

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213436Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 30, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 213436
Product Name and Strength:	Trudhesa (dihydroergotamine mesylate) nasal spray, 0.725 mg per spray
Applicant/Sponsor Name:	Impel NeuroPharma (Impel)
OSE RCM #:	2020-2356-1
DMEPA 2 Safety Evaluator:	Murewa Oguntimein, PhD, MHS, CHES, CPH
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU), container labels, and carton labeling received on August 9, 2021 for Trudhesa. The Division of Neurology 2 (DN 2) requested that we review the revised IFU, container labels, and carton labeling for Trudhesa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

1.1 RELEVANT BACKGROUND INFORMATION

On August 4, 2021, the Applicant sent the following justification and clarifying question via email regarding linear barcode requirements for Trudhesa container labels and carton labeling, “Based on our product distribution, our expectation is that these distributed to patients not hospitals. It appears that would be an exemption under the 21 CFR 201.25...Would this bar code requirement apply to us in this case?”

Subsequently on August 10, 2021, we sent the following response via email to the Applicant,

^a Oguntimein, M. Human Factors Study Report and Label and Labeling Review for Trudhesa (NDA 213436). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 AUG 03. RCM No.: 2020-2356, 2020-2357.

According to the regulation 21 CFR 201.25(b)(1) and 21 CFR 201.25(c)(2), the bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients. Because your product will not be distributed directly to patients (e.g., patients will receive your product from a pharmacy), we maintain our recommendation to provide a linear barcode to align with the regulation.

On August 12, 2021, the Applicant responded via email, “We did provide a linear barcode on the saleable unit which is the 4-pack carton.” Therefore, in an effort to clarify our previous recommendation to include a linear barcode on the container label, we provide a recommendation for Impel in section 3 below.

2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. The Applicant did not implement our recommendation to include a linear barcode on the container label in accordance with 21 CFR 201.25(c)(2).

3 RECOMMENDATIONS FOR IMPEL NEUROPHARMA

We recommend the following be implemented prior to approval of this NDA:

A. Vial Container Label

1. Per 21 CFR 201.25, the linear barcode must appear on the drug’s label as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)). The linear barcode should be presented the outside container or wrapper, as well as on the immediate container unless the barcode is readily visible and machine-readable through the outside container or wrapper. Therefore, the vial container label for your proposed product should include a linear barcode. Thus, we maintain our previous recommendation to add the product’s linear barcode to the vial container label in accordance with 21 CFR 201.25(c)(2). Please refer to the Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (June 2021). The guidance is available at: <https://www.fda.gov/media/116304/download>.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 26, 2021

To: Daniel Ngembus
Regulatory Project Manager
Division of Neurology II (DN2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Sapna Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): TRUDHESA (dihydroergotamine mesylate)

Dosage Form and Route: nasal spray

Application Type/Number: NDA 213436

Applicant: Impel NeuroPharma, Inc.

1 INTRODUCTION

On November 6, 2020, Impel NeuroPharma, Inc. submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) for dihydroergotamine mesylate nasal spray. The Applicant is seeking FDA approval for prescription marketing of the drug product for the treatment of adults with acute migraine with or without aura.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on June 25, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TRUDHESA (dihydroergotamine mesylate) nasal spray.

2 MATERIAL REVIEWED

- Draft TRUDHESA (dihydroergotamine mesylate) MG and IFU received on November 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 10, 2021.
- Draft TRUDHESA (dihydroergotamine mesylate) Prescribing Information (PI) received on November 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 10, 2021.
- Product X (dihydroergotamine mesylate) IND 130133 IFU review completed by DMPP on October 29, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: August 24, 2021

To: Ryan Kau, M.D.
Division of Neurology 2 (DN2)

Daniel Ngembus, Regulatory Project Manager, (DN2)

Tracy Peters, Associate Director for Labeling, (DN2)

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for Trudhesa™ (dihydroergotamine mesylate), nasal spray

NDA: 213436

In response to DN2's consult request dated May 6, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Trudhesa (dihydroergotamine mesylate).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN2 (David Ngembus) on August 10, 2021, and are provided below.

MG and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 9, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 19, 2021

To: Nicholas Kozauer, MD, Director (Acting)
Division of Neurology 2

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: **Product:** Dihydroergotamine mesylate nasal spray (DHE; INP104; trade name: Trudhesa)
NDA number: 213436
Indication: Treatment of migraine, with or without aura
Dosages: 1.45 mg DHE in two sprays, one spray in each nostril, up to twice a day
Sponsor: Impel NeuroPharma

Materials reviewed: NDA for Trudhesa (November 6, 2020); CSS consult review (Dr. Bonson, March 24, 2021)

I. Background

On March 24, 2021, CSS provided a consult review to the Division of Neurology 2 (DN2) regarding NDA 213436 for Trudhesa, a dihydroergotamine mesylate (DHE) nasal spray (utilizing the I123 Precision Olfactory Delivery device) that was submitted on November 6, 2020, by Impel NeuroPharma. In this consult, we revise our recommendations regarding the need for section 9 Drug Abuse and Dependence in the drug label for DHE nasal spray.

Trudhesa is proposed for the treatment of migraine headaches, with or without aura. The NDA for Trudhesa was submitted under the 505(b)(2) pathway, referencing DHE45 Injection (NDA 005929) for safety and Migranal Nasal Spray (NDA 20148) for efficacy. Each bottle of Trudhesa will contain 4 mg DHE, 10 mg caffeine, and 50 mg dextrose in 1 mL of water. DHE is an ergot alkaloid that has been marketed as a treatment for migraine since 1946. It is currently marketed as Migranal and DHE45 for acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache

episodes. DHE is currently available in these products as a nasal spray and in ampules for subcutaneous, intramuscular, and intravenous injection.

Adverse events described in the drug label for the marketed DHE products include “vasospasm, paraesthesia, hypertension, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, and increased sweating.”

