CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212937Orig1s000

OTHER ACTION LETTERS

NDA 212937

COMPLETE RESPONSE

Fennec Pharmaceuticals, Inc.
Attention: Robert McCormack, Ph.D.
Regulatory Affairs Agent
PO Box 13628
68 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated February 10, 2020, received February 10, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PEDMARK (sodium thiosulfate injection).

We acknowledge receipt of your amendment dated May 27, 2021, which constituted a complete response to our August 10, 2020, action 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.

FACILITY INSPECTIONS AND MANUFACTURING PROCESSES

1) During a recent inspection of [redacted] (b) (4) manufacturing facility for this NDA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA can be approved.

2) In your May 27, 2021 amendment, you removed [redacted] (b) (4) previously proposed in the application from 3.2.P.3.4. During review of your amendment, we asked you to confirm if you were proposing no commercial production [redacted] (b) (4), and if so, to revise your master batch records accordingly. You confirmed that there will be [redacted] (b) (4) specified for commercially manufactured drug product and that the commercial master batch record for the drug product has [redacted] (b) (4) listed.

We note that your registration batch records all include (b) (4) [redacted]

(b) (4) [redacted]

CLINICAL

3) There is an increased incidence of Grade 3 – 4 hypophosphatemia (in SIOPEL6 and ACCL0431) and Grade 3 – 4 hyponatremia (in ACCL0431) in patients receiving sodium thiosulfate injection with cisplatin compared to patients receiving cisplatin alone. Your November 3, 2021 response to our information request provided insufficient information to rule out a causal role for sodium thiosulfate injection in these events. Provide an analysis of hypophosphatemia and hyponatremia in your safety database to support your conclusion that these treatment-emergent adverse events are not related to sodium thiosulfate injection to inform our decision-making regarding whether hypophosphatemia and hyponatremia should be described in Section 5 (Warnings and Precautions) of product labeling for sodium thiosulfate injection. Include an assessment of whether patients experienced recurrent hyponatremia or hypophosphatemia with subsequent administration of sodium thiosulfate injection following initial occurrence of one of these events.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, August 24, 2021 which addresses the proposed proprietary name, PEDMARK. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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.

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

b. 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 in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application 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.

c. 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.

d. 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.

e. 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 application data.

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

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

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

OTHER

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 under21 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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference 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 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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

If you have any questions, call Idara Ojofeitimi, Chief, Project Management Staff, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

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/

MARTHA B DONOGHUE
11/26/2021 04:17:40 PM

NDA 212937

COMPLETE RESPONSE

Fennec Pharmaceuticals, Inc.
Attention: Anne McKay
Regulatory Affairs Agent
P.O. Box 13628
68 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. McKay:

Please refer to your new drug application (NDA) dated February 10, 2020, received February 10, 2020, submitted under pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for PEDMARK (sodium thiosulfate injection), for intravenous use, 12.5 grams/100 mL.

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.

PRODUCT QUALITY

1. Test PEDMARK registration batches in accordance to the USP monograph for Sodium Thiosulfate Injection. You may use an alternative test method for assay, however, the USP method will be considered the regulatory method. Refer to USP General Notices and Requirements: 6.30 Alternative and Harmonized Methods and Procedures for more details.

2. Submit a new assay test method, intended for commercial use, that expresses assay in terms of the pentahydrate. Alternatively, you may revise the calculations for the currently proposed non-compendial ion chromatography assay method so that the drug product assay is calculated based on the sodium thiosulfate pentahydrate form.

3. If you plan to use the currently proposed non-compendial assay test method, provide comparative data to show that the method is comparable to the compendial test method. Per the USP monograph, the assay must be calculated based on sodium thiosulfate pentahydrate.

FACILITY INSPECTIONS

4. During a recent inspection of [redacted] (b) (4) anufacturing facility for this NDA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

PRESCRIBING INFORMATION

5. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances. If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

6. Submit draft labeling that incorporates the proposed revisions identified in the attached labeling. In addition, submit 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.

   When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. 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. Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[4]

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

7. Submit draft carton and container labeling revised based on the final determination of product strength.

   a. Change [redacted] (b) (4) to "12.5 grams/100 mL (125 mg/mL)" on both container and carton labeling to be consistent with the USP drug product monograph, where the strength is expressed as that of the pentahydrate. The Agency does not agree with the justification provided in your response dated July 27, 2020 to continue calculating the strength as [redacted] (b) (4) as it does not comply with Section 502(g) of the FD&C Act.

   b. On the container and carton labeling, replace [redacted] (b) (4) with "each mL contains the equivalent of sodium thiosulfate pentahydrate 125 mg (provided as sodium thiosulfate anhydrous 80 mg), 0.25 mg boric acid, NF and water for injection, USP. May contain sodium hydroxide and hydrochloric acid for pH adjustment".

   c. The proposed carton labeling submitted on July 27, 2020 indicates the product is [redacted] (b) (4) Remove the boxed statement that reads [redacted] (b) (4)

PROPRIETARY NAME

Please refer to correspondence dated, April 14, 2020 which addresses the proposed proprietary name, Pedmark. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please submit a new request for name review for your proposed proprietary name when you respond to the application deficiencies.

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.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) 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 in the original submission.

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

- Include tables that compare frequencies of adverse events in the original application 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.

(3) 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.

(4) 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.

(5) 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/supplemental application data.

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

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug/product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314. 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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference 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 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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

If you have any questions, call Anuja Patel, Lead Regulatory Project Manager, at 301-796-9022.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Labeling with FDA proposed revisions

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

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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/

B HARPREET SINGH
08/10/2020 04:20:23 PM