NDA 201848

NDA APPROVAL

Delcath Systems Incorporated
Attention: John Purpura
Chief Operating Officer
1633 Broadway, 22nd Floor
New York, NY 10019

Dear John Purpura:

Please refer to your new drug application (NDA) received August 15, 2012, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for which a Complete Response letter was issued on September 12, 2013. We acknowledge receipt of your amendment dated February 14, 2023, which constituted a complete response to our September 12, 2013, letter.

This NDA provides for the use of the HEPZATO KIT Hepatic Delivery System (HDS) which includes HEPZATO (melphalan) for injection as a component, as a liver-directed treatment of adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling Prescribing

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information and Instructions for Use, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

We acknowledge your August 4, 2023, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for HEPZATO (melphalan) for injection shall be 24 months from the date of manufacture when stored at controlled room temperature 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted between 15°C- 30°C (59°F-86°F) [see USP Controlled Room Temperature].

The expiration date for the packaged product, HEPZATO KIT Hepatic Delivery System (HDS) which includes HEPZATO (melphalan) for injection as a component shall be dependent on the shortest expiration date of any component.

ADVISORY COMMITTEE

Your application for HEPZATO KIT was not referred to an FDA advisory committee because outside expertise was not necessary; the application did not raise significant safety or efficacy issues in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for HEPZATO KIT to ensure the benefits of the drug outweigh the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events.

Your proposed REMS must also include the following: Elements to assure safe use, an implementation system, and a timetable for submission of assessments.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that HEPZATO KIT can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified, the drug be dispensed to patients only in certain health care settings, and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on February 14, 2023, amended and appended to this letter, is approved.

The REMS consists of a elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce HEPZATO KIT into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

Unless otherwise noted, data for the two previous reporting periods, current reporting period, and cumulative reporting periods (where applicable) will be provided for each metric.

Program Implementation and Operations

1. Program Implementation (6-month assessment only)
    a. Date HEPZATO KIT REMS launched
    b. Date of first commercial distribution of HEPZATO KIT
    c. Date the **REMS Website** went live and fully operational
    d. Date the REMS Coordinating Center was established and fully operational
    e. Date healthcare settings were able to complete the REMS certification process (online and by e-mail)
2. REMS Certification and Enrollment Statistics
    a. Healthcare Setting Certification Statistics
        i. List of all certified healthcare settings, location, date of enrollment, method of enrollment (e.g., online, e-mail) and date of certification notification
        ii. Number and percentage of newly certified healthcare settings, and the number and percentage of active healthcare settings (i.e., who have received at least one HEPZATO KIT shipment) stratified by geographic region (as defined by US Census)
        iii. Number of and percentage of newly enrolled Authorized Representatives, and the number and percentage of changed Authorized Representatives stratified by their reported credentials
        iv. Number of Preceptorships and Proctorships completed
        v. Number and percentage of incomplete healthcare setting enrollments out of the total number of healthcare setting enrollments
        vi. Time between certification and first order for HEPZATO KIT for each healthcare setting
    b. Healthcare Setting Certification Status
        i. Number and percentage of healthcare settings that did not maintain their certification to dispense, accompanied by a summary of the reason(s) for decertification

3. Utilization Data
    a. Number of HEPZATO KIT shipments sent to certified healthcare settings
        i. Proportion of HEPZATO KIT(s) shipped to the certified healthcare settings that obtained an order authorization code for distribution out of the total number of HEPZATO KITs distributed
        ii. Proportion of HEPZATO KIT(s) dispensed for each planned procedure that obtained an authorization code to dispense out of the total number of procedures performed and attempted
    b. Number of HEPZATO KIT(s) returned or not used, accompanied by a summary of the reason(s)
    c. An evaluation of dispensing delays which results in an actual treatment delay (defined as a delay in shipment or dispense of ten or more days)
    d. Total number of PHP procedures performed
        i. The mean, median, and range of PHP procedures performed per healthcare setting
4. REMS Compliance
    a. Number of healthcare settings that received HEPZATO KIT that were not certified, number of these healthcare settings that treated a patient with HEPZATO KIT and any corrective actions taken to prevent future occurrences (e.g., provision of **REMS Didactic Modules, Healthcare Setting Enrollment Form**) and the number of these that subsequently became certified
    b. Summary of audit findings from first order audits and annual audits and any action taken and outcome of actions to prevent future occurrences
        i. Type of audit deficiencies
        ii. Number of audits expected
        iii. Number of audits performed
        iv. Number and type of deficiencies noted and resulting Corrective Action Preventative Action (CAPA), to include but not be limited to the number of healthcare settings that did not have documentation of training (completed **Criteria for Procedural Competency Checklist**) for each percutaneous hepatic perfusion team member who performed percutaneous hepatic perfusion procedure(s) with HEPZATO KIT
        v. The existence of documented processes and procedures for complying with the REMS requirements
    c. Any additional noncompliance, source of report, and resulting CAPA