The Sponsor conducted a bioavailability study with Trudhesa but did not conduct a bioequivalency study. Local safety was assessed from a Phase 3 clinical safety study in patients with migraine. The Sponsor claims that the novel device allows for a more consistent drug uptake but lower systemic exposure due to delivery of DHE to the upper nasal passages. The NDA states that, “The drug formulation of DHE Nasal Spray solution in INP104 is the same as that of the commercially available Migranal Nasal Spray and is manufactured by the same contract manufacturing organization (Mipharm).”

The therapeutic effects of DHE are thought to occur as the result of its agonist activity at serotonin 5HT_{1B} and 5HT_{1D} receptors. Neither of these receptors are associated with abuse potential. Dihydroergotamine is not a scheduled drug under the Controlled Substances Act.

II. Conclusions

DHE has been marketed since 1946 and is not controlled under the Controlled Substances Act as a drug of abuse. Its mechanism of action as a serotonin 5HT_{1B} and 5HT_{1D} agonist is not associated with abuse potential.

III. Recommendation

CSS confirms its conclusion from our March 2021 consult that there is no need for an abuse potential assessment to be conducted on NDA 213436 for Trudhesa. For a drug with no abuse potential, we would typically recommend that the product not include section 9 Drug Abuse and Dependence in the drug label, as we informed you in our March 2021 consult.

However, the listed drug for Dihydroergotamine Mesylate Injection, DHE 45 (NDA 005929), contains section 9 in its label, consisting of a single paragraph:

9 DRUG ABUSE AND DEPENDENCE

Currently available data have not demonstrated drug abuse or psychological dependence with dihydroergotamine. However, cases of drug abuse and psychological dependence in patients on other forms of ergot therapy have been reported. Thus, due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages.

The Sponsor-proposed labeling for Dihydroergotamine Mesylate Injection includes the identical text for section 9. Given that the drug labels for 505(b)(2) should parallel those

of the listed drug, we recommend the inclusion of section 9 of the drug label. To better adapt this language to Physician Labeling Rule (PLR) formatting, we recommend the following revised form of the proposed section 9:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

[Tradename] contains dihydroergotamine (as the mesylate salt), which is not a controlled substance.

9.2 Abuse

Currently available data have not demonstrated drug abuse with dihydroergotamine. However, cases of drug abuse in patients on other forms of ergot therapy have been reported.

9.3 Dependence

Currently available data have not demonstrated physical or psychological dependence with dihydroergotamine. However, cases of psychological dependence in patients on other forms of ergot therapy have been reported. Thus, due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages.

The proposed text for section 9.1 is consistent with recommendations in the 2019 draft guidance for industry: *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* at line 181 [<https://www.fda.gov/media/128443/download>].

If there are further questions about product labeling, or should any abuse-related questions or concerns arise during the review cycle, DN2 may contact us again to assist with these questions.

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/s/

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 28, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 213436
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength	Trudhesa (dihydroergotamine mesylate, USP) nasal spray, 4 mg/mL
Device Constituent:	nasal spray device
Rx or OTC:	Rx
Applicant/Sponsor Name:	Impel NeuroPharma (Impel)
Submission Date:	November 06, 2020; February 9, 2021, February 11, 2021; June 23, 2021
OSE RCM #:	2020-2357; 2020-2356
DMEPA 2 Human Factors Evaluator:	Murewa Oguntimein, PhD, MHS, CHES, CPH
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA 2 Deputy Director/ Director:	Danielle Harris, PharmD

1. REASON FOR REVIEW

This review evaluates of a human factors (HF) validation study report and labels and labeling submitted under NDA 213436 for Trudhesa (dihydroergotamine mesylate) nasal spray.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed Precision Olfactory Delivery (POD) nasal spray device constituent part that is indicated for the acute treatment of migraine headaches with or without aura in adults. Trudhesa is supplied in a carton consisting of 4 units. Each unit includes a glass vial containing 4 mg (1 mL) of dihydroergotamine mesylate, a POD nasal spray device, and an instructions for use (IFU). The glass vial and POD nasal spray device must be assembled at the time of administration. For additional product information see Appendix A.

(b) (4)



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On September 12, 2018, Impel submitted a Type C meeting request under IND 130133. Impel asserted that no further HF studies were required to establish the safe and effective use of their proposed product. However, in our written response dated November 26, 2018, we recommended that Impel conduct a HF validation study and submit their HF protocol for feedback from the Agency due to overdose medication error concerns related to priming, methodology concerns in the formative study and differences in the identified comparator.¹
- On August 30, 2019, Impel submitted a HF Validation Study Protocol for adult patients under IND 130133. Our review of the HF validation study protocol identified several areas of concern. On October 29, 2019 we provided our recommendations to Impel in a HF Validation Study Protocol Advice Letter.²
- On April 07, 2020, Impel submitted a Type B meeting request under IND 130133. Impel requested the Agency to confirm that the proposed change in color of the finger grip of the nasal spray device from (b) (4) to (b) (4) will have a minor impact on the proposed product and can be implemented based on the plan outlined in the meeting package. In the meeting minutes dated July 16, 2020, we stated that their proposed change in finger grip color appears reasonable provided that it does not impact critical tasks or introduce new risk to the user interface. We suggested Impel include rationale in their NDA submission to support that the finger grip color change does not require additional HF validation study data to be submitted.³

¹ Papanastasiou, E. Type C Meeting Written Response for IND 130133. Silver Spring (MD): FDA, CDER, DN2 (US); 26 NOV 2018. Available from:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af804c7541&_afRedirect=1687013795327314

² Killen, M. Human Factors Validation Study Advice for IND 130133. Silver Spring (MD): FDA, CDER, DMEPA (US); 29 OCT 2019. Available from:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af80523cf5&_afRedirect=1686822705214879

³ Ngembus, D. Type B Meeting Minutes for IND 130133. Silver Spring (MD): FDA, CDER, DN2 (US); 16 JUL 2020. Available from:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af8057d5cc&_afRedirect=324527954305396

- On October 6, 2020, Impel submitted a HF validation study protocol under IND 130133 to evaluate safe and effective use in pediatric users. Our review of the HF validation study protocol identified several areas of concern. We provided recommendations to Impel in a HF Validation Study Protocol Advice Letter dated December 02, 2020.⁴
- On November 11, 2020, Impel submitted NDA 213436 to seek approval for Trudhesa in adults. As such, the NDA submission included the results of their HF validation study for adults to support their marketing application, which is the subject of this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
HF Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface is designed to support the safe and effective use of the proposed product.

