November 22, 2022

Dr. Leonard A. Valentino, M.D.
President & Chief Executive Officer
National Hemophilia Foundation
7 Penn Plaza Suite 1204
New York, NY 10001

Sent via email to: jgray@artemispolicygroup.com

Re: Citizen Petition (Docket No. FDA-2022-P-1444)

Dear Dr. Valentino:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA, the Agency, we) by the National Hemophilia Foundation (NHF) (Petitioner) dated July 1, 2022 (the Petition). Petitioner requests that FDA:

1. "Require a REMS [Risk Evaluation and Mitigation Strategy] as a condition of approving valoctocogene roxaparvovec and etranacogene dezaparvovec," and
2. "Include the eligibility (inclusion and exclusion) criteria utilized in the clinical trials on the drug label."[1]

This letter responds to the Petition in part. Specifically, we respond to the requests in the Petition only with respect to etranacogene dezaparvovec.

We have carefully reviewed the Petition, comments to the docket, and other information available to the Agency. Based on our review of these materials, and for the reasons described below, we do not agree that the approval of etranacogene dezaparvovec requires a REMS or that it would be appropriate to include the complete eligibility criteria utilized in the clinical trials in its prescribing information. In accordance with Title 21 Code of Federal Regulations (CFR) 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition in part and will respond to the remainder of the Petition at a later date.

[1] Petition at 2.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. BACKGROUND

CSL Behring submitted a biologics license application (BLA) under section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)) seeking approval of etranacogene dezaparvovec, an adeno-associated virus vector-based gene therapy,[2] for the treatment of adults with hemophilia B. Hemophilia B, also known as Christmas disease, is a genetic bleeding disorder caused by a deficiency in blood. Following a thorough review, FDA approved CSL Behring's BLA for etranacogene dezaparvovec (BLA 125772; HEMGENIX) for the treatment of adults with hemophilia B (congenital Factor IX deficiency) who: currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes, on November 22, 2022.

II. BIOLOGICAL PRODUCTS THAT ARE FDA-LICENSED MEET RELEVANT STATUTORY REQUIREMENTS

A. Approval of a BLA Is Granted Only If the Relevant Statutory Standards Are Met

FDA has a stringent regulatory process for licensing biological products.[3, 4] The PHS Act authorizes FDA to license biological products if, among other things, they have been demonstrated to be "safe, pure, and potent."[5] As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a biological product requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its proposed indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency of a biological product have been demonstrated.

FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[6] Therefore, the manufacturers of biological products that have been licensed in the United States

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[2] Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Gene therapy products meet the definition of "biological product" in section 351(i) of the PHS Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993)). FDA Guidance: Human Gene Therapy for Hemophilia; Guidance for Industry (January 2020), fn. 1 at 1, https://www.fda.gov/media/113799/download.)

[3] See 21 CFR 601.2.

[4] For more information about FDA's approval process for licensing biological products, *see* Biologics License Applications (BLA) Process (CBER) | FDA.

[5] Section 351(a)(2)(C)(i)(I) of the PHS Act.

[6] 21 CFR 601.2(d).

have necessarily demonstrated the safety of the products within the meaning of the applicable statutory and regulatory provisions before the products were licensed and allowed to be marketed.

B. Labeling

The core labeling regulations for approved prescription drug products and biological products promulgated by FDA are located at 21 CFR 201.56 and 21 CFR 201.57. These regulations outline information that must be included in package inserts for human prescription drugs and biological products. In addition to requiring information on indications, usage, dosage and administration, they also describe the requirements for warnings, precautions, contraindications, adverse reactions and drug interactions. The labeling provides health care practitioners with a summary of the essential scientific information that FDA has determined is needed for the safe and effective use of the drug.

C. Risk Evaluation and Mitigation Strategy (REMS)

Section 505-1(a) of the Food, Drug, and Cosmetic Act (FD&C Act) authorizes FDA to require applicants to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.[7] A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of the medication outweigh its risks. Generally, a REMS may include a Medication Guide, a patient package insert, a communication plan, and certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose.[8] FDA may also require a REMS with Elements to Assure Safe Use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[9] ETASU include medical interventions or other actions that healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient, or ETASU may include that the drug is only dispensed to patients with documentation of safe-use conditions, such as laboratory test results. ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience, that patients using the drug be subject to certain monitoring, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions.[10]

