

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212501Orig1s000**

**OTHER ACTION LETTERS**



NDA 212501

**COMPLETE RESPONSE**

Ingenus Pharmaceuticals, LLC  
c/o Ricon Pharma, LLC  
Attention: Mukteeshwar Gande, Chief Scientific Officer  
100 Ford Road, Suite #9  
Denville, NJ 07834

Dear Dr. Gande:

Please refer to your new drug application (NDA) dated September 27, 2018, received September 27, 2018, 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 amendment dated July 24, 2019, which constituted a complete response to our July 18, 2019, action letter.

We also acknowledge receipt of your amendment dated December 26, 2019, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this 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**

During a recent inspection of the [REDACTED] (b) (4) manufacturing facility for this application, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this application may be approved. In response to this deficiency, provide a statement from the facility stating that all issues have been resolved. Do not submit actual inspectional correspondence to this application.

**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<sup>1</sup> and Pregnancy and Lactation Labeling Final Rule<sup>2</sup> 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.<sup>3</sup>

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

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<sup>1</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

<sup>2</sup> <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

<sup>3</sup> <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

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

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, contact Fatima Rizvi, PharmD, Regulatory Project Manager, at (240) 402-7426 or [Fatima.Rizvi@fda.hhs.gov](mailto:Fatima.Rizvi@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Amna Ibrahim, MD  
Deputy Director  
Division of Oncology 1  
Office of Oncologic Diseases  
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.**  
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/s/  
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AMNA IBRAHIM  
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NDA 212501

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Ricon Pharma, LLC  
Agent for Ingenus Pharmaceuticals, LLC  
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Amna Ibrahim, MD  
Deputy Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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AMNA IBRAHIM  
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