⁴ Killen, M. Human Factors Validation Study Advice for IND 130133. Silver Spring (MD): FDA, CDER, DMEPA (US); 02 DEC 2020. Available from:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805b5b79&_afRedirect=1693573881306592

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2: Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• n=15 adult nasal spray experienced patients • n=15 adult nasal spray naïve patients
Training	No training was provided to the 30 patient participants.
Test Environment	The test room was setup to simulate the intended use environment of a home.
Sequence of Study	Simulated use scenario Root cause analysis (RCA) Knowledge Task Questions RCA IFU Feedback

3.2 DISCUSSION OF PREVIOUS INFORMATION REQUEST, RESULTS AND ANALYSES

During the course of our review, we noted that the HF report did not include justification to support that the finger grip color change does not require additional HF validation study data (See Section 1.2 above). Thus, on June 22, 2021, we issued an Information Request (IR) to request the missing justification that the finger grip color change does not require additional HF validation study data. Impel stated that this is a minor change based on the engineering design of the device and does not impact the results of the HF validation study. Impel also stated that no additional user risk has been created, nor have the critical tasks been altered due to the proposed color change. Therefore, per Impel, this color change will have no impact on the HF data generated using the proposed device in support of the NDA submission.

Based on the above considerations, we accept the Impel's justification and analysis of risk, we disagree that the finger grip color change is a minor change based on the engineering design of the device because it impacts the intended users ability complete the critical task of administering the dose. However, we agree with the Applicant that the color change does not create any additional use risk or impact the user's ability to administer the dose in a clinically significant way. In addition, we agree that the finger grip color change does not alter any critical tasks associated with the safe and effective use of the proposed product. Therefore, we agree that the finger grip color change does not require additional HF validation study data to be submitted.

Table 3 describes one critical task use error identified in the HF validation study which we find requires additional mitigation, Impel NeuroPharma's analyses of the use error, and DMEPA's

analyses and recommendations. In addition, in sections 3.3 we discuss other critical and non-critical task failures where we found the residual risk acceptable.

Table 3. Identified Issues and Recommendations		
	Identified Issue, Subjective Feedback, Root Cause Analysis and Mitigations	DMEPA's Analysis and Findings
1.	For the critical task to identify the maximum number of doses in a 7-day period, there was 1 use error for the knowledge task question, "What is the maximum number of doses can you take in a 7-day period?" - Participant (b) (6) (nasal spray naïve) stated that the maximum number of doses in a 7-day period was 14 doses. The subjective data and Impel's RCA indicated that: (b) (6) calculated the maximum weekly dose based on the maximum daily dose without referencing the IFU. For example, (b) (6) stated, "14? Yeah, 7x2 is 14." Per Impel, (b) (6) identified the correct answer when reviewing the IFU and stated the information was clearly presented. Additionally, Impel states that the information regarding the maximum number of doses in a 7- day period is presented in 3 different sections of the IFU. However, Impel did not implement additional mitigations to further address this use error.	Based on Impel's provided information in this submission, no more than 3 doses should be administered in a 7-day period. According to the URRR, there is "unlikely harm" if more than 3 doses are administered in a 7-day period because the Cmax for the dose delivered in 4 sprays is "likely much less than" the Cmax for intravenous dihydroergotamine. We sought input from the DN2 medical officer to determine the clinical impact of taking more than 3 doses of the proposed product in a given 7-day period. The medical officer responded via email on December 17, 2020 that we do not have safety data for patients taking greater than 3 doses in 7 days. Thus, due to the lack of safety data available, we are concerned with the residual risk for this error. Based on our review of the data submitted, we disagree with Impel's conclusion that this use error was not attributed to the IFU. We acknowledge that (b) (6) provided the correct response after the moderator stated, "See if you can find that answer in the instructions." However, our review of the subjective data identified participant feedback that indicated the information regarding the maximum number of doses in a 7- day period in the IFU can be overlooked. For example, (b) (6) stated that the information should not only be in the Frequently Asked Questions (FAQs) section of the IFU. The moderator then informed (b) (6) that the aforementioned information is located in two other locations in addition to the FAQ section in the IFU. Our review of the IFU notes that the information regarding the maximum of 3 sprays in a 7-day period is in three locations of the IFU

		(Important Information You Need to Know Before Dosing with Product X, Step 7 and Important Frequently Asked Questions Section). However, our review finds that improvements can be made. Specifically, we find that: - the maximum 7-day dose information lacks prominence because this information appears in the same sentence as the maximum daily dose information in all three locations. - the maximum 7-day dose information is provided (b) (4) in the “Important information You Need to Know Before Dosing with Product X” and “Important Frequently Asked Questions” sections of the IFU. Based on our overall assessment, we disagree with Impel that no additional mitigations are required to further mitigate this risk. As such, our review of the IFU finds that the instructions can be improved to minimize the risk of users overlooking the information related to the maximum number of doses in a 7-day period. We provide a recommendation in Table A to address this concern. We find that this change can be implemented without additional HF validation testing.
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3.3 ANALYSIS OF OTHER CRITICAL AND NON-CRITICAL TASKS ERRORS

