CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201848Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201848

COMPLETE RESPONSE

Delcath Systems, Incorporated
Attention: John Purpura
Executive Vice President, Regulatory Affairs and Quality Assurance
810 Seventh Avenue, Suite 3500
New York, NY 10019

Dear Mr. Purpura:

Please refer to your New Drug Application (NDA) dated December 21, 2010, received December 22, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Melblez Kit, [melphalan for injection, 50 mg per vial, and Delcath hepatic delivery system].

We acknowledge receipt of your amendments dated August 15, 2012, August 31, 2012, September 11, 2012 (2), October 1, 2012, October 16, 2012, October 19, 2012, October 23, 2012, November 2, 2012, November 16, 2012, December 3, 2012, December 4, 2012 (2), December 26, 2012, December 31, 2012, January 11, 2013, January 18, 2013, February 6, 2013, February 8, 2013, February 11, 2013, February 15, 2013, March 6, 2013, March 19, 2013, and March 26, 2013.

Your August 15, 2012, submission constituted your response to our February 18, 2011, Refusal-To-File letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Clinical

1. The NDA does not contain data demonstrating substantial evidence of effectiveness for the claimed indications for the clinical trial configuration of the Melblez Kit. Demonstration of substantial evidence of effectiveness requires a conclusion that the benefits of a product outweigh its risks. The Melblez Kit cannot be approved because the results of clinical investigations do show that the product is not safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling since the risks outweigh its benefits [21 CFR 314.125(b)(3)]. Based on the demonstration of a 5.4-month improvement in median hepatic progression-free survival, the 3-month improvement in median overall progression-free survival, and the trend suggesting a detrimental effect on overall survival in Protocol DSI-MEL-2005-001 and the 7%

incidence of toxic death and observed risks of serious cardiovascular, hepatic, gastrointestinal, and bone marrow toxicities in the overall safety experience in 122 patients treated at the proposed recommended dose and route of administration, we have concluded that these risks of Melblez Kit treatments, obtained with an earlier version of the product which you do not intend to market, outweigh its benefits for the proposed indication of treatment of patients with hepatic-dominant metastatic ocular melanoma.

To address this deficiency, you must conduct and provide the results of an adequate and well-controlled clinical trial(s) which demonstrate substantial evidence of effectiveness on an endpoint where the clinical benefits of Melblez Kit outweigh its risks. Given the serious risks of Melblez Kit treatment, we recommend that you perform an adequate and well-controlled randomized trial(s) to establish the safety and efficacy of the Melblez Kit using overall survival as the primary efficacy outcome measure. You should ensure that the trial is designed to ensure applicability of the results from this(these) trial(s) to the United States (US) population. The design, conduct, and results of this trial will determine whether one additional trial will be sufficient to support a marketing approval.

2. The NDA lacks substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126, that the drug product for which you are seeking approval (i.e., the proposed commercial product containing the "to-be-marketed" device configuration) will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(5)]. We have determined that safety and efficacy data obtained with other versions of the device cannot be extrapolated to the combination product which is the subject of this NDA, either directly or through bridging studies. To address this deficiency, you must provide data demonstrating substantial evidence of effectiveness in which these benefits outweigh its risks using the combination product that you intend to market.

Clinical Pharmacology

3. The NDA does not contain sufficient information to characterize the pharmacokinetic profile of melphalan when administered by the dose and route of administration proposed for the Melblez Kit, as required under 21 CFR 314.50 (d)(3) and the investigations required under section 505(b) of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(2)]. Because of the differences in the dose and route of administration for melphalan as proposed in product labeling and as studied in clinical trials of Melblez Kit to that in the approved labeling for melphalan, FDA cannot rely on the prior findings for Alkeran (melphalan hydrochloride) for Injection (NDA 020207), for all aspects of the characterization of pharmacokinetics of melphalan.

To address this deficiency, you must provide data from clinical trials using the combination product that you intend to market. The collection of melphalan pharmacokinetic samples should be sufficient to adequately characterize the systemic

exposure to melphalan and its major metabolites and to characterize the pharmacokinetic profile in special populations in order to meet the requirement to identify any modifications of dose or dose interval needed for specific subgroups, as discussed in 21 CFR 314.50(d)(v).

Product Quality (Melblez Constituent Part)

4. The NDA does not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, as required under 21 CFR 314.125 (b)(2), for testing of extractables, leachables of the Delcath Hepatic Delivery System, melphalan simulated in-use stability, and melphalan interaction (adsorption) with the Delcath Hepatic Delivery System.

   To address this deficiency, you must provide the following:

   a. A complete description of the Gas Chromatography (GC) and High Performance Liquid Chromatography (HPLC) Standard Test Methods used to analyze for extractables of the Melblez Kit.

   b. A method validation summary demonstrating that the analytical methods are suitable for their intended use, as described in ICH Q2(R1) *Validation of Analytical procedures: Test and Methodology (Nov. 2005).* Validation summary(ies) should be submitted for the analytical procedures used in the following studies:

      - Leachables of the Delcath Hepatic Delivery System
      - Melphalan simulated in-use stability in Delcath Hepatic Delivery System
      - Melphalan interaction (adsorption) testing with components of the device

Product Quality (Delcath Hepatic Delivery System Constituent Part)

5. The NDA does not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, as required under 21 CFR 314.125 (b)(2). Specifically, the NDA did not contain a comprehensive toxicological risk assessment of all the leachables from the device components in the proposed commercial product. Instead, the NDA contained study reports demonstrating that twenty target chemicals in a leachable study of the device component of the to-be-marketed product were at or below pre-specified acceptance criteria ([(b) (4)] #1717106, 1717109, 1717110). Although it was not clearly explained, it appears that the acceptance criteria specified in the reports were developed based on the toxicological risk assessment of the clinical trial configuration. Such an approach is not valid to evaluate the potential risks of systemic toxicity from the device components of the commercial product because the changes in manufacturing of the filter components (manufacturer, material source, manufacturing method and process, etc.), which are significant. In study 1715313, new

chemicals that were not previously identified in exhaustive extraction studies of clinical trial configuration of this product were present in the extracts of the commercial configuration. In addition, the leachable chemicals that were previously found at an acceptable level and not included in the targeted list might present at a higher level and be a toxicological concern. To address these deficiencies, you must provide a new toxicological risk assessment of the commercial configuration that includes the following additional information:

a. Determine the leachable profile of the device components in the proposed commercial product in nonpolar solvents (e.g., alcoholic solution) under simulating extraction conditions. The leachable profile in the proposed commercial product was determined only on simulated extraction by saline or purified water (PW). The leachable profile of the device in blood could be significantly different from the profile of the device components in polar solutions (e.g., saline and PW), both qualitatively and quantitatively, since blood contains lipids and proteins and can result in more hydrophobic chemicals leaching out of the device than the polar solvents.

b. Determine and provide justification for the acceptance criteria for the leachable study of the commercial configuration, which should be based on proper toxicological risk assessment of the leachable and extractable profiles of the commercial confiuguration. It is inappropriate to re-estimate the tolerable exposure (TE) for those chemicals for which the LD50 value was used in the TE calculation in the toxicological risk assessment of the clinical trial configuration ((b) (4) N102053).

   The TE for many chemicals in your previous toxicological risk assessment (N102053) was derived from the LD50 value, often with a modifying factor (MF) of 1000 being applied. The LD50 value represents a dose with a very severe endpoint. In your re-evaluation, please follow the recommendations in the ISO 10993-17:2002 standard, e.g., if only acute lethality data are available, a MF greater than 10,000 should be used. The study by Venman and Flaga (1985) indicated that a no observable adverse effect level (NOAEL) value could be conservatively estimated from the LD50 using a conversion factor of 1000. Adding the default values for uncertainty factor (UF) 1 (10) and UF 2 (10), an overall conversion factor of 1×10^5 is reasonable when estimating a TE from the LD50 value.

c. Based on the material chemical characterization study (report 1715313), it appears that only the filter (b) (4) of the Gen 2 cartridge without housing material were tested, despite the change in filter housing material from (b) (4) in the Gen 1 cartridgeto (b) (4) in the Gen 2 cartridge.

   Determine the extractable profile of the housing material to complete the toxicological risk assessment of the Gen 2 cartridge of the commercial configuration. In addition, provide additional information regarding the filter

[redacted], to include the total amount of each detected chemical per device and chemical identification and quantification of all peaks detected by liquid chromatography/mass spectrometry(LC/MS). Report all the chemicals that can be detected and identified in the leachable study and conduct a new toxicological risk assessment of the proposed device in the commercial configuration using principles outlined in the ISO 10993-17:2002 standard.

d. Provide justification for the determination of acceptable limits of certain leachables (e.g., [redacted]) that were beyond the estimated TE based on findings from the simulating leachable study. The justification should discuss the acceptability of the risk of exposure to these leachables under for the proposed indication and intended clinical use of the commercial product.

e. Unless these chemicals could not be detected in the commercial configuration, please expand the list of target chemicals to be verified in the leachable study. We note that certain chemicals (e.g., [redacted] that have been identified to pose significant concern in the toxicological risk assessment ([redacted] N102053) are not listed as the targeted chemicals to be verified in the leachable study.

   Report the level of these chemicals in the simulating leachable study of the device components of this combination product and provide justification of the safety of the proposed levels based on their respective TEs.

f. Provide the total weight and the surface area or volume of the filter media [redacted] per each cartridge and the weight or surface area specifications for components that have blood contact and are the subject for toxicological risk assessment.

With regard to items 6-14, the NDA cannot be approved because there is insufficient information about the product to determine whether it is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(4)].

6. The NDA contains insufficient information on the source of raw materials for the device components of the proposed commercial product, as described under 21 CFR 814.20(b)(4)(ii). In Section 3.2.R.4.3, only the materials of construction are listed for the the device configuration and various device components of the proposed product.

   To address this deficiency, you must include the specific formulation and model numbers for your raw materials, as well as these materials' suppliers.

7. The NDA does not contain information on the [redacted], a component of the GEN2 filter cartridge. To address this deficiency, you must provide a complete description of

this new device component, including [redacted] size and the rationale and justification for the [redacted] size.

8. The NDA contains insufficient information on testing for filter [redacted] particle size. To address this deficiency, you must describe the methodology for determining the particle size distribution of the filter [redacted], including specification of detection limits for the method used in the evaluation and acceptance criteria for the particle size distribution.

9. The NDA contains incomplete information on results of bench testing of the Isofuse Double Balloon Catheter (Section 3.2.R.4.5.2.4). We note that the NDA includes information on some of the aspects of testing of the balloons, such as deflation time, cyclic testing and extended time use and these tests are adequate.

   To address this deficiency, you must provide catastrophic failure data for these balloons (e.g., testing balloon burst points) to establish their failure points.

10. The NDA contains insufficient information to assess the potential risks of the change in the supplier for the 5F Infusion Catheter ([redacted]) from [redacted] to [redacted].

    To address this deficiency, you must specify whether use of this new supplier resulted in changes to the materials of fabrication of this component or to its manufacturing. In addition, depending on the extent of the changes in material of fabrication or manufacturing, you must also provide data characterizing the potential risks of this new component under the proposed indication and intended clinical use.

11. The NDA contains insufficient information to determine the completeness of the risk evaluation of the extracorporeal circuit. As described in the NDA, the Extracorporeal Circuit - Commercial Configuration consists of filter inflow and outflow assemblies, as well as a prime/flush line, a return line with integrated bubble trap with filter, and pressure monitoring lines for connection of the circuit to pressure transducers.

    To address this deficiency, you must confirm that the bench testing described in Table 3.2.R.4.5.2.3-2 included all these components. Please note that all components must be verified and tested, particularly for tensile strength, functionality (e.g., connection to pressure transducers), and pressure/leak endurance. In addition, you must specify how many samples were tested in your Saline Spike to Saline Bag Compatibility Test (DV-B081R, Rev. 0), as this value was not identified in your Table 3.2.R.4.5.2.3-2, and provide justification for the number of samples tested.

12. Additional information is needed to determine the adequacy of the biocompatibility testing to support the proposed commercial product.

    In order to ensure that the results of testing are valid, the following information must be provided:

a. Provide additional biocompatibility testing of the extracts of the filter media from the commercial configuration using the proper extraction ratio and condition to maximize the exposure to the filter media.

The filter media were not separately tested. In addition, the extracts were prepared using the (b) (4) ratio instead of the surface area/volume ratio, which is generally preferred for testing of a device with direct contact with circulating blood. Therefore, it is unclear whether the filter media were adequately represented in the test article. Provide cytotoxicity, sensitization, and hemolysis testing of the filter media alone using an extraction ratio that is appropriately justified when it is compared with the intended clinical exposure. Alternatively, provide adequate justification that such testing is not necessary.

b. Provide an explanation as to how the test article was divided into two test groups in complement activation testing ((b) (4) study 160944). If filter media were not separately tested in this study, conduct C3-a and SC5b-9 complement activation testing of the filter media alone.

c. Identify all the components of the commercial product that were considered part of the circuit and included in the testing.

13. The NDA contains insufficient information on the maximum pre- and post-filter pressure and the rationale for the acceptance criteria. Per the study protocol of studies DV-C034 and DV-C037, the acceptance criterion for in-line pressure differential across filters is specified as "shall not exceed (b) (4) at the clinical flow rate of 500 milliliter/min/filter." Since the actual pressure difference in both the GEN1 and GEN2 filters was considerably smaller than the acceptance criterion of (b) (4) the rationale for this acceptance criterion is unclear and has not been adequately justified. In addition, it appears that a maximally allowable pre-filter pressure has not been specified.

Since higher pressure may cause mechanical hemolysis and may be associated with thrombosis or tubing kink, in addition to the specification on differential pressure across the filters, the maximal pre- and post-filter pressure must be specified and the acceptance criteria must be adequately justified.

14. The NDA does not contained detailed colorant information, such as the chemical identity, for colorants used in the manufacture of device components which are in direct contact with the systemic circulation. Therefore we cannot assess the risks to human subjects from colorants in the commercial product under its intended use and proposed indication. To address this deficiency, you must provide the following information:

a. Chemical name and the Chemical Abstract Services (CAS) number of each key colorant in the formulation.

b. Estimated absolute amount of colorant (in weight) per device.

c. Size range of colorant.

d. Purity level of colorant.

e. Release capability of colorant.

f. Material Safety Data Sheet (MSDS) for each colorant.

g. Identification of other US marketed medical devices by device name, manufacturer, and submission #, where the colorants have been previously used, if known.

h. Toxicity assessment of the colorant or a rationale for why additional toxicity testing for the device containing the colorant is unnecessary.

15. The NDA cannot be approved because the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability [21 CFR 314.125(b)(1)]. The shelf life validation studies you have performed are not sufficient to support your proposed two-year expiration date. This is because you used accelerated aging methods for your test samples, but did not validate or correlate your accelerated aging protocols with real-time, ambient conditions testing. To resolve this deficiency, you must change your device's shelf life to a value based on the real-time, ambient storage testing of your device. Alternatively, you can provide adequate real-time aging validation data for the accelerated aging methods you are using.

Human Factors Study:

The NDA cannot be approved because there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(4)]. Specifically, the NDA does not contain data from an adequate human factors study.

16. The Human Factors engineering summary report indicated that the product design and labeling were modified after completion of clinical studies in order to address six use-related hazards observed. However, there were no data demonstrating that the modifications have adequately addressed all of the hazards and that they did not introduce any new hazards.

    In addition, the use Failure Mode and Effect Analysis showed about 30 use-related hazards, where the risk severity is estimated at a 4 and 5 on a 5-point risk scale, where potential use errors and failures could result in serious patient harm i.e. drug-infused blood leaks into the patient general. However, the NDA did not include data that demonstrate that proposed mitigations have adequately minimized/reduced all of the risks.

To address this deficiency, you must either provide the results of a Human Factors validation study performed with at least 15 representative US users in each of the major user groups or provide evidence that demonstrates the effectiveness of the certification program with representative US users prior to the initiation of additional efficacy trials required to address items 1 and 2 of this letter. The purpose of a human factors validation study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use- related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Please refer to the FDA Guidance: Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, found at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

In addition, please refer to the draft FDA Guidance: Applying Human Factors and Usability Engineering to Optimize Medical Device Design, found at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.
This draft Guidance may be useful in understanding FDA's current thinking and recommended approach to human factors studies.

