CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213436Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 213436
Review 1

Drug Product Name	TRUDHESA (dihydroergotamine mesylate)
Dosage Form	Nasal spray
Strength	(b)(4) mg/mL, 0.725 mg/spray
Route of Administration	Intranasal
Rx/OTC Dispensed	Rx
Applicant	Impel NeuroPharma
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Zhixing Shan	Donna Christner
Drug Product	Andrei Ponta	Julia Pinto
Manufacturing	Frank Wackes	Joanne Wang
Microbiology	Hemlata Tamta	Denise Miller
Biopharmaceutics	N/A	
Device Engineering	Michaela Schulman (CDRH)	Courtney Evans (CDRH)
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	
Environmental	N/A	

Submission(s)	Document Date	Discipline(s) Affected
SD-001, Original NDA	11/6/2020	All
SD-003, Response to information request (IR)	12/22/2020	Manufacturing
SD-004, Response to IR	1/4/2021	Microbiology
SD-005, Response to IR	2/1/2021	Manufacturing
SD-007, Labeling	2/9/2021	Drug Product

SD-010, Response to IR	2/16/2021	Drug Product
SD-012, Response to IR	3/9/2021	Device/CDRH
SD-014, Response to IR	4/12/2021	Device/CDRH
SD-015, Response to IR	4/20/2021	Drug Product
SD-017, Response to IR	4/26/2021	Device/CDRH
SD-019, Response to IR	6/7/2021	Drug Product
SD-021, Response to IR	7/2/2021	Drug Product

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	4/6/2018	Reviewer: W. Dai
	III			N/A [1]	--	--
	III			N/A	--	--
	III			N/A	--	--
	III			N/A	--	--
	III			N/A	--	--
	III			N/A	--	--
	III			N/A	--	--
	III			N/A	--	--
	III			N/A	--	--
	IV			N/A	--	--

[1] Not applicable. Adequate information was provided in the application; thus, the DMF was not reviewed.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	130133	Development of Impel's DHE POD nasal spray product
NDA	5929	D.H.E 45 injection NDA referenced under 505(b)(2) to support safety and efficacy of dihydroergotamine
NDA	20148	Migranal NDA referenced under 505(b)(2) to support safety and efficacy of dihydroergotamine

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2. CONSULTS

Discipline	Recommendation	Date	Assessor
Nonclinical	Per email from nonclinical reviewer, proposed acceptance criterion of ≤ (b) (4)% for the principal degradant, (b) (4) was not qualified in adequate nonclinical studies.	6/21/2021	Edmund Nesti
CDRH-Office of Product Evaluation and Quality (OPEQ)	Device aspects, including device performance, biocompatibility (non-drug contact components only), and quality systems are acceptable. No device related facility inspections were recommended. Allowable shelf life for the device constituent is (b) (4) months. Shelf life for the combination product will be limited to the shorter of the device and drug component shelf lives.	4/26/2021	Michaela Schulman

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 213436 for TRUDHESA (dihydroergotamine mesylate) nasal spray is recommended for **APPROVAL**. From a quality perspective, the application, as amended, provides adequate information to ensure that the Applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Dihydroergotamine mesylate (DHE) was initially developed by Sandoz Pharmaceuticals (later part of Novartis International) for treatment of migraine. The active moiety, dihydroergotamine is a semi-synthetic derivative of the ergot alkaloid ergotamine. Sandoz developed two products, D.H.E. 45® (DHE) injection, which was approved in 1946 (NDA 5929), and Migranal® (DHE) nasal spray (NS), which was approved in 1997 (NDA 20148).

The Applicant is seeking approval under 505(b)(2) for an alternative DHE NS that incorporates the firm's "Precision Olfactory Delivery" (POD) technology. The product formulations for Migranal and TRUDHESA are stated to be identical and the Applicant states that the drug component is manufactured by the same contract manufacturer, Mipharm S.pA., that manufactures the Migranal formulation. Unlike Migranal, which is administered using a conventional (b) (4), the TRUDHESA product uses a hydrofluoroalkane-134a (HFA) pressurized, disposable actuator. The Applicant indicates that administration of DHE with their product is independent of head position, coordinated sniffing, or breathing cycle, as HFA propels the DHE drug product solution in a thin, targeted plume to pass through the nasal valves onto the absorptive mucosa of the upper nasal space (olfactory region), resulting in more consistent deposition and hence uptake into the systemic circulation relative to standard nasal pumps Dosing for the two products is also different, with Migranal administered as four 0.5 mg/0.125 mL sprays (2 mg total) versus two 0.725 mg/0.181 mL sprays (1.45 mg total) for the POD-DHE product.

