Our STN: BL 125781/189

SUPPLEMENT APPROVAL
November 14, 2025

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
215 First Street
Cambridge, MA 02142

Dear Patrick O'Malley:

We have approved your request received July 18, 2025, and subsequent amendments, with the final US Prescribing Information (USPI) submitted in amendment 28 dated November 7, 2025, to supplement your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for delandistrogene moxeparvovec-rokl (ELEVIDYS). This supplement was submitted to update the USPI to include new safety information (NSI) on the risk of serious liver injury and acute liver failure including fatal outcomes, following administration of ELEVIDYS, in Boxed Warning; Section 1, Indications and Usage; Section 2 Dosage and Administration; Section 5, Warnings and Precautions; Section 6 Adverse Reactions (6.2 Postmarketing Experience); Section 8 Use in Specific Populations; Section 14 Clinical Studies; Section 17 Patient Counseling Information, of the Prescribing Information and the Medication Guide, in accordance with section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA). The revised Indications and Usage limits the indication to ambulatory patients with Duchenne Muscular Dystrophy (DMD) at least 4 years of age who have a confirmed mutation of the *DMD* gene; use in the non-ambulatory population will no longer be licensed under the BLA.[1]

The review of this supplement was associated with our June 20, 2025, SAFETY LABELING CHANGE NOTIFICATION LETTER, notifying you, under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), of new safety information that we determined should be included in the labeling for delandistrogene moxeparvovec-rokl (ELEVIDYS). This information pertains to the risk of hepatotoxicity including reports of fatal acute liver failure.

Additional labeling changes were made to update Section 5, Warnings and Precautions to include information on the risks of immune mediated myositis, myocarditis, and

[1] During the iterative review process between FDA and Sarepta regarding drafts of the revised labeling, there were some questions about the revisions to the Indications and Usage section. FDA's responses to Sarepta explained that in removing the non-ambulatory population from the Indications and Usage section of the labeling, use in the non-ambulatory population will no longer be licensed under the BLA.

serious infections; Section 4, Contraindications; Experience Section 11 Description; and Section 12 Clinical Pharmacology.

LABELING

We hereby approve the draft content of labeling Package Insert submitted under amendment 28, dated November 7, 2025, and Medication Guide submitted under amendment 30, dated November 12, 2025.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on November 7, 2025, and the Medication Guide submitted on November 12, 2025. 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* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125781 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71–G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other

products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

For each pending supplemental application for this BLA that includes proposed revised labeling, please submit an amendment to update the proposed revised labeling with the changes approved today.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

Since delandistrogene moxeparvovec-rokl (ELEVIDYS) was approved in 2023, we have become aware of new safety information on the risk of serious liver injury and acute liver failure including fatal outcomes, following administration of ELEVIDYS (delandistrogene moxeparvovec-rokl). Fatal reports of acute liver failure in non-ambulatory pediatric patients with Duchenne Muscular Dystrophy were received from clinical trial and postmarketing data. Therefore, we consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of hepatotoxicity, including serious liver injury and acute liver failure.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

1. Study titled, “A Long-term Multicenter Prospective Observational Study Evaluating the Comparative Effectiveness and Safety of Sarepta Gene Transfer Therapy vs. Standard of Care in Participants with Duchenne Muscular Dystrophy under Conditions of Routine Clinical Practice – Safety PMR Cohort” to assess serious liver injury and acute liver failure. This study will enroll at least 200 patients with DMD who received treatment with delandistrogene moxeparvovec. The enrolled patients will be followed for at least 12 months after product administration. The study design will include monitoring (at pre-specified intervals) for hepatotoxicity with adequate testing strategies.

We acknowledge the timetable you submitted on November 12, 2025, which states that you will conduct this study, according to the following schedule:

Final Protocol Submission: February 28, 2026

Study Completion Date: October 31, 2029

Final Report Submission: April 30, 2030

Please submit the protocol to your IND 17763, with a cross-reference letter to BLA STN BL 125781 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to BLA STN BL 125781. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of the approval of BLA STN BL 125781 until all requirements and commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

We will include information contained in the above-referenced supplement in your BLA files.

Sincerely,

Asha Das, MD
Acting Director
Division of Clinical Evaluation General Medicine
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Enclosures: Labeling, Medication Guide