

NDA 217865

NDA APPROVAL

Italfarmaco S.p.A.
US Agent: Freyr Inc.
Attention: Chandrika Lucki
150 College Road West
Suite 102
Princeton, NJ 08540

Dear Chandrika Lucki:

Please refer to your new drug application (NDA) dated April 21, 2023, received April 21, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Duvyzat (givinostat) oral suspension.

We acknowledge receipt of your major amendments dated November 15, 2023 (SN0033), November 16, 2023 (SN0034), and November 17, 2023 (SN0035), which extended the goal date by three months.

This NDA provides for the use of Duvyzat (givinostat) oral suspension for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years 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.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) 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*.²

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

² 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>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on March 19, 2024, 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 *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 217865.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Duvyzat (givinostat) oral suspension shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

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 217865. All correspondences related to this voucher should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351(a) 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 PRV must notify FDA of its intent to submit an application with a PRV 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 PRV 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 PRV may be transferred, but each person to whom the PRV 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 PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV 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 PRV was transferred.

- FDA may revoke the PRV if the rare pediatric disease product for which the PRV 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 PRV 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.³

ADVISORY COMMITTEE

Your application for Duvyzat was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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.

³ <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 assess a known serious risk of thrombocytopenia, assess a signal of serious risk of bleeding, or identify an unexpected serious risk of carcinogenicity after exposure to givinostat.

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:

4575-1 Conduct a carcinogenicity study of givinostat in mouse.

The timetable you submitted on February 16, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2022 (submitted)

Study Completion: 12/2024

Final Report Submission: 12/2025

4575-2 Conduct a 2-year carcinogenicity study of givinostat in rat.

The timetable you submitted on February 16, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2022 (submitted)

Study Completion: 12/2024

Final Report Submission: 12/2025

4575-3 Conduct a prospective observational registry for a minimum of 5 years to characterize the incidence, frequency, and severity of thrombocytopenia and incidence, frequency, and severity of serious events of bleeding in patients with Duchenne muscular dystrophy exposed to givinostat. For each case of thrombocytopenia and severe bleeding identified, provide detailed case narratives that include, but are not limited to, information on concomitant medications, complete blood count results at baseline, and during and after the event, and disposition (e.g., was the givinostat dose

reduced in response to the event, discontinued temporarily or permanently, and outcomes if the dose was reduced).

The timetable you submitted on March 12, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 09/2024
Final Protocol Submission: 07/2025
Study Completion: 09/2031
Final Report Submission: 03/2032

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.⁴

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks resulting from altered pharmacokinetics of givinostat due to hepatic impairment.

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

- 4575-4 Conduct a clinical trial to evaluate the effect of hepatic impairment on the exposure of givinostat relative to that in subjects with normal hepatic function after oral administration. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (<https://www.fda.gov/media/71311/download>).

The timetable you submitted on February 20, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 07/2024
Final Protocol Submission: 12/2024
Trial Completion: 06/2025
Final Report Submission: 12/2025

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.⁵

⁴ 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>.

⁵ 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 126598 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.

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(a)(1) 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(a)(1) 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 4575-5 Perform experimental activities to evaluate if the drug product matrix can be suppressed (e.g., drug product dilutions or interfering matrix precipitation/liquid extraction with recovery evaluation).

The timetable you submitted on January 16, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2024

4575-6 **If matrix interference can be suppressed:** Test the three drug product submission batches at their 36 months stability endpoint at 25°C/60%RH.

In addition, to assess any trending, test the first three postapproval batches at multiple time points - from release through the end of proposed shelflife. [Results from the postapproval batches will be submitted in the NDA annual reports.]

The timetable you submitted on January 16, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 07/2024

Final Report Submission: 12/2024

4575-7 **If matrix interference cannot be suppressed:** Update regarding the ongoing leachable study with simulant solvent and provide an overall risk assessment to evaluate if there is any significant risk associated to presence of leachables in the drug product.

The timetable you submitted on January 16, 2024, states that you will conduct this study according to the following schedule:

Interim Report Submission: 12/2024

Final Report Submission: 12/2025

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 126598 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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*.⁶

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.⁷ Information and Instructions for completing the form can be found at FDA.gov.⁸

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

- 1) We request that for Duvyzat you submit all serious cases of bleeding as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)).
- 2) We request that you provide a narrative summary including analyses of serious events of bleeding, thrombocytopenia, and other hematologic abnormalities in a report submitted to your NDA as a “Clinical/Clinical Information” submission on a quarterly basis for 5 years following initial U.S. approval date.

Your analyses should include interval and cumulative data relative to the date of approval of Duvyzat. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, information regarding dose adjustment in response to the event, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

REPORTING REQUIREMENTS

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

⁶ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

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

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website⁹.

If you have any questions, contact Annie Nguyen, Regulatory Project Manager at Anhthu.Nguyen@fda.hhs.gov or at (240) 402-4460.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
 - Instructions for Use

⁹ <https://www.uspnf.com/>

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.

/s/

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