Based on an initial risk assessment, the product was considered low risk for all critical quality attributes (CQAs) except extractables/leachables, which were considered moderate risk.

Proposed indication(s) including intended patient population	Acute treatment of migraine headaches with or without aura in adults
Duration of treatment	Chronic intermittent
Maximum daily dose	2.9 mg/day (two doses)
Alternative methods of administration	None

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B. Quality Assessment Overview

Note: The Applicant has used different terminology during development, which may be reflected in individual discipline reviews. The various terms used are summarized in the table below.

Term	Definition / Description
DHE	Dihydroergotamine mesylate (drug substance/active pharmaceutical ingredient)
DHE Solution or DHE Nasal Spray solution	Refers to the DHE drug formulation; it does not include reference to a specific container closure (i.e., vial).
DHE DP	Dihydroergotamine mesylate drug product. Refers to the DHE formulation/solution in the primary container closure (i.e., vial with stopper and crimp seal). It is the "drug constituent" of the INP104 product.
I123 POD device, also referred to as the reservoir device	Refers to the finished and assembled POD® device specific to the DHE program. The I123 POD device product includes the HFA canister. It is the "device constituent" of INP104 product
INP104, INP104 Product, or POD-DHE	Refer to the assembled INP104 product containing both the DHE DP (drug constituent) and the I123 POD device (device constituent)

Drug Substance: Adequate

The CMC information for the drug substance, Dihydroergotamine Mesylate, is cross-referenced to Type II DMF (b) (4) Dihydroergotamine Mesylate is manufactured by the Holder of the referenced DMF – (b) (4) The DMF was originally submitted on 16-JAN-2009. The DMF has been reviewed and deemed adequate.

The Applicant refers to the DMF and provides a brief description of the general properties of the drug substance and potential organic impurities in the NDA. Based on information submitted in the DMF, no potentially genotoxic impurities and omission of testing for elemental impurities could be justified. As the drug product manufacturer requires that all drug substance batches conform to a limit of not more than (NMT) (b) (4) ppm for (b) (4), testing for (b) (4) will be performed.

Information provided in the NDA regarding drug substance, general properties, impurities, specification and analytical methods, and batch analyses is consistent with information in the DMF.

The DMF holder has assigned a retest period of (b) (4) months for drug substance stored at (b) (4). The retest period is supported by stability data in the DMF.

Drug Product: Adequate

The drug product solution (Drug Constituent) contains dihydroergotamine mesylate, 4 mg/1 mL compendial excipients that include caffeine, dextrose, water, and carbon

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dioxide. The drug product solution is stored in a 3.5 mL amber glass vial with a (b) (4) stopper and a plastic/aluminum flip-tear seal cap.

The test methods used for control of the drug product are adequately detailed and validated for quality control purposes. With one exception, proposed acceptance criteria are also adequate. However, the proposed shelf-life limit of NMT (b) (4)% for the principal degradation product, (b) (4) ((b) (4) was not qualified in adequate toxicology studies, or by testing versus the innovator. Thus, the Applicant was asked to revise the limit for this impurity to the ICH qualification threshold of NMT 1.0%. The Applicant agreed to lower the limit accordingly. The Applicant has provided release results for eight drug product batches, three of which are used as registration batches. All batches met the proposed specifications.

Note that the finished combination product specification includes controls CQAs for the drug constituent and essential performance requirements (EPRs) for the device constituent. The latter controls were reviewed by CDRH and deemed adequate.

Stability studies are being conducted per ICH guidelines on three batches of the combination product in commercial packaging. Due to the lower limit for (b) (4) the maximum shelf life that can be granted for the combination product is **12 months when stored at 20°C to 25°C (controlled room temperature)**. It is noted that the allowable shelf life for the device is (b) (4) months based the available data. Thus, a longer shelf life may be granted in the future if the Applicant is able to qualify a higher limit for the (b) (4) impurity.

Labeling: Adequate with Revisions Recommended

Several labeling deficiencies were identified during review of the package insert and container labels. CMC-related deficiencies include use of the term " (b) (4) " in the product name, incorrect presentation of product strength (i.e., potency stated as mg DHE per (b) (4) instead of mg DHE per spray), and absence of the required "Rx Only" statement. It is also noted that the package insert contains promotional statements and other information (e.g., (b) (4)) that is normally not included in labeling for a nasal spray. Final labeling edits will be made by the clinical division with input from OPDP[1] and DMEPA[2].