Errors (e.g. failures, difficulties) occurred in the HF validation study with the following ten critical tasks and three non-critical tasks not included in Table 3 above. However, based on our review of the available participants’ subjective feedback, the Applicant’s root cause analysis, and the Applicant’s proposed risk mitigation strategy, we determined the residual risk is acceptable. In addition, we considered the use tasks of the proposed product with the use tasks in similar marketed products with the same user groups to determine if there are any known concerns of vulnerability to use error and did not identify any concern. Subsequently, our assessment of the aforementioned considerations in totality finds

the residual risk is acceptable without further need for risk mitigation strategies at this time to address the use errors related to the following use tasks:

- Storage
- Remove components from case
- Check product name
- Check expiration date
- Check glass vial and blue cap for damage
- Opens glass vial
- Remove cover from nasal device
- Screw Glass vial into nasal device
- Prime nasal device
- Administer dose by spraying once in each nostril
- Dispose of used nasal device and glass vial

3.4 LABELS AND LABELING

Tables 4 and A below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information: Section 2.1 (b) (4) Dosing Information (b) (4)			
2.	It is unclear how soon users can administer a second dose after the first dose. Specifically, the maximum dosage statement, “Do not use more than 2 doses of Trudhesa within a 24-hour period” does not state when user can administer the second dose.	We are concerned that the lack of dosing clarity may lead to overdose medication errors leading to patient harm.	Consider revising the statement “Do not use more than 2 doses of Trudhesa within a 24-hour period” to include how long the user should wait before administering the second dose, if the wait time is clinically meaningful for this product.
3.	Important information about the intended route of administration lacks prominence. Specifically, the statement, “(b) (4) Trudhesa is for nasal administration only and must not be injected.” is included as the last statement in section 2.1 (b) (4) Dosing Information (b) (4).	We are concerned that this important administration information may be overlooked.	We recommend relocating (or repeating) the statement, “(b) (4) Trudhesa is for nasal administration only and must not be injected.” so that it is the first statement under section 2.2 Important Administration Instructions.
Full Prescribing Information: Section 3 Dosage Forms and Strengths			
1.	The dosage form statement is missing.	Section 3 should include the dosage form statement per 21 CFR 201.57(c)(4).	We recommend revising the first line of Section 3 to include the dosage form statement.
Full Prescribing Information: Section 16 How Supplied/ Storage and Handling			

1.	Important administration information lacks prominence. Specifically, the statement, (b) (4) (b) (4) (b) (4) is located in section 16.	We are concerned that this important administration information may be overlooked and lead to administration of degraded drug product.	Consider relocating (or repeating) the statement, (b) (4) (b) (4) (b) (4) to section 2.2. Additionally, revise the word, “(b) (4)” to “Trudhesa” for clarity.
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Table A: Identified Issues and Recommendations for Impel NeuroPharma Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.(entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
General (All Labels and Labeling)			
1.	The proposed labels and labeling include the place holders “Product X” or “Tradename” instead of the conditionally acceptable proprietary name.	We reference our December 23, 2020 letter informing you that the proprietary name, Trudhesa, was found conditionally acceptable.	Replace “Product X” and “Tradename” with the conditionally acceptable proprietary name, “Trudhesa” throughout labels and labeling.
2.	We note inconsistencies in terminology with regards to the description of your device constituent part. For example, the Instructions for use (IFU) states, “nasal spray device” while the commercial secondary molded packaging labeling	We generally expect terminology to be consistent throughout labels and labeling to minimize confusion.	Revise the description of your device constituent part on labels and labeling to use a consistent term that aligns with the Prescribing Information.

	state, “ (b) (4) ”.		
Instructions for Use (IFU)			
1.	The dosage form statement is missing.	The established name for drug products should include the finished dosage form, and the finished dosage form should appear on the same line as the active ingredient. ⁵	Revise the established name to include the dosage form (i.e., “Trudhesa (dihydroergotamine mesylate) nasal spray”). If space does not permit allowing the dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient.
2.	Your IFU can be improved to better present information related to the maximum number of allowed sprays per 7-daysdose. In your HF study, a participant overlooked the maximum 7-day dose information in the IFU. We also note that the	We acknowledge that the maximum number of sprays per 7-days dose information is presented in three locations of the IFU (Important Information You Need to Know..., under Step 7 and Important Frequently Asked Questions Section). However, our review identified participant feedback that suggests that the information regarding the maximum number of doses in a 7- day period in the IFU can be overlooked. For example, (b) (4)	Revise your IFU to prominently state information regarding the maximum 7-day dose as follows: - In the “Important Information You Need To know...” Section: Revise and relocate the statement, (b) (4) to “Do not take more than 2 doses within a 24-hour period. Do not take more than 3 doses in a 7-day period” and relocate to appear immediately after statement “A complete dose is 2 sprays; 1 spray in each nostril.” - In the “Important Tip” under Step 7: Revise and relocate the statement, “ (b) (4)

⁵ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

	maximum 7-day dose information lacks prominence because this information appears in the same sentence as the maximum daily dose information in three locations in the IFU.	stated that the information should not only be in the Frequently Asked Questions (FAQs) section of the IFU. The moderator then replied, "It actually is in two other places [moderator indicates location in IFU]." Thus, we disagree with your root cause analysis that the use error related to this information was not attributed to the IFU. Thus, we are concerned that the lack of prominence in the IFU regarding the maximum 7-day dose information may lead to overdose medication error.	(b) (4) to "Do not take more than 2 doses within a 24-hour period. Do not take more than 3 doses in a 7-day period" and relocate to appear immediately after the statement "A complete dose is 2 sprays; 1 spray in each nostril." In the "Important Frequently Asked Questions (FAQs) section: Revise the statements, (b) (4) to "Do not take more than 2 doses within a 24-hour period. Do not take more than 3 doses in a 7-day period.
Vial Container Label			
1.	The dosage form statement is missing.	The established name for drug products should include the finished dosage form, and the finished dosage form should appear on the same line as the active ingredient. ⁶	Revise the established name to include the dosage form. (i.e., "Trudhesa (dihydroergotamine mesylate) nasal spray"). If space does not permit allowing the finished dosage form to appear on the same line as the active ingredient, we recommend placing the

