA agree?*

FDA Response to Question 1:

Clinical Response: No. Your proposal is not sufficient in detail to agree. In addition to your bridging pharmacokinetic and toxicology studies, you must provide published clinical trial data which isolates the effect of high dose (100 mg/m² on 2 consecutive days) IV melphalan as a conditioning treatment prior to autologous hematopoietic progenitor cell transplantation for patients with multiple myeloma. The specific drug product (Alkeran) that was used in your bridging study must also have been used in the published clinical trial data isolating the effect of melphalan as a preparatory agent. Please provide prior to the meeting a list of the published literature you will use to support the proposed indication.

Clinical Pharmacology Response: Your BE study could support the currently labeled indications and doses approved for the listed drug. See also clinical response. Data from published literature will need to adequately describe the formulation used of the reference product. Depending upon the formulation used additional BE studies may be needed to link back to the efficacy and safety data from the published literature.

Pharmacology/toxicology Response: Based on the information provided for the bridging pharmacokinetic study in rats and the clinical trials with your drug formulation, no further nonclinical studies are needed at this time.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-

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2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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/s/

PATRICIA N GARVEY
01/03/2014