Manufacturing: Adequate

The drug constituent is a nonsterile aqueous solution containing DHE, caffeine and dextrose, with carbon dioxide as (b) (4) .
The manufacturing process involves: (b) (4) Registration batches were manufactured at the proposed commercial batch size, i.e., (b) (4) L. Due to the sensitivity of the drug

[1] Office of Prescription Drug Promotion
[2] Division of Medical Errors Presentation and Analysis

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substance to light and oxygen, the product must be protected from light and oxygen. During development, the firm conducted an extensive investigation and process improvement activities to address observation of a bright yellow solution found in some vials of two clinical batches (Lots 001 and 002). The root causes were assigned to: (b) (4) . To ensure suitable product quality, the following improvements and controls were established:

(b) (4)

During the subsequent manufacture of new process qualification batches, the manufactured no degradation of DHE was observed. The Applicant has established appropriate in-process controls to ensure consistent product quality and demonstrated compatibility of the formulation with manufacturing and filling equipment.

(b) (4) The proposed commercial trade package is a 4-count carton of four complete single use kits.

All facilities involved in the manufacture and testing of Dihydroergotamine Mesylate USP, the DHE drug formulation, POD nasal spray device, and finished combination product are currently acceptable. Facility status should be verified prior to final action.

Microbiology: Adequate

The drug and device constituents are tested for viable bioburden using procedures outlined in USP<61> and USP<62> appropriate for non-sterile, aqueous solutions for nasal administration. The microbial limits acceptance criteria are consistent with the USP chapter <1111> for nonsterile aqueous preparations for nasal use. Microbiological test procedures for Total Aerobic Microbial Count (TAMC), Total Yeast and Mold Count (TYMC) and specified microorganism (*E. coli, S. aureus, P. aeruginosa, S. abony, B. cepacia*) are adequately validated and suitable for quality control.

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The container closure system is designed to maintain product microbiological quality and the product is a single dose container. Since the product is single dose, antimicrobial effectiveness testing is not required.

Environmental: Adequate

The Applicant claimed a categorical exclusion for submission of an environmental assessment based on 21 CFR Part 25 and has included a statement of no extraordinary circumstances, in accordance with 21 CFR 25.15. It is noted that the Applicant provided information that would justify the claim under either 21 CFR 21.31(a), i.e., no net increase use as their product would be used in place of existing products, or 21 CFR 21.31(b), i.e., calculated EIC-aquatic ((b) (4) ppb) is less than the 1 ppb threshold.

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C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay/stability	Formulation, container closure, raw materials, process parameters, scale, equipment	**Low**	(b) (4)	**Adequate**	
Spray Content/Dose uniformity	Formulation, filling process, device performance parameters	**Low**		**Adequate**	
Droplet size distribution (DSD)	Device/actuator design, viscosity	**Low**		**Adequate**	
Spray pattern	Device/actuator design, viscosity	**Low**		**Adequate**	
Leachables / Extractables	Formulation, container closure, raw materials, process parameters, scale, equipment	**Moderate**		**Adequate**	
Biocompatibility	Pump component materials	**Low**		**Adequate**	
Microbial limits	Formulation, raw materials, process parameters, container closure	**Low**		**Adequate**	
Foreign matter	Particulates from excipient, (b) (4) equipment, device components	**Low**		**Adequate**	

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D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead for Neurology Products
Office of New Drug Products

8/4/2021

Reference ID: 4836790

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Heimann

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LABELING

I. Package Insert

(b) (4)

[redacted]

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Trudhesa (dihydroergotamine mesylate) nasal spray
Dosage form, route of administration	Nasal spray, nasal
Controlled drug substance symbol	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	0.725 mg / spray

Is the information accurate? ☐ Yes ☒ No

The Applicant includes (b) (4) in the name and will be asked to remove it. The Applicant presents the strength as (b) (4), whereas it should be mg/spray.

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2. *Section 2 Dosage and Administration*

(b) (4)

[redacted]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Prior to use, the olfactory delivery device is to be primed (four sprays). Exposing the drug product solution to ambient temperature for eight hours does not impact assay or impurities.

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

(b) (4)

[redacted]

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Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Nasal spray
Strengths: in metric system	0.725 mg/spray
Active moiety expression of strength with equivalence statement	Salt
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	It is a single-use drug-device combination product for nasal administration of dihydroergotamine mesylate. The drug product solution (clear, faintly yellow solution) is contained in an amber vial (b) (4)

Is the information accurate? ☐ Yes ☒ No

The Applicant presents the strength as (b) (4), whereas it should be mg/spray.

The Applicant also includes a promotional statement in this section and additional information that is not appropriate for this section. Significant edits are required.