⁶ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

			finished dosage form on the next line below the active ingredient.
2.	The strength statement lacks prominence.	The product strength should be prominent per 21 CFR 201.15(a)(6).	Increase the prominence (i.e., font size) of the strength, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
Vial Container Label, Commercial Carton Labeling			
1.	As currently presented, the inclusion and location of a linear barcode is not indicated.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label.	Add the product's linear barcode in accordance with 21 CFR 201.25(c)(2).
2.	The expiration date is missing.	The expiration date is required on the immediate container and carton labeling in accordance with 21 CFR 211.137.	Add the expiration date to the container labels and carton labeling. Furthermore, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

Vial Container Label, Commercial Carton Labeling and Professional Sample Carton Labeling			
1.	The location of the lot number is missing.	The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10 (i)(1).	Add the lot number to the container label and carton labeling.
2.	The strength statement is either not included or presented incorrectly (i.e. (b) (4) on the principal display panel (PDP).	The product strength statement is considered to be important product information that should be prominently displayed on the PDP to minimize confusion and medication errors.	Include the strength statement “0.725 mg per spray” immediately following the established name on the PDP and in accordance with 21 CFR 201.15 (a)(6).
Commercial and Professional Sample Secondary Packaging, Commercial Carton Labeling and Professional Sample Carton Labeling			
1.	The dosage form is presented as (b) (4) on the carton labeling; however, the PI states, “nasal spray.”	The dosage form statement should be consistent throughout labels and labeling to minimize confusion.	Revise the dosage form throughout labels and labeling to consistently state “nasal spray” (i.e., “Trudhesa (dihydroergotamine mesylate) nasal spray”). If space does not permit the dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient. See Guidance for Industry: <i>Safety Considerations for Container</i>

			<i>Labels and Carton Labeling Design to Minimize Medication Errors (lines 326 – 343).⁷</i>
Commercial Carton Labeling and Professional Sample Carton Labeling			
1.	The terminology, “(b) (4)” and “(b) (4)” is not consistent with the PI.	We generally expect terminology to be consistent throughout labels and labeling to minimize confusion.	Revise the statement “(b) (4)” to “Instructions for Use and Prescribing Information.”
2.	The carton labeling does not include a usual dose statement.	The usual dose statement is required per 21 CFR 201.55.	Revise the labeling to include the statement “Recommended Dosage: See prescribing information.”
Commercial Carton Labeling			
1.	The carton labeling does not contain an “Rx Only” statement.	The “Rx Only” statement is required on the drug label and the outside container by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Add the “Rx Only” statement to an area on the carton labeling that does not interfere with important product identifying information (i.e., product name, product strength).
2.	The carton labeling is misleading because it includes the statement,	We are concerned that patients may be confused and dispose of all contents in the carton	Revise the statement “(b) (4)” to “Contents are

⁷ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

	“(b) (4) however, each carton contains 4 nasal spray devices, which provides 4 doses.	including unused nasal spray devices after one dose.	disposable; discard used nasal spray device and vial after use”.
3.	As currently presented, the intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The 2D data matrix barcode should be located in an area that allows sufficient space between it and the linear barcode so that both can be read correctly upon scanning.	We recommend identifying the intended location of the 2D matrix barcode. Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the linear barcode. For more information, see guidance, Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers (June 2021).⁸
Professional Sample Carton Labeling			

⁸ Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: <https://www.fda.gov/media/116304/download>

1.	The route of administration statement lacks prominence because it is located on the side panel.	The route of administration statement should be displayed on the PDP. ⁹	Relocate the route of administration statement, “For Nasal Use Only” from the side panel to the PDP.
2.	The expiration date is missing.	The omission of the expiration date may lead to degraded drug medication error.	Add the expiration date to the container labels and carton labeling. Furthermore, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

⁹ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

Professional Sample Secondary Packaging and Professional Sample Carton Labeling			
1.	The statement, “ (b) (4) [REDACTED] does not clearly denote its status as a drug sample.	The container label and carton labeling should clearly denote this packaging configuration as a professional sample in accordance with 21 CFR 203.38(c).	Add a statement similar to “Samples- Not for sale” on the side panel.

4. CONCLUSION AND RECOMMENDATIONS

Based on our review of the HF validation study results and labels and labeling, we determined that certain changes should be implemented in the design of the user interface to further support safe and effective use of the product and minimize the risk for medication errors.

Above, we have provided recommendations in Table 4 for the Division and Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA. These changes can be implemented without submitting additional HF validation testing for Agency review.

4.1 RECOMMENDATIONS FOR IMPEL NEUROPHARMA

Our evaluation of the results of your human factors (HF) validation study, including participant subjective feedback and root cause analyses, indicates that there are additional mitigations that can be implemented to address one use error that occurred with a critical task. Additionally, our review of the labels and labeling identified areas of vulnerability that may lead to medication errors. We provide these recommendations in Table A and we recommend that you implement these recommendations and submit the revised labels and labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Trudhesa (dihydroergotamine mesylate) nasal spray that Impel NeuroPharma submitted on February 9, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Ergotamine derivative
Active Ingredient (Drug or Biologic)	dihydroergotamine mesylate
Indication	For the acute treatment of migraine headaches with or without aura in adults.
Route of Administration	intranasal
Dosage Form	nasal spray
Strength	4 mg/mL
Dose and Frequency	A single dose (1.45 mg) of Trudhesa is administered as two metered sprays into the nose (one spray into each nostril). Do not use more than 2 doses of Trudhesa within a 24-hour period or 3 doses within a 7-day period.
How Supplied	(b) (4)

Storage	The storage and handling conditions for TRUDHESA are as follows: • Keep away from heat and light. • Store at controlled room temperature, 68°F to 77°F (20°C to 25°C), with excursions allowed between 59°F to 86°F (15°C to 30°C). Do not refrigerate or freeze. • Do not throw Trudhesa into fire or incinerators as the HFA canister may explode. • Trudhesa is to be discarded after using. • If not used, discard of the product within 8 hours after opening the drug vial or after the Trudhesa product has been assembled.	
Container Closure/Device Constituent	(b) (4)	
Intended Users	Adults,	(b) (4)
Intended Use Environment	Home	

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 1,2020 we searched FDA previous reviews using the terms, IND 130133 and dihydroergotamine to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews^{10,11}, and we confirmed that our previous recommendations were implemented or considered.

¹⁰ Whaley E. Human Factors Validation Protocol Review for Dihydroergotamine IND 130133. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 Oct 28. RCM No.2019-1322.

¹¹ Oguntimein M. Human Factors Validation Protocol Review for Dihydroergotamine IND 130133. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2020 NOV 19. RCM No.2020-2201.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in the HF study result report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\evsprod\nda213436\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine-headache\5354-other-stud-rep\human-factors\hf-valid-rpt-iaa-2009.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On February 8, 2021, we issued an Information Request (IR) to request detailed information about (b) (6) response during the administer dose knowledge assessment task.

The Applicant provided an acceptable response on February 11, 2021, that can be accessible in EDR via:

<\\CDSESUB1\evsprod\nda213436\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine-headache\5354-other-stud-rep\human-factors\response-11feb2021.pdf>

On June 22, 2021, we issued an Information Request (IR) to request the following information:

- Please confirm the color of the finger grip for your intend-to-market nasal spray device.
- If the finger grip color for the nasal spray device used in your HFVS differs from your intend-to-market nasal spray device, please provide your rationale to support that the finger grip color change does not require additional HF validation study data to be submitted.

The Applicant provided an acceptable response on June 23, 2021, that can be accessible in EDR

via: <\\CDSESUB1\evsprod\nda213436\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine-headache\5354-other-stud-rep\human-factors\response-23jun2021.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

- Vial container label received on November 11, 2020
- Commercial secondary molded packaging received on November 11, 2020
- Commercial carton labeling received on November 11, 2020
- Professional sample secondary packaging received on November 11, 2020
- Professional sample carton labeling received on November 11, 2020

- Instructions for Use (Image not shown) received on November 11, 2020 can be accessible in EDR via: <\\CDSESUB1\evsprod\nda213436\0001\m1\us\114-labeling\114a-draft-label\labeling-text-ifu.pdf>
- Prescribing Information (Image not shown) received on February 9, 2021 can be accessible in EDR via: <\\CDSESUB1\evsprod\nda213436\0007\m1\us\114-labeling\114a-draft-label\labeling-text-pi-word.docx>

F.2 Label and Labeling Images



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

OLUWAMUREWA OGUNTIMEIN
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COLLEEN L LITTLE
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LOLITA G WHITE
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DANIELLE M HARRIS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: 7/26/2021 **Date consulted:** 4/16/2021

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

To: Division of Neurology 2 (DN2)

Drug: MIGRANAL (dihydroergotamine) nasal spray
D.H.E. 45 (dihydroergotamine) injection

NDA: 020148 and 005929

Applicant: Bausch

Subject: Non-Pregnancy and Lactation Labeling Rule (PLLR) Pregnancy and
Lactation Labeling Updates

Indication(s): MIGRANAL

- Acute treatment of migraine headaches with or without aura
D.H.E. 45
- Acute treatment of migraine headaches with or without aura
- Acute treatment of cluster headache episodes

Materials Reviewed:

- DPMH consult request dated April 16, 2021, DARRTS Reference ID
4780676

- DPMH Consult review TRUDHESA (dihydroergotamine) Nasal Spray, NDA 213436, Catherine Roca, MD, Medical Officer, June 30, 2021. DARRTS Reference ID 4813984¹
- DPMH Consult review (b) (4)

Consult Question: “Dihydroergotamine products MIGRANAL NDA 20148 and D.H.E. 45 NDA 005929 are not in PLR, and therefore not in PLLR format. We would appreciate DPMH’s input on the non-PLLR language.”

BACKGROUND

MIGRANAL was originally approved for use in the United States on December 8, 1997 and D.H.E. 45 Injection was approved for use in the U.S. on April 12, 1946.

Drug Characteristics and Serious Adverse Reactions^{3,4}

Drug Class	MIGRANAL and D.H.E. 45 are ergotamine drugs.
Mechanism of action	Dihydroergotamine binds with 5HT _{1Dα} and 5HT _{1Dβ} receptors. It also binds to 5HT _{1A} , 5HT _{2A} and 5HT _{2C} , noradrenaline α _{2A} , α _{2B} and α ₁ receptors and dopamine D _{2L} and D ₃ receptors.
Molecular weight	Approximately 680 Daltons
Protein Binding	93%
Half-life	• Approximately 10 hours after nasal administration (MIGRANAL) • Approximately 9 hours after intramuscular or intravenous injection (D.H.E. 45)
Absorption/Bioavailability	• Poor oral bioavailability • Bioavailability after MIGRANAL nasal spray approximately (b) (4)% • Bioavailability after subcutaneous or intramuscular injection has not been determined.

¹ The TRUDHESA consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

² The Dihydroergotamine mesylate injection consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

³ MIGRANAL (dihydroergotamine) package insert, current labeling approved 8/1/2019, Drugs@FDA

⁴ D.H.E 45 Injection package insert, current labeling approved 9/1/2009, Drugs@FDA

Serious Adverse Reactions	• Use with CYP3A4 inhibitors (macrolide antibiotics and protease inhibitors) – serious adverse events resulting in vasospasm including cerebral ischemia and/or ischemia of the extremities. • Fibrotic complications (pleural and retroperitoneal) have been reported following prolonged daily use. • Risk of myocardial ischemia and/or infarction and other cardiac events • Cardiac events and fatalities have been reported with dihydroergotamine injection • Drug-associated cerebrovascular events and fatalities (cerebral hemorrhage, subarachnoid hemorrhage, and stroke) have been reported with dihydroergotamine injection. • Other vasospasm related events • Increased blood pressure • Local irritation has been reported with the nasal spray
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Current State of MIGRANAL Labeling⁵

Approved labeling is not is Physician Labeling Rule formatting (PLR), and therefore not in Pregnancy and Lactation Labeling Rule (PLLR) formatting.

There is a boxed warning for “Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.”

CONTRAINDICATIONS:

- Coadministration with potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is contraindicated.
- Should not be given to patients with ischemic heart disease or to patient consistent with coronary artery vasospasm including Prinzmetal’s variant angina.
- Should not be given to patients with uncontrolled hypertension.
- 5HT1 agonists (e.g., sumatriptan), ergotamine-containing, ergot-type medications, or methylsergide should not be used within 24 hours of each other.
- Should not be administered to patients with hemiplegic or basilar migraine.
- In addition to the above, it is also contraindicated in patients with known peripheral artery disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function.
- Pregnancy is included in the contraindications- the language is listed below under

⁵ MIGRANAL (dihydroergotamine) package insert, current labeling approved 8/1/2019, Drugs@FDA

“Pregnancy” • Use is contraindicated in Nursing Mothers • Contraindicated with use of peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure. • Contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids.
Pregnancy (Under CONTRAINDICATIONS) • Pregnancy letter category – X • May cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties, and therefore, should not be administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. • There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryofetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposure [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryofetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.
Nursing Mothers (also listed under CONTRAINDICATIONS) • Ergot drugs are known to inhibit prolactin. It is likely that MIGRANAL (dihydroergotamine mesylate) is excreted in human milk, but there are no data on the concentration of dihydroergotamine in human milk. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in nursing infants. Because of the potential for these serious adverse events in nursing infants exposed to MIGRANAL (dihydroergotamine mesylate) Nasal Spray, nursing should not be undertaken with the use of MIGRANAL (dihydroergotamine mesylate) Nasal Spray (<i>see CONTRAINDICATIONS</i>).
Impairment of Fertility • There was no evidence of impairment of fertility in rats given intranasal doses of MIGRANAL (dihydroergotamine) Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposure [AUC] approximately 9 to 11 times those in

humans receiving the MRDD of 4 mg).
Oral Contraceptives The effect of oral contraceptive on the pharmacokinetics of MIGRANAL (dihydroergotamine mesylate) Nasal Spray has not been studied.

Current State of D.H.E. 45 Injection Labeling⁶

Approved labeling is not is Physician Labeling Rule (PLR) formatting, and therefore not in Pregnancy and Lactation Labeling Rule (PLLR) formatting
There is a boxed warning for “Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.”
CONTRAINDICATIONS: - Coadministration with potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is contraindicated. - Should not be given to patients with ischemic heart disease or to patient consistent with coronary artery vasospasm including Prinzmetal’s variant angina. - Should not be given to patients with uncontrolled hypertension. 5HT1 agonists (e.g., sumatriptan), ergotamine-containing, ergot-type medications, or methylsergide should not be used within 24 hours of each other. - Should not be administered to patients with hemiplegic or basilar migraine. - In addition to the above, it is also contraindicated in patients with known peripheral artery disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function. - May cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties and therefore should not be administered during pregnancy. - Contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids. - Should not be used by nursing mothers - Contraindicated with use of peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure.

⁶ D.H.E 45 Injection package insert, current labeling approved 9/1/2009, Drugs@FDA

Pregnancy (Under CONTRAINDICATIONS)

- Pregnancy letter category – X
- May cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties, and therefore, should not be administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryofetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposure [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryofetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

Nursing Mothers (also listed under CONTRAINDICATIONS)

- Ergot drugs are known to inhibit prolactin. It is likely that D.H.E. 45 Injection (dihydroergotamine mesylate) is excreted in human milk, but there are no data on the concentration of dihydroergotamine in human milk. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in nursing infants. Because of the potential for these serious adverse events in nursing infants exposed to D.H.E. 45 Injection (dihydroergotamine mesylate), nursing should not be undertaken with the use of D.H.E. 45 Injection (dihydroergotamine mesylate) (*see CONTRAINDICATIONS*).

Impairment of Fertility

- Impairment of fertility was not evaluated for D.H.E. 45 Injection (dihydroergotamine mesylate). There was no evidence of impairment of fertility in rats given intranasal doses of MIGRANAL (dihydroergotamine) Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposure [AUC] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg).

Oral Contraceptives

- The effect of oral contraceptive on the pharmacokinetics of D.H.E. 45 Injection (dihydroergotamine mesylate) has not been studied.

Review of the Literature

For a review of the literature regarding migraine headache and pregnancy and dihydroergotamine use in pregnancy, lactation, and effects of dihydroergotamine on fertility, the reader is referred to the DPMH Consult review of TRUDHESA (dihydroergotamine).⁷

Summary of conclusions from the literature review:

- Data from cohort studies indicate an increased risk for preterm birth with the use of dihydroergotamine during pregnancy.^{8,9}
- Data from cohort studies do not indicate that dihydroergotamine is a major teratogen.^{10,11}
- Dihydroergotamine inhibits prolactin, and therefore adversely affects milk supply.¹²
- Adverse events in infants exposed to ergotamine products during breastfeeding include vomiting, diarrhea, weak pulse, and unstable blood pressure.¹³
- There are no data on the effects of dihydroergotamine on human fertility.

DISCUSSION/CONCLUSIONS

Since dihydroergotamine is not a major teratogen, the contraindication for use in pregnancy can be removed. However, there should be a Warning regarding the risk for preterm birth with the use of dihydroergotamine during pregnancy.

