



NDA 213535

**NDA APPROVAL**

Genentech, Inc.  
Attention: Huy Nguyen  
Senior Regulatory Program Director  
1 DNA Way, Mail Stop: 45-N-1  
South San Francisco, CA 94080

Dear Mr. Nguyen:

Please refer to your new drug application (NDA) dated and received September 24, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Evrysdi (risdiplam) for oral solution.

We acknowledge receipt of your major amendment dated February 28, 2020, which extended the goal date by three months.

This new drug application provides for the use of Evrysdi (risdiplam) for oral solution for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

### **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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at [FDA.gov](http://FDA.gov).<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. 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.

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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>.

## **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on July 14, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 213535.**” Approval of this submission by FDA is not required before the labeling is used.

## **EXPIRATION DATING PERIOD**

The expiration dating period for Evrysdi is 24 months from the date of manufacture when stored at 20°C – 25°C [USP controlled room temperature].

## **RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER**

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 213535. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this

letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - The estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - The estimated demand in the U.S. for the product, and
  - The actual amount of product distributed in the U.S.
- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.<sup>3</sup>

### **ADVISORY COMMITTEE**

Your application for Evrysdi was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the 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.

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<sup>3</sup> <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs>

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of carcinogenicity resulting from the use of Evrysdi or adverse maternal, fetal, and infant outcomes resulting from exposure to Evrysdi during pregnancy.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3886-1        A 2-year carcinogenicity study in rat.

The timetable you submitted on June 26, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 08/2020  
Final Protocol Submission: 12/2020  
Study Completion:            12/2022  
Final Report Submission: 08/2023

3886-2        Establish a single-arm pregnancy safety study to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes for exposed pregnancies, including women exposed to Evrysdi (risdiplam) during pregnancy or one month prior to the start of pregnancy. Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures, measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis.

The timetable you submitted on June 26, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	10/2021
Annual Interim Report Submissions:	10/2022
	10/2023
	10/2024
	10/2025
	10/2026
	10/2027
	10/2028
	10/2029
	10/2030
	10/2031
Study Completion:	10/2031

Final Report Submission: 10/2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>4</sup>

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of QTc prolongation or of toxicity in patients with hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3886-3 A trial to characterize the risk of QTc prolongation associated with the oral administration of risdiplam.

The timetable you submitted on June 26, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Trial Completion:	06/2022
Final Report Submission:	06/2023

3886-4 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of risdiplam to minimize toxicity in patients with different degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling”.

The timetable you submitted on June 26, 2020, states that you will conduct this trial according to the following schedule:

Trial Completion:	Completed
Final Report Submission:	12/2020

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>5</sup>

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<sup>4</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>5</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Submit clinical protocol(s) to your IND 128972 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 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 submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **REQUESTED PHARMACOVIGILANCE**

We request that you perform postmarketing surveillance for oral mucosal ulceration or other non-herpetic oral lesions, including chelitis, and for serious adverse events in the skin, including alopecia, rash, skin erosion, and exfoliation after exposure to Evrysdi. Include analyses of individual events as well as comprehensive summaries and analyses of these events, including incidence, quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Include analyses of the events by age. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with extent of exposure to Evrysdi and most recent exposure to Evrysdi, concomitant therapies, treatment given for the event, and outcome.

## **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>6</sup>

As required under 21 CFR 314.81(b)(3)(i), 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>7</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>8</sup>

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.<sup>9</sup>

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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<sup>6</sup> For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

<sup>7</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>8</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>9</sup> <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>



If you have any questions, contact Brenda Reggett, PharmD, Regulatory Health Project Manager, by email at [Brenda.Reggett@fda.hhs.gov](mailto:Brenda.Reggett@fda.hhs.gov) or by phone at (240) 402-6220.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, MD  
Director (Acting)  
Office of Neuroscience  
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Constitution
  - Instructions for Use



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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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