4. ***Section 11 Description***

(b) (4)

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(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	TRUDHESA (dihydroergotamine mesylate) Nasal Spray
Dosage form and route of administration	Nasal spray / nasal
Active moiety expression of strength with equivalence statement (if applicable)	dihydroergotamine mesylate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	DHE (4.0 mg), caffeine (10.0 mg), dextrose 50.0 mg), water (q.s. 1.0 mL)
Statement of being sterile (if applicable)	Not Applicable
Pharmacological/ therapeutic class	NA
Chemical name, structural formula, molecular weight	Molecular weight: 679.78 Empirical formula: $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Not Applicable

Is the information accurate? ☒ Yes ☐ No

This section contains information that is promotional and that is not appropriate for this section of the label. Significant edits are required.

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(b) (4)

[redacted]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	TRUDHESA (dihydroergotamine mesylate) Nasal Spray
Available units (e.g., bottles of 100 tablets)	TRUDHESA is supplied as a package of 4 single-dose units
Identification of dosage forms, e.g., shape, color, coating,	Each single-dose unit contains: • One amber glass vial containing 4 mg

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scoring, imprinting, NDC number	dihydroergotamine mesylate in a 1 mL clear and colorless to faintly yellow solution. The stopper is not made with natural rubber latex. • One nasal spray device.
Special handling (e.g., protect from light)	Not Applicable
Storage conditions	Controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by: Mipharm, S.p.A. Milano, Italy Manufactured for: Impel NeuroPharma Inc 201 Elliott Ave West, Suite 260 Seattle, WA 98119 USA

Is the information accurate? ☒ Yes ☐ No

This section contains information that is promotional and that is not appropriate for this section of the label. Significant edits are required.

Reviewer's Assessment of Package Insert: ***Inadequate, deficiencies communicated to OND PM***

Prescribing Information does not comply with all regulatory requirements from a CMC perspective. Significant issues have been identified throughout, all of which are to be communicated to the OND PM for correction.

II. Labels:

1. ***Container Labels***

Vial

(b) (4)

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Incorrect, should be: Trudhesa (dihydroergotamine mesylate) Nasal Spray	Incorrect, should be: Trudhesa (dihydroergotamine mesylate) Nasal Spray
Dosage strength	Incorrect, should be: 0.725 mg/spray	Incorrect, should be: 0.725 mg/spray
Net contents	(b) (4)	4 nasal delivery devices 4 vials The terms "(b) (4) should be removed.
"Rx only" displayed prominently on the main panel	Rx only displayed	RX only not included
NDC number (21 CFR 207.35(b)(3)(i))	NDC number included	NDC number included
Lot number and expiration date (21 CFR 201.17)	Expiration date not included	Expiration date not included
Storage conditions	Not included	Controlled room temperature The statements: store in the case in a clean, dry area away from heat and light should be removed.
Bar code (21CFR 201.25)	Space for bar code included	Space for bar code included
Name of manufacturer/distributor	Manufactured by Mipharm S.p.A., Milan, Italy	Manufactured by Mipharm S.p.A., Milan, Italy
And others if space is available	NA	NA

Reviewer's Assessment of Labels: ***Inadequate, deficiencies communicated to OND PM***

The carton/container label does not comply with regulatory requirements from a CMC perspective. The carton/container is missing or contains inaccurate information regarding the following: storage conditions, expiration date, Rx only display, net contents, dosage strength, and proprietary name. These deficiencies will be communicated to the OND PM.

List of Suggested Edits Communicated to Applicant: Please see above comments.

Overall Assessment and Recommendation: Adequate Pending Edits to Labels

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Andrei Ponta

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Julia Pinto

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CHAPTER VII: MICROBIOLOGY

Product Information	This is a non-sterile, aqueous, non-preserved, single-use, nasal spray drug device combination product that is indicated for the acute treatment of migraine (b) (4) with or without aura in adults.
NDA Number	213436
Assessment Cycle Number	001
Drug Product Name/ Strength	Trudhesa (INP104 [POD-DHE] dihydroergotamine mesylate nasal spray), 4 mg/mL
Route of Administration	Nasal spray
Applicant Name	Impel NeuroPharma
Manufacturing Site	*Drug product manufacturing, packaging, release, and stability testing:* Mipharm S.p.A. Via Bernardo Quaranta, 12 20141 Milano, MI, Italy FEI: 3002807647 *Device manufacturing, microbial testing of canister during stability*: (b) (4) *Device component inspection, assembly and certification:* (b) (4) *INP104 product commercial packaging and labelling*: (b) (4)
Method of Sterilization	Non-sterile, aqueous, non-preserved drug device combination product

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A
Assessment Summary: (b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0000 (1)	11/06/2020
000 (4)	01/04/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is an eCTD submission. Information request conveyed to the applicant on 12/4/2020 and the response received on 1/4/2021 was incorporated in the submission.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None.

Supporting Documents: None

Select Number of Approved Comparability Protocols: 0

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MARTHA R HEIMANN
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