Dihydroergotamine is not recommended for use during lactation, due to its adverse effects on milk supply and potential for adverse effects on infants. However, these are not contraindications. Language regarding lactation will be described in the Nursing Mother's section of labeling, rather than under Contraindications.

RECOMMENDATIONS

DPMH revised the Pregnancy and Nursing Mothers section of labeling (see below). DPMH refers to the final NDA action for final labeling.

⁷ DPMH Consult review TRUDHESA (dihydroergotamine) Nasal Spray, NDA 213436, Catherine Roca, MD, Medical Officer, DATE/DARRTS Reference ID

⁸ Berárd A, Kori S. Dihydroergotamine (DHE) use during gestation and the risk of averse pregnancy outcomes. *Headache*. 2012;52:1085-1093.

⁹ Kallen B, Lygner PE. Delivery outcomes in women who used drugs for migraine during pregnancy with special reference to sumatriptan. *Headache*. 2001;41:351-356.

¹⁰ Ibid.

¹¹ Berárd A, Kori S. Dihydroergotamine (DHE) use during gestation and the risk of averse pregnancy outcomes. *Headache*. 2012;52:1085-1093.

¹² Hale, Thomas. Hale's Medications and Mother's Milk, online, <https://www.halesmeds.com/monographs/61547?q=lexapro>, accessed 04/28/2021

¹³ Ibid.

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/

CATHERINE A ROCA
07/26/2021 03:10:03 PM

MIRIAM C DINATALE
07/26/2021 05:17:50 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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and Reproductive Medicine
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Division of Pediatric and Maternal Health Review

Date: 6/30/2021 **Date consulted:** 4/16/2021

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Neurology 2 (DN2)

Drug: TRUDHESA (dihydroergotamine mesylate) 4mg/ml Nasal Spray

NDA : 213436

Applicant: Impel NeuroPharma

Subject: Pregnancy and Lactation Labeling

Indication: Acute treatment of migraine headaches with or without aura

Materials

Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 213436
- DPMH Consult Request dated April 16, 2021. DARRTS Reference ID 4780676

Consult Question: Provide assistance with labeling review.

INTRODUCTION AND BACKGROUND

On November 6, 2020, Impel NeuroPharma submitted a 505(b)(2) for TRUDHESA (dihydroergotamine) Nasal Spray. DN2 consulted DPMH on April 16, 2021 to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

TRUDHESA (dihydroergotamine) NDA 213436 is a 505 (b)(2) application for a single use drug-device combination product to treat acute migraine with and without aura. The relied upon products are MIGRANAL Nasal Spray (dihydroergotamine mesylate, 4mg/mL) NDA 020148, and D.H.E. 45 (dihydroergotamine mesylate, 1mg/mL) Injection NDA 005929.

MIGRANAL was originally approved for use in the United States on December 8, 1997 and D.H.E. 45 Injection was approved for use in the U.S. on April 12, 1946.

TRUDHESA (dihydroergotamine)¹

Drug Class	TRUDHESA is an ergotamine
Mechanism of action	Dihydroergotamine binds with 5HT _{1Dα} and 5HT _{1Dβ} receptors. It also binds to 5HT _{1A} , 5HT _{2A} and 5HT _{2C} , noradrenaline α _{2A} , α _{2B} and α ₁ receptors and dopamine D _{2L} and D ₃ receptors.
Molecular weight	679.80 Daltons
Protein Binding	93%
Half-life	11.777 hours ± 2.8229
Absorption/Bioavailability	Poor oral bioavailability. Bioavailability after nasal spray approximately (b) (4) %
Serious Adverse Reactions	• Cardiac events in patients with risk factors for coronary artery disease. • Cerebrovascular events (cerebral hemorrhage, subarachnoid hemorrhage, and stroke) have been reported with dihydroergotamine injection. • Fibrotic complications, including pleural and retroperitoneal fibrosis, have been reported. Administration of TRUDHESA should not exceed dosing guidelines or be used for chronic daily administration. • Local irritation in the nose and throat have been reported following administration of TRUDHESA.

Current State of the Labeling of the relied upon drug MIGRANAL²

Approved labeling is not is Physician Labeling Rule formatting (PLR), and therefore not in Pregnancy and Lactation Labeling Rule (PLLR) formatting.

¹ TRUDHESA proposed package insert

² MIGRANAL (dihydroergotamine) package insert, current labeling approved 8/1/2019, Drugs@FDA

There is a boxed warning that states “Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.”

CONTRAINDICATIONS:

- Coadministration with potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is contraindicated.
- Should not be given to patients with ischemic heart disease or to patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal’s variant angina.
- Should not be given to patients with uncontrolled hypertension.
- 5HT₁ agonists (e.g., sumatriptan), ergotamine-containing, ergot-type medications, or methylsergide should not be used within 24 hours of each other.
- Should not be administered to patients with hemiplegic or basilar migraine.
- In addition to the above, it is also contraindicated in patients with known peripheral artery disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function.
- Pregnancy is included in the contraindications- the language is listed below under “Pregnancy”
- Use is contraindicated in Nursing Mothers
- Contraindicated with use of peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure.
- Contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids.

Pregnancy (Under CONTRAINDICATIONS)

- Pregnancy letter category – X
- May cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties, and therefore, should not be administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryofetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposure [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryofetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was

administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no-effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.
Nursing Mothers (also listed under CONTRAINDICATIONS) Ergot drugs are known to inhibit prolactin. It is likely that MIGRANAL (dihydroergotamine mesylate) is excreted in human milk, but there are no data on the concentration of dihydroergotamine in human milk. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in nursing infants. Because of the potential for these serious adverse events in nursing infants exposed to MIGRANAL (dihydroergotamine mesylate) Nasal Spray, nursing should not be undertaken with the use of MIGRANAL (dