CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213436Orig1s000

Trade Name:	Trudhesa nasal spray
Generic or Proper Name:	*dihydroergotamine mesylate*
Sponsor:	Impel NeuroPharma Inc.
Approval Date:	September 2, 2021
Indication:	TRUDHESA is an ergotamine derivative indicated for the acute treatment of migraine with or without aura in adults. Limitations of Use: TRUDHESA is not indicated for the preventive treatment of migraine or for the management of hemiplegic or basilar migraine.

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APPROVAL LETTER

NDA 213436

NDA APPROVAL

Impel NeuroPharma Inc.
Attention: Lynn Gold, PhD
Senior Vice President, Regulatory Affairs
201 Elliott Avenue West, Suite 260
Seattle, WA 98119

Dear Dr. Gold:

Please refer to your new drug application (NDA) dated and received November 6, 2020, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trudhesa (dihydroergotamine mesylate) nasal spray.

This NDA provides for the use of Trudhesa (dihydroergotamine mesylate) nasal spray for the acute treatment of migraine with or without aura in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended, and 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, Medication Guide, 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 carton labeling submitted on August 9, 2021, and container label submitted on August 31, 2021, 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 213436."** 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 Trudhesa (dihydroergotamine mesylate) nasal spray shall be 12 months from the date of manufacture when stored at 20°C to 25°C. The expiration date for the packaged product, Trudhesa (dihydroergotamine mesylate) nasal spray plus the nasal spray device shall be dependent on the shortest expiration date of any component.

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.

We are waiving the pediatric study requirement for children under 6 years of age because necessary studies are impossible or highly impracticable. This is because very few children of this age can be definitively diagnosed with migraine.

We are deferring submission of your pediatric studies for children and adolescents 6 to less than 18 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4136-1 A juvenile animal toxicology study of dihydroergotamine mesylate in rat.

Study Completion:	03/2022
Final Report Submission:	06/2022

4136-2 An open-label, pharmacokinetic study under PREA of Trudhesa in pediatric migraine patients 6 to less than 12 years of age to select dose(s) to be used in the efficacy portion of the study.

Study Completion:	12/2022
Final Report Submission:	12/2024

4136-3 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA to evauluate Trudhesa for the acute treatment of migraine in children 6 to less than 18 years of age. This study should include an initial blinded placebo run-in period to identify placebo-nonresponders for enrollment into the efficacy portion of the study. The efficacy study must be designed to show superiority of Trudhesa over placebo and is to be submitted as a special protocol assessment (SPA).

Final Protocol Submission:	02/2022
Study Completion:	07/2024
Final Report Submission:	12/2024

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.[3]

Submit the protocols to your IND 130133, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] 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.

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.*[4]

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

REPORTING REQUIREMENTS

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[7]

If you have any questions, call Daniel Ngembus, Regulatory Project Manager at (301) 837-7345.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Director
Division of Neurology 2
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

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

ENCLOSURES:

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

NICHOLAS A KOZAUER
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