Additional information regarding human factors studies, including the conduct of a human factors validation study, may be found at:
http://www.medicaldevicehumanfactors.org.
This website offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

17. Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS on December 3, 2012, which contains a (b) (4) elements to assure safe use, implementation system and a timetable for submission of assessments of the REMS.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Melblez Kit, if it is approved for ocular melanoma metastatic to the liver, to ensure that the benefits of the drug outweigh the serious risks of hepatic failure, gastric ulceration or perforation, hemorrhage, and procedural complications.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

Facility inspections

18. During a recent inspection of the Queensbury, New York, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Clinical Pharmacology

19. The NDA did not contain the results for exposure-response analyses exploring the relationships between melphalan systemic exposure and common or serious adverse reactions using either the "clinical trial" version of investigational product or the version of the product, Melblez Kit, for which you are seeking marketing approval in accordance with 21 CFR 314.50 (d)(3) and as described in FDA Guidance for Industry: Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications (April 2003), found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf.

    Please identify your plan for conducting an assessment of the exposure-response relationships between melphalan concentration and adverse drug reactions based on complete pharmacokinetic profile obtained in clinical trials using the version of the product you intend to market. This plan should describe the data to be used, the analysis plan, and the timeline, including key milestones, for submission of this information.

20. Based on the observed toxicity profile obtained with the clinical trial version of the Melblez Kit at the proposed dose of 3 mg/kg IBW, we recommend that additional clinical trials be conducted to explore the potential efficacy of a lower dose of melphalan and of a longer filtration time to reduce systemic exposure following completion of the melphalan

infusion (i.e., filtration for longer than 30 minutes following completion of the melphalan infusion). The goal of such trials would be to investigate whether such modifications to the proposed recommended dose would result in a favorable benefit: risk profile.

Product Quality (Melblez Constituent Part)

21. The HPLC [redacted] (b) (4) analysis data in the report 10T_32509_01 (Delacath System Circuit) indicate that the [redacted] (b) (4) was used to generate the data whereas the description of HPLC conditions for [redacted] (b) (4) indicates that the [redacted] (b) (4) should be used. Please explain this discrepancy.

Product Quality (Delcath Hepatic Delivery System Constituent Part)

22. The NDA did not contain the results of genotoxicity testing of the Gen 2 filter and the new extracorporeal circuit components according to ISO 10993-3:2003 nor did it contain adequate justification that such testing is not necessary based on comparable leachable profiles of the filter and extracorporeal circuit components of the two configurations and negligible concerns with genotoxicity of your device based on a toxicological risk assessment. Since the device components of the Melblez Kit are considered to be an external communicating device with limited contact with circulating blood during each treatment, in accordance with the FDA blue book memo G#95-1, genotoxicity testing of your device is recommended. The genotoxicity testing of device components used in the clinical trial version of this product is not sufficient to address this recommendation because of the different filters used in the clinical trial version (Gen 1) and in the product you intend to market (Gen 2). Since the Gen 1 and 2 filters are manufactured by different manufacturers, a different manufacturing process and source of materials may lead to different leachable profiles of your device, qualitatively and quantitatively.

23. The NDA contains insufficient information to fully characterize the hemocompatibility of the device components in the proposed commercial product. Clinical trial data and non-clinical studies indicate that filtration alters cellular (e.g., hemolysis, leukopenia, thrombocytopenia) and other components (40% decrease in amylase levels and 30% decrease in albumin, cholesterol, and fibrinogen from prescreen through post-filtration) of the blood and also results in hemodynamic instability. The non-clinical studies that evaluated the hemocompatibility of the Gen 2 filter included an invalid control, i.e., the GEN1 filter, and data on all effects, especially those not resulting in specific toxic effects, were not reported.

    a. We recommend that non-clinical studies of adequate design be conducted to evaluate the hemodynamic effects of the device components of your proposed commercial product. In these non-clinical studies, the control should be a sham control, either an FDA cleared, approved predicate, or reference device, or both, and the study should be conducted without administration of melphalan to isolate effects attributable to the device component of the proposed commercial product.

Assessments should be obtained at multiple, different time points, with a specific plan for histopathological examination of major organs, examination of thrombus formation, and close monitoring to characterize cardiovascular adverse event rates.

b. In non-clinical studies, information on a standard panel of hematology and clinical chemistry parameters were collected, however the report contains information on, and analysis of, a subset of these parameters. Since these parameters might characterize the adsorption selectivity of the filter component, this information should be reported and analyzed as part of product characterization.

24. The NDA states that you purchased a sterile extracorporeal circuit that is manufactured, packaged, and sterilized (b) (4). However, it is unclear whether the extracorporeal circuit components included in the proposed commercial product, which have been modified since the completion of the major efficacy trial, are from the same manufacturer and cleared by FDA. To allow FDA to document the supplier of the components in your product to track future supplier change of your device, please specify the manufacturer of the extracorporeal circuit components included in the proposed commercial product. Please clarify whether the modified extracorporeal circuit components have been cleared by FDA and specify the 510(k) number of the submission. If the modified extracorporeal circuit components have not been cleared by FDA or modified since clearance, please remove the reference to (b) (4) and specify which component is not a cleared device.

Labeling

In your resubmission, submit revised draft labeling that addresses the following comments.

General Comments:

25. The prescribing information contains trailing zeros in the following sections: Highlights of Prescribing Information (Dosage and Administration), Full Prescribing Information (Dosage and Administration), Overdosage, Clinical Studies and How Supplied. We recommend deleting the use of the trailing zeros in these areas of the insert because they can lead to ten fold dosing errors when the number is misinterpreted. For example, 3.0 mg/kg may be misinterpreted as 30 mg/kg.

Highlights of Prescribing Information:

26. Dosage and Administration

First Bullet - Insert the word “for” between the established name and “Injection” since the product is a powder for reconstitution and not already in solution.

Full Prescribing Information

27. As discussed in CDER's Manual of Policies and Procedures (MAPP) 5020.1, which describes how CDER will apply the United States Pharmacopeia (USP) *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations* (the USP Salt Policy) to prescription drug products to ensure consistent drug product naming when the USP Salt Policy becomes official on May 1, 2013, the strength of melphalan (hydrochloride), for Injection should be expressed in terms of the active moiety (melphalan base) and the names and strengths of both the active moiety and specific salt forms are to be provided in the labeling."

Dosage Forms and Strengths - Section 3:

28. You must describe any co-packaged diluent, any identifying characteristics of the lyophyilized powder, and the components included the Melblez Kit.

29. In the Description section (Section 11) of the product labeling, present the structural formula as melphalan hydrochloride, as the salt is part of the drug product composition.

Instructions for Use:

30. General Comments:

    a. Spell out the abbreviations "IJV", "IV", "IA", and "IVC" wherever they occur.

    b. Change the abbreviation "cc" to the abbreviation 'mL' wherever it occurs.

Your response must include updated 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.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

Please submit draft carton and container labeling revised as follows:

Carton Labeling – Primary and Secondary Carton Labeling:

31. Move the NDC number to the top third of the carton labeling to comply with 21 CFR 207.35(b)(3)(i).

Hepatic Delivery System Labels and Labeling:

32. [redacted] (b) (4)

33. Remove the [redacted] (b) (4) and provide written statements in their place to convey the information. Some of the [redacted] (b) (4) may not be familiar with the United States market. For example, change the [redacted] (b) (4) to read "Expiration Date".

Other

34. Provide procedural steps to ensure that the person ordering the Melblez Kit understands there are two kits (if adequate clinical data are provided to support the safety and effectiveness of the Melblez Kit containing the 50 mm catheter) and that before placing the order, the person ordering must confirm with the procedural team which Isofuse double balloon catheter spacing (50 mm or 62 mm spacing) product is required for the patient. Include this distinction in the appropriate REMS materials.

35. Provide procedural steps to ensure the Melblez Kit is delivered to the pharmacy to ensure the drug is available and prepared in the pharmacy.

36. As part of your pharmacovigilance program, ensure that all reports of medication errors associated with Melblez Kit and the procedure are submitted to FDA regardless of patient harm. Include product complaints and problems related to ordering, delivery of the Melblez Kits, and product storage.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

37. Describe in detail any significant changes or findings in the safety profile.

38. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

39. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

40. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

41. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

42. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

43. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

44. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This combination product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

RICHARD PAZDUR
09/12/2013