[7] 21 U.S.C. § 355-1(a). Please note that the term "drug" includes biological products licensed under section 351 of the PHS Act. BLA holders are subject to REMS requirements. Section 351(a)(2)(D) of the PHS Act.
[8] 21 U.S.C. § 355-1(e).
[9] 21 U.S.C. § 355-1(f)(3).
[10] *Id.*

III. DISCUSSION

A. Petitioner's Request that FDA Require a REMS as a Condition of Approving Etranacogene Dezaparvovec

In this section, we address Petitioner's request that FDA "[r]equire a REMS as a condition of approving…etranacogene dezaparvovec."[11]

In support of its request, Petitioner reviews information about etranacogene dezaparvovec in the context of statutory factors FDA is required to consider[12] in determining whether to impose a REMS, noting among other things the adverse events that may be associated with use of this product as support for requiring a REMS.[13]

We have reviewed the concerns raised and the studies cited by Petitioner, taking into account, among other things, the risks of known or potential adverse events, and do not agree that a REMS is necessary to ensure that the benefits of etranacogene dezaparvovec outweigh its risks. The statutory standard for FDA approval of a biological product is that the biological product is shown to be "safe, pure, and potent"[14] for its labeled indications under its labeled conditions of use. FDA's determination that a biological product is safe, however, does not suggest an absence of risk. A biological product is considered safe, pure, and potent if it has an appropriate benefit-risk balance. For the majority of biological products, routine risk mitigation measures, such as providing healthcare providers with risk information through FDA-approved prescribing information (also referred to as a product's labeling), are sufficient to preserve benefits while minimizing risks.

We believe the labeling for etranacogene dezaparvovec adequately informs prescribers and patients of the risks associated with its use. For example, Petitioner states that "[s]teroid use should be an outcome of interest, given … the high proportion of related adverse events" and "recent events with adeno-associated virus (AAV) therapy including thromboses, requirement for prophylactic anticoagulant treatment, as well as three reports of cancer (deemed unrelated to the vector) highlight the many unknowns."[15] However, in our review of the clinical studies for etranacogene dezaparvovec, we did not observe any significant reports of thrombosis or adverse events related to steroid use. Thus, the approved labeling for etranacogene dezaparvovec[16] does not include thrombosis or adverse events related to steroid use as risks associated with the

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[11] Petition at 2.

[12] Section 505-1(a)(1) of the FD&C Act requires FDA to consider six factors in making a decision about whether to require a REMS, including the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, the seriousness of the disease or condition that is to be treated with the drug, and the estimated size of the population likely to use the drug. All six factors are considered together to inform FDA's REMS decision-making process and no single factor is determinative as to whether a REMS is necessary. The relative importance or weight of each factor is a case-specific inquiry. For more information on how FDA applies the six statutory factors, see FDA Guidance for Industry "REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary," https://www.fda.gov/media/100307/download.

[13] Petition at 2-4.

[14] Section 351(a)(2)(C)(i)(I) of the PHS Act.

[15] Petition at 2.

[16] See www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix.

product. As noted in the Summary Basis for Regulatory Action for etranacogene dezaparvovec[17] there was a report of hepatocellular carcinoma during the clinical trials; however, given other underlying risk factors, such as Hepatitis B, as well as the results of vector integration analyses, the carcinoma could not be definitively attributed to the vector. Nonetheless, the FDA-approved Prescribing Information (PI) specifically discusses the potential risks of hepatocellular carcinoma in the Warnings/Precautions section regulations and alerts prescribers to potential risks associated with the product, including hepatocellular carcinoma and other adverse events observed in clinical trials.[18]

Petitioner also specifies that the requested REMS for etranacogene dezaparvovec should include ETASU such as physician training and education regarding the management of patients who receive a gene therapy product, "[t]raining and education on shared decision making for physicians and HCPs [healthcare providers] who will evaluate, administer, and follow people with hemophilia who are candidates to receive a gene therapy product," and limiting administration of etranacogene desaparvovec to "federally recognized hemophilia treatment center[s] with knowledge and expertise in evaluating, administering and managing people with hemophilia who have received investigational gene therapy products."[19] In doing so, Petitioner emphasizes the seriousness of hemophilia and the fact that, currently, AAV gene therapy can only be administered once. FDA has considered these factors but does not agree that such measures are necessary in order for the benefits of etranacogene dezaparvovec to outweigh its risks. Because the treatment of this condition is generally managed by hematologists who have expertise in treating patients with hemophilia, and because this product will be administered by healthcare providers to patients in hospitals and healthcare centers, such as hemophilia centers, that are familiar with IV infusion-related procedures and monitoring, the types of restrictions requested by Petitioner are not necessary.

For the reasons described above, FDA does not agree that a REMS is necessary to ensure the benefits of etranacogene dezaparvovec outweigh its risks at this time. As with all FDA-regulated products, FDA will continue to carefully monitor the safety of etranacogene dezaparvovec and will take appropriate regulatory action as warranted.

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[17] This letter incorporates by reference FDA's Summary Basis for Regulatory Action (SBRA) for the etranacogene dezaparvovec BLA, see www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix. This memorandum will be posted on www.fda.gov.

[18] Petitioner also cites to an article in the journal *Haemophilia* in support of its arguments regarding adverse events. Based on the abstract for the publication cited in the Petition, the coreHEM outcome set is "a set of outcome measures required to evaluate efficacy, safety, comparative effectiveness and value of gene therapy for haemophilia." Thus, Petitioner is not referencing any specific adverse event but a long list of potential adverse events for gene therapies in general. Iorio A, Skinner MW, Clearfield E, et al.; for the coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia. 2018;00:1–6. https://doi.org/10.1111/hae.13504. FDA does not agree that this list of potential adverse events for gene therapies necessitates the imposition of a REMS for etranacogene dezaparvovec.

[19] Petition at 2.

B. Petitioner's Request that FDA Require the Sponsor of Etranacogene Dezaparvovec to Include the Eligibility (Inclusion and Exclusion) Criteria Utilized in the Clinical Trials in its Labeling

In this section, we address Petitioner's request that FDA "[i]nclude the eligibility (inclusion and exclusion) criteria utilized in the clinical trials on the drug label."[20] We interpret this to be a request that FDA require the sponsor of etranacogene dezaparvovec to include the complete eligibility (inclusion and exclusion) criteria utilized in the clinical trials in the labeling of that product. Petitioner provides no information or data in support of this request.

The CLINICAL STUDIES section of labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively (21 CFR 201.57(c)(15)). This is usually accomplished by providing concise, accurate summaries of information from studies concerning a drug's effectiveness (and sometimes safety) that practitioners consider important to clinical decision making. In the guidance document Clinical Studies Section of Labeling for Prescription Drug and Biological Products — Content and Format (Labeling Guidance), FDA provided recommendations for describing studies in the clinical studies section of labeling.[21] In the Labeling Guidance, FDA explained that the primary objective of the CLINICAL STUDIES section is to summarize (1) the evidence supporting effectiveness in the subjects who were studied, (2) the critical design aspects of the studies, including the populations studied and endpoints measured, and (3) the important limitations of the available evidence.

The prescribing information for etranacogene dezaparvovec includes a description of the study population that is consistent with the Labeling Guidance which states that "the description of the study population should identify those characteristics that are important for understanding how to interpret and apply the study results." For example, the labeling describes the study population in the clinical efficacy study as "adult male subjects aged 19 to 75 years, with severe or moderately severe Hemophilia B."[22] Petitioner has not provided information showing that including the complete eligibility (inclusion and exclusion) criteria utilized in the clinical trials in the drug labeling for etranacogene dezaparvovec would provide meaningful information regarding how to use the drug safely and effectively and, based on our review, FDA is not aware of any reason why its inclusion would do so. FDA therefore denies the request to require the sponsor to include such information in the labeling of that product.[23]

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[20] Petition at 2.

[21] Clinical Studies Section of Labeling for Prescription Drug and Biological Products — Content and Format; Guidance for Industry, January 2006, (Labeling Guidance), https://www.fda.gov/media/72140/download.

[22] See www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix.

[23] While not styled as a request, Petitioner also states that "[i]n order to ensure the optimal outcomes for people who do wish to receive a gene therapy product, FDA should authorize/approve the products use in the same population as studied in the controlled clinical trials precluding off-label use." Petition at 4. FDA has determined that this product is safe and effective for the treatment of adults with hemophilia B (congenital Factor IX deficiency) who: currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. For more information about the relationship between a product's approved indication and the population studied in supporting clinical trials, see FDA Draft Guidance, Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format" (July 2018) (available at https://www.fda.gov/media/114443/download." When final, this will represent the Agency's current thinking on this topic.

IV. CONCLUSION

For the reasons described above, we are denying Petitioner's request to require a REMS as a condition of approving etranacogene dezaparvovec and Petitioner's request that FDA require that the complete eligibility criteria for the clinical trials be included in the labeling for etranacogene dezaparvovec. We will respond to the remaining issues in the Petition at a later date.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff