CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210735Orig1s000

OTHER ACTION LETTERS

NDA 210735

COMPLETE RESPONSE

AuroMedics Pharma LLC
Attention: Vincent P. Andolina
Vice President, Regulatory Affairs
279 Princeton-Hightstown Road
East Windsor, NJ 08520

Dear Mr. Andolina:

Please refer to your new drug application (NDA) dated June 28, 2017, received June 28, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Injection, 500 mg/2.5 mL and 1 g/5 mL.

We acknowledge receipt of your amendments dated July 21, 2018, and April 3, 2019, which constituted a complete response to our April 26, 2018, and January 15, 2019, action letters, respectively.

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

During a recent inspection of (b) (4), the drug substance 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. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

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. As you develop your proposed PI, 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, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

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.[3]

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

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised, as attached, based on our proposed revisions.

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

[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

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 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 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 314.110. 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 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 Sherry Hou, PharmD, Regulatory Project Manager, at (240) 402-1813.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Labeling
- Carton/Container Labeling

21 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/

AMNA IBRAHIM
10/01/2019 12:16:07 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210735

COMPLETE RESPONSE

AuroMedics Pharma LLC
Attention: Vincent P. Andolina
Vice President, Regulatory Affairs
279 Princeton-Hightstown Road
East Windsor, NJ 08520

Dear Mr. Andolina:

Please refer to your New Drug Application (NDA) dated July 21, 2018, received July 23, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Solution, 500 mg/2.5 mL and 1 g/5 mL.

We acknowledge receipt of your amendment dated July 30, 2018, July 31, 2018, August 1, 2018, and August 10, 2018, which constituted a complete response to our April 26, 2018, 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.

PRODUCT QUALITY

1. In the resubmission, the presence of visible particles at the 24-month timepoint for the 1 g configuration is reported that you attribute to (b) (4). The observed particles could be present but not detected at release and at earlier stability timepoints due to inadequate inspection procedure. Provide the following information to demonstrate that this issue has been satisfactorily resolved:

   a) Detailed analytical procedures for the proposed and the original inspection methods for visible particulate matter in English. Identify the differences between these two methods and provide evidence to demonstrate that the detection capability of the proposed method is sufficient to detect all the visible particulate matter in the filled vials.

   b) Any non-compliant observations or results from 100% visual inspection of the filled placebo (trial batch FE-17-005) and drug product vials manufactured with (b) (4) (b) (4) should be included. In CAPA-16-015 you indicate tha (b) (4) after filling one Cyclophosphamide Placebo batch. This indicates that there

are quality issues with [redacted]. The rejected vials were found to contain particles [redacted]. Propose your approach to resolve this issue and demonstrate that visible particulate matter will not be an issue for the proposed commercial product.

c) A copy of CAPA-15-006.

d) Results of investigations on stoppers as a possible source of visible particles.

e) Status and results of the corrective and preventive actions you proposed on Page 28 - 30 of the quality event report Req-16-117, req-16-119, req-16-123 in the amendment dated 12/13/2017 (Sequence 0007).

f) Data to demonstrate that visible particles are not observed for the 500 mg configuration. If the results show that 500 mg strength vials do not have visible particulates, provide your rationale for the observation and justification of not manufacturing three registration batches using [redacted]. If visible particulates were observed for the 500 mg configuration, see 2(a) below.

2. Based on the information you provided, we determined that the detection capability of the original inspection method for visible particulate matter is not sufficient to detect all the particulate matter in the stability and batch release samples, which made the release and stability data for visible particulate matter at time 0, 3, 6, 9, 12 and 18 months invalid. Since all three registration batches for the 1 g configuration, 000663, 000664 and 000665, failed the visible particulate matter test, you should:

a. Manufacture three new registration batches for the 1 g strength as well as the 500 mg strength (if visible particulates are not observed, see 1(f) above) with [redacted] which is compatible with the drug product and provide adequate batch release and stability data as recommended in ICH Q1A. Provide the executed batch records and revised master batch records.

b. If stoppers are potential source of visible particles, the registration batches should be manufactured using the new stopper that will not cause particulates in the filled vials (see 2(a) above). If a change to the stopper is proposed and the proposed stopper dimensions do not significantly overlap with or fall within the critical (i.e., at the stopper/vial interface) dimensions of the previously validated stopper, then container-closure integrity validation data should be provided for the proposed container-closure system. A change in the stopper should be supported [redacted] validation information or a Letter or Authorization (LOA) authorizing access to the Agency to review the associated DMF for the [redacted] processes used by the manufacturer of the rubber stoppers.

c. Inspect [redacted] after each batch and provide pictures of the [redacted] filling operation. Note any [redacted] deterioration or leak and take appropriate action (e.g., [redacted] replacement).

3. Revise the quantitative statement of the immediate container and carton labels to include the amount of dehydrated alcohol, as described in Section 11 of the Package Insert.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) 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.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. Upon resubmission of your application, you must submit a revised proposed label that is current with any revisions in the reference listed drug. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling with your resubmission. We reserve comment on the proposed labeling until the application is otherwise adequate.

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 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 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 314.110. 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 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

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 Sherry Hou, PharmD, Regulatory Project Manager, at (240) 402-1813.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/

AMNA IBRAHIM
01/15/2019 03:20:12 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210735

COMPLETE RESPONSE

AuroMedics Pharma LLC
Attention: Vincent P. Andolina
Vice President, Regulatory Affairs
279 Princeton-Hightstown Road
East Windsor, NJ 08520

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Please refer to your New Drug Application (NDA) dated June 28, 2017, received June 28, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Solution, 500 mg/2.5 mL, 1 g/5 mL [redacted (b) (4)].

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.

NONCLINICAL AND PRODUCT QUALITY

The proposed specified levels of Related Compound [redacted (b) (4)] and Related Compound [redacted (b) (4)] exceed the ICH Q3B qualification threshold. The safety of the proposed levels of [redacted (b) (4)] or the proposed combined levels of [redacted (b) (4)] were not adequately justified. We note that the submitted reference [redacted (b) (4)] provided an LD50 after a single intraperitoneal injection of [redacted (b) (4)] with no corresponding line listed data (i.e., hematology, clinical chemistry, histopathology). The published data are inadequate to assess the safety of the specified impurities or to set a permissible daily exposure due to evaluation of a single dose, lack of details about the study design and conduct, lack of data (i.e., standard toxicological endpoints), and a different route of administration. In addition, using a severely toxic dose (i.e., LD_{50}) of [redacted (b) (4)] is inappropriate to determine the safety of the specified impurities.

Provide an adequate justification for the safety of the proposed shelf life specification levels of [redacted (b) (4)] or the proposed combined levels of [redacted (b) (4)].

Submit a final study report from a GLP repeat-dose toxicology study in rodents to qualify the proposed specified levels of [redacted (b) (4)] or the proposed combined levels of

[redacted] (b) (4) in Cyclophosphamide Injection Concentrate at the recommended maximum dose of 25 mg/kg/day (50 mg/kg in divided doses over two days).

PRESCRIBING INFORMATION

6. 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* and *Pregnancy and Lactation Labeling Final Rule* 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

CARTON AND CONTAINER LABELING

7. We reserve comment on the proposed labeling until the application is otherwise adequate. Submit draft carton and container labeling with your resubmission.

SAFETY UPDATE

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{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
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/

AMNA IBRAHIM
04/26/2018