

BLA 761136/S-006

**SUPPLEMENT APPROVAL**

Celgene Corporation, a Bristol-Myers Squibb Company  
Attention: Amandeep Riar, PharmD  
Senior Manager, Global Regulatory Strategy and Policy  
86 Morris Avenue  
Summit, NJ 07901

Dear Dr. Riar:

Please refer to your supplemental biologics license application (sBLA), dated and received June 10, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Reblozyl (luspatercept -aamt) injection.

We also refer to our letter dated May 13, 2022, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for Reblozyl (luspatercept-aamt) injection. This information pertains to the risk of extramedullary hematopoietic (EMH) masses in patients with beta thalassemia.

This supplemental biologics license application provides for revisions to the labeling for Reblozyl (luspatercept -aamt) injection. The agreed upon changes to the language included in our May 13, 2022, letter are as follows (additions are noted by underline and deletion are noted by ~~striketrough~~).

Prescribing Information (PI)

2. Dosage and Administration

Table 2: Beta Thalassemia - REBLOZYL Dosing Modifications for Adverse Reactions

	REBLOZYL Dosing Recommendation*
Grade 3 or 4 hypersensitivity reactions	<ul style="list-style-type: none"><li>Discontinue treatment</li></ul>
Other Grade 3 or 4 adverse reactions	<ul style="list-style-type: none"><li>Interrupt treatment</li></ul>

	<p>REBLOZYL</p> <p>Dosing Recommendation*</p>
	<ul style="list-style-type: none"> <li>Restart when the adverse reaction resolves to no more than Grade 1</li> </ul>
<p><u>Extramedullary hematopoietic (EMH) masses causing serious complications</u></p>	<ul style="list-style-type: none"> <li><u>Discontinue treatment</u></li> </ul>

### 5.3 Extramedullary Hematopoiesis Masses

In adult patients with transfusion dependent beta thalassemia, (b) (4) EMH<sup>(b)</sup><sub>(4)</sub> masses were observed in 3.2<sup>(b)</sup><sub>(4)</sub>% (b) (4) of REBLOZYL-treated patients, with (b) (4) spinal cord compression symptoms due to EMH masses occurring (b) (4) in 1.9<sup>(b)</sup><sub>(4)</sub>% (b) (4) of patients (BELIEVE and REBLOZYL long-term follow-up study) (b) (4)

In a study (b) (4) of adult patients with non-transfusion dependent beta-thalassemia, a higher incidence of EMH (b) (4) was observed in 6<sup>(b)</sup><sub>(4)</sub> 3% (b) (4) of REBLOZYL-treated patients vs. 2% (b) (4) of placebo treated patients in the double-blind phase of the study, with spinal cord compression due to EMH masses occurring in 1 patient with a prior history of EMH. REBLOZYL is not indicated for use in patients with non-transfusion dependent beta-thalassemia.

Possible risk factors for the development of EMH masses in patients with beta thalassemia include history of EMH masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin (<8.5 g/dL). Signs and symptoms may vary depending on the anatomical location. Monitor patients with beta thalassemia at initiation and during treatment for symptoms and signs or (b) (4) complications resulting from the EMH masses and treat according to clinical guidelines. (b) (4)

Discontinue treatment with REBLOZYL in case of serious complications due to EMH masses. Avoid use of REBLOZYL in patients requiring treatment to control the growth of EMH masses.

## 6. Adverse Reactions

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thrombosis/Thromboembolism [see Warnings and Precautions (5.1)]
- Hypertension [see Warnings and Precautions (5.2)]
- Extramedullary Hematopoietic Masses [see Warnings and Precautions (5.3)]

### 6.1 Clinical Trials Experience

Clinically relevant adverse reactions in <5% of patients include vertigo/vertigo positional, syncope/presyncope, injection site reactions, hypersensitivity, (b) (4) extramedullary hematopoietic (b) (4) masses, and spinal cord compression.

## 17. Patient Counseling Information

### Extramedullary Hematopoietic Masses

Advise patients with beta thalassemia of the potential risk of extramedullary hematopoietic masses. Review possible risk factors for developing extramedullary hematopoietic masses. Instruct patients to report possible signs and symptoms of EMH masses [see Warnings and Precautions (5.3)].

### Patient Package Insert (PPI)

Before receiving REBLOZYL, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had blood clots  
(b) (4)
- take hormone replacement therapy or birth control pills (oral contraceptives)
- have had your spleen removed (splenectomy)
- smoke
- have or have had high blood pressure (hypertension)
- have a history of extramedullary hematopoietic (EMH) masses
- have or have had enlarged spleen or liver
- are pregnant or plan to become pregnant. REBLOZYL may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with REBLOZYL.

What are the possible side effects of REBLOZYL?

REBLOZYL may cause serious side effects, including:

- Blood clots. Blood clots in the arteries, veins, brain, and lungs have happened in people with beta thalassemia during treatment with REBLOZYL. The risk of blood clots may be higher in people who have had their spleen removed or who take hormone replacement therapy or birth control (oral contraceptives). Call your healthcare provider or get medical help right away if you get any of these symptoms:
  - chest pain
  - trouble breathing or shortness of breath
  - pain in your leg, with or without swelling
  - a cold or pale arm or leg
  - sudden numbness or weakness that are both short-term or continue to happen over a long period of time, especially on one side of the body
  - severe headache or confusion
  - sudden problems with vision, speech, or balance (such as trouble speaking, difficulty walking, or dizziness)
- High blood pressure. REBLOZYL may cause an increase in your blood pressure. Your healthcare provider will check your blood pressure before you receive your REBLOZYL dose. Your healthcare provider may prescribe you medicine to treat high blood pressure or increase the dose of medicine you already take to treat high blood pressure, if you develop high blood pressure during treatment with REBLOZYL.
- Extramedullary Hematopoietic (EMH) Masses. EMH masses have happened in people with beta thalassemia during treatment with REBLOZYL. You may have a higher risk for developing EMH masses if you have a history of EMH masses, have had your spleen removed, have or have had enlarged spleen or liver, or have low hemoglobin levels. Your healthcare provider will monitor you before you start and during treatment with REBLOZYL. Call your healthcare provider or get medical help right away if you get any of these symptoms:
  - severe pain in the back
  - numbness, or weakness or loss of voluntary movement in feet, legs, hands or arms
  - loss of bowel and bladder control

## **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.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling

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

[21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,<sup>1</sup> that is identical to the enclosed labeling (text for the Prescribing Information, and Patient Package Insert) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements.

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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effectuated” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **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*.<sup>3</sup>

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup>

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent

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

<sup>2</sup> 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>.

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

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Caden Brennen, Acting Regulatory Project Manager for Safety, at 301-796-6591 or at [Caden.Brennen@fda.hhs.gov](mailto:Caden.Brennen@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Rosanna Setse, MD, PhD  
Deputy Director for Safety  
Division of Non-malignant Hematology  
Office of Oncology, Hematology, Endocrinology  
and Nephrology  
Center for Drug Evaluation and Research

### ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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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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