i. Summary report of noncompliance, associated CAPA plans, and the status of CAPA plans, including but not limited to:

a) Copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS

1) For those with deficiencies noted, report the number that successfully completed a CAPA plan within the timeframes specified in the audit plan

2) For any that did not complete the CAPA plan within the timeframe specified in the audit plan, describe actions taken

b) Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1) Unique Identifiers (ID(s)) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

2) Source of the noncompliance data

3) Results of root cause analysis

4) Action(s) that were taken in response

d. Number and percentage of shipments sent to non-certified healthcare settings compared to all shipments, accompanied by the source of the report, actions taken to remove the HEPZATO KIT from the healthcare settings, actions taken to prevent future occurrences and the outcome of such actions

e. Number and percentage of healthcare settings that did not notify the REMS of a change in Authorized Representative

f. Total number and percentage of healthcare settings compared to all active healthcare settings for which noncompliance with the REMS is detected, stratified by the type of non-compliance event

g. The number of certified healthcare settings decertified for noncompliance with the REMS and reasons for such actions

h. Proportion of HEPZATO KIT(s) shipped where an order authorization code to release the shipment for distribution was issued out of the total number of HEPZATO KITs distributed. The order authorization code for distribution includes verification that the healthcare setting meets the REMS requirements to include review of each healthcare setting's certification status and the **Procedure Team Qualification Status Form**

i. Proportion of HEPZATO KIT(s) dispensed where the healthcare setting obtained an authorization code to dispense from the REMS out of the total number of procedures completed and procedures attempted

j. A comparison of the findings to the previous audit findings and an assessment of whether any trends are observed

k. Submit the current noncompliance and audit plans with each assessment

5. REMS Infrastructure and Performance

   a. **REMS Website** Metrics

      i. Number of total visits and unique visits to the **REMS Website**

      ii. Number and type of REMS materials downloaded or accessed

   b. REMS Coordinating Center

      i. Number of contacts by stakeholder credentials (AR, other healthcare provider) and the reason for the call(s) (both inbound and outbound calls)

      ii. Description of each call, including stakeholder credentials, that may indicate an issue with product access due to the REMS, REMS burden or adverse event, accompanied by a summary analysis of any actions taken to address the issue

      iii. Summary of Frequently Asked Questions (FAQs) by stakeholder credentials

      iv. Summary of any noncompliance that is identified through REMS Coordinating Center contacts, source of report and resulting CAPA

      v. Summary of CAPAs resulting from issues identified

Safe Use Behaviors

6. Safe Use

   a. Report of the **Procedure Team Qualification Status Form**

      i. Number and percentage of forms received out of the total number of forms expected

      ii. Number of forms outstanding, accompanied by a summary of due diligence activities to obtain them

      iii. Proportion of **Procedure Team Qualification Status Forms** received by the REMS Coordinating Center compared to the total number of procedures performed

b. Number of **Severe Peri-Procedure-Related Complications Adverse Events Documentation Forms** received; number of reported events of hemorrhage, hepatocellular injury, thromboembolic events, and other severe peri-procedural complication events (by MedDRA PT and summary count for each)

   i. Total number and proportion of reported outcomes to include death, hospitalization, life-threatening, and important medical event out of the total number of reported events stratified by:

      a) Hemorrhage events

      b) Hepatocellular injury events

      c) Thromboembolic events

      d) Other severe peri-procedural complication event (by MedDRA PT and summary count for each)

