NDA 218808
NDA 218820

NDA APPROVAL

Neurocrine Biosciences, Inc.
Attention: Kristine Kim
Executive Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Kristine Kim:

Please refer to your new drug applications (NDAs) dated and received April 29, 2024, and April 30, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Crenessity (crinecerfont) oral capsules and oral solution, respectively.

These NDAs provide for the use of Crenessity (crinecerfont) oral capsules and oral solution as adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH).

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are 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, 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

[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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on December 12, 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 218808 and NDA 218820**." 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 Crenessity (crinecerfont) oral capsules shall be 15 months from the date of manufacture when stored at 15°C to 25°C in the commercial packaging. The expiry period for Crenessity (crinecerfont) oral solution shall be 18 months from the date of manufacture when stored under refrigeration at 2°C - 8°C (36°F to 46°F). Once the oral solution bottle is opened for use, it may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature (15°C to 25°C [59°F to 77°F]) for up to 30 days.

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 218808. 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 applications for Crenessity (crinecerfont) oral capsules and oral solution were 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.

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

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.

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 an unexpected serious risk of infant exposure to Crenessity during lactation.

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 this serious risk.

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

4738-1 Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received Crenessity to measure concentrations of crinecerfont and its major metabolites in breast milk using a validated assay and to assess the effects on the breastfed infant, if a mother-infant pair study is conducted.

The timetable you submitted on December 11, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2025
Final Protocol Submission: 12/2025
Study Completion: 12/2027
Final Report Submission: 06/2028

We have also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of inhibition of adrenocorticotropin hormone (ACTH) secretion in the developing fetus, which may lead to growth restriction, preterm delivery, or demise.

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 study:

4738-2 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Crenessity during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The study should also collect adverse event data for lactating women and infants exposed to Crenessity through breastfeeding to assess for any potential risks to the infant from breastfeeding. The minimum number of patients will be specified in the protocol

The timetable you submitted on December 11, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2025
Final Protocol Submission:	12/2025
Interim Study Report:	11/2030
Study Completion:	12/2035
Final Report Submission:	06/2036

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]

Submit clinical protocols to your IND 132849 with a cross-reference letter to NDAs 218808 and 218820. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDAs. 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.

[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.

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.

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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

1. We request that for Crenessity (crinecerfont) you submit all serious and non-serious domestic and/or foreign cases of neutropenia as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the 5th year following initial U.S. approval. We also request that for Crenessity (crinecerfont) you provide a

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

narrative summary including analyses of events of neutropenia as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)), through the 5th year following initial U.S. approval . You should, at a minimum, use the following MedDRA terms to retrieve reports:

High Level Term (HLT) Neutropenias

Your analyses should include interval and cumulative data relative to the date of approval of Crenessity (crinecerfont). Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, laboratory values (e.g., neutrophil count), confounders, underlying risk factors, treatment given for the event, outcome, and drug disposition, in addition to analyses of any serious and/or opportunistic infections associated with neutropenia within these reports.

2. We request that for Crenessity (crinecerfont) you submit all serious and non-serious domestic and/or foreign cases of suicidal behavior and/or ideation as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)) through the 5th year following initial U.S. approval. We also request that for Crenessity (crinecerfont) you provide a narrative summary including analyses of suicidal behavior and/or ideation as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)), through the 5th year following initial U.S. approval. You should, at a minimum, use the following MedDRA terms to retrieve reports:

   Preferred Terms (PTs) Completed suicide, Suicide attempt, Suicidal behaviour, Suicidal ideation

   Your analyses should include interval and cumulative data relative to the date of approval of Crenessity (crinecerfont). Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors (e.g., psychiatric history), treatment given for the event, outcome, and drug disposition.

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 website[8].

If you have any questions, contact Dana Smith, Regulatory Project Manager, at 240-402-9906.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

[8] 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/

HYLTON V JOFFE
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