

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**216099Orig1s000**

**OTHER ACTION LETTERS**



NDA 216099

**TENTATIVE APPROVAL**

Nanocopoeia, LLC  
Attention: Jennifer Pilate  
Director, Regulatory Affairs  
639 Campus Drive  
New Brighton MN 55112

Dear Ms. Pilate:

Please refer to your new drug application (NDA) dated January 27, 2022, received January 27, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for PHYRAGO (dasatinib) tablets.

We acknowledge receipt of your amendment dated November 22, 2022, which constituted a complete response to our November 17, 2022, action letter.

This NDA proposes the use of PHYRAGO (dasatinib) oral tablets for the treatment of adult patients with

- newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105(a); therefore, it is not approved and will not be approved until FDA issues an approval after any necessary additional review of the NDA. Enclosed are the tentatively approved labeling (text for the Prescribing Information, Patient Package Insert), and submitted labeling (carton and container labeling submitted March 9, 2023). This tentative approval determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

Final approval of your application is subject to expiration of the 30-month period provided for in section 505(c)(3)(C) of the FD&C Act. Therefore, final approval of your application may not be granted at this time.

A listed drug(s) upon which your application relies is subject to a period of patent protection, and your application contains a certification(s) to one or more patents under section 505(b)(2)(A)(iv) of the FD&C Act stating that the patent(s) is/are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("paragraph IV certification").

Section 505(c)(3)(C) of the FD&C Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the FD&C Act that includes a paragraph IV certification shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of a paragraph IV certification. If such a patent infringement action is brought prior to the expiration of 45 days from the later of the date the notice provided under section 505(b)(3) is received by the patent owner or approved application holder, then your application would be subject to a 30-month stay of approval, unless other conditions are met. You notified us that you complied with the requirements of section 505(b)(3) of the FD&C Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patents 7,491,725 and 8,680,103 in the United States District Court for the District of Minnesota (22-cv-01283). With respect to the patent infringement suit, final approval cannot be granted until:

(1)

- expiration of the 30-month period provided for in section 505(c)(3)(C) beginning on the later of the date of receipt by any owner of the listed patent or application holder of the notice required under section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
- the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii), or (iv) of the FD&C Act, or,
- the date the court disposes of the patent litigation as described in 21 CFR 314.107(b)(3)(viii),
- the listed patent(s) has/have expired, and

(2) we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as "**REQUEST FOR FINAL APPROVAL**". This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If

there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

This drug product is not approved and cannot be legally marketed until you have been notified in writing that this NDA is approved. The use of the enclosed tentatively approved labeling is not permitted for marketing this drug product.

### **METHODS VALIDATION**

We expect your continued cooperation to resolve any problems that may be identified.

If you have any questions, call Saumya Nathan, Senior Regulatory Project Manager, at 301-348-1963.

Sincerely,

*{See appended electronic signature page}*

R. Angelo de Claro, MD  
Division Director  
Division of Hematologic Malignancies I  
Office of Oncologic Diseases  
Center for Drug Evaluation and Research

ENCLOSURE(S): (tentatively approved)

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide

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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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ROMEO A DE CLARO  
05/18/2023 12:22:34 PM



NDA 216099

**COMPLETE RESPONSE**

Nanocopoeia, LLC  
Attention: Jennifer Pilate, RAC  
Director, Regulatory Affairs  
639 Campus Drive  
New Brighton, MN 55112

Dear Ms. Pilate:

Please refer to your new drug application (NDA) dated January 27, 2022, received January 27, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Phyrago (dasatinib) oral tablets.

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.

**PRESCRIBING INFORMATION**

- (1) Submit draft labeling that is responsive to our electronic communication dated August 3, 2022.

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>1</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.

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 Prescription Drug Labeling Resources<sup>2</sup> and Pregnancy and Lactation Labeling Final Rule<sup>3</sup> websites, which include:

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

<sup>3</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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.
- Additional resources for the PI, patient labeling, and carton/container labeling.

### **CARTON AND CONTAINER LABELING**

- (2) We reserve comment on the proposed labeling until the application is otherwise adequate.

### **PROPRIETARY NAME**

- (3) Please refer to correspondence dated, October 13, 2022, which addresses the proposed proprietary name, Phyrago. 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.

### **FACILITY INSPECTIONS**

Following inspection of (b) (4) (FEI (b) (4)) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **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 subject 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 Saumya Nathan, Senior Regulatory Project Manager, at 301-348-1963.

Sincerely,

*{See appended electronic signature page}*

R. Angelo de Claro, MD  
Division Director  
Division of Hematologic Malignancies I  
Office of Oncologic Diseases  
Center for Drug Evaluation and Research

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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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ROMEO A DE CLARO  
11/17/2022 11:18:05 AM