   ii. Stratify by time of severe peri-procedural complication event compared to the time of procedure:

      a) During the procedure

      b) Post-procedure

         1) Less than 24 hours

         2) 24 to 48 hours

         3) 49 to 72 hours

         4) Greater than 72 hours

c. Number of percutaneous hepatic perfusion (PHP) team member(s) needed to re-train for each healthcare setting due to not performing a procedure with the HEPZATO KIT within the preceding six months or who had not performed two procedures with the HEPZATO KIT annually, and stratify by:

   i. Summary of the reasons for re-training and count for each

   ii. Number involving Didactic Modules

   iii. Number involving Proctorship Training

d. The proportion of procedures where reported cases of severe peri-procedural complications that mention hemorrhage, hepatocellular injury, or thromboembolic events included evidence that the REMS processes and procedures (including training and documentation of competency) were not followed out of the number of procedures with reports of severe peri-procedural complications that include hemorrhage, hepatocellular injury, or thromboembolic events

Health Outcomes and/or Surrogates of Health Outcomes

7. Health Outcomes and/or Surrogates of Health Outcomes

    a. A summary analysis of all reported cases to include a comparison of events both in the United States and outside of United States of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT

        i. For all reported cases in the United States:

            a) Where possible a root cause analysis of whether REMS processes and training were followed

            b) Using quantitative data, a comparison of hemorrhage, hepatocellular injury, and thromboembolic events occurring prior to REMS approval (during clinical trials) and events of interest occurring post REMS approval

                1) If events are more frequently reported post REMS approval, using both quantitative and qualitative data include a summary of possible contributing factors and ways to further mitigate these events in the future, including potential REMS modifications

    b. Proportion of aborted procedures compared to total number of procedures

        i. Number and percentage of procedures aborted due to hemorrhage, hepatocellular injury, thromboembolic events, other severe adverse event, or any other reasons compared to the total number of procedures

Knowledge

8. Knowledge (12 month and annual assessments)

    a. Healthcare Provider Survey

        i. Surveys of certified healthcare setting authorized representatives and percutaneous hepatic perfusion team members (based on data collected on submitted **Procedure Team Qualification Status Forms**) will be conducted to assess their awareness and understanding of the risks of HEPZATO KIT, the HEPZATO KIT REMS requirements and the goals and objectives

            a) Include an evaluation of the PHP procedure teams' experience with the training program and experience with performing the procedure

                1) PHP procedure team member(s) had adequate training to perform the procedure

                2) Any changes PHP procedure team members would propose to improve training.

3) Any changes to the protocol or changes to the training material necessary to improve procedure outcome.

4) PHP procedure team member(s) monitored their patients for 72 hours.

5) Any changes PHP procedure team members would propose to improve training and provide an assessment as to why the peri-procedural complications occurred

b. Report on PHP Procedure Team Focus Group and Authorized Representative Interviews

i. A copy of the PHP procedure team focus group protocol. The focus group should provide an evaluation of their experience with the REMS training program, experiences with the procedure to include outcomes and monitoring, and any unintended REMS burden on the healthcare system or patient access issues

ii. A copy of the Authorized Representative interview questions. The interview questions should be used to provide an evaluation of the training program, REMS processes and procedures, and any unintended REMS burden on the healthcare system or patient access issues

iii. Results and analysis of the focus group and interviews to include, but is not limited to, the REMS training program, experiences with the procedure, REMS processes and procedures and any unintended REMS burden on the healthcare system or potential patient access issues identified

Overall Assessment of REMS Effectiveness

9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

1. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

2. Submit your proposed protocols for the knowledge survey, focus group, and Authorized Representative interview for FDA review within 90 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 201848 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment if you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

1. An evaluation of how the benefit-risk profile will or will not change with the new indication;

2. A determination of the implications of a change in the benefit-risk profile for the current REMS;

3. *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

4. *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

5. *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

6. *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 201848 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 201848/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 201848/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA201848/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 201848/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 201848

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

If you have any questions, call Haroon Vohra, Pharm.D., Senior Regulatory Project Manager, at 240-402-4471.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, M.D.
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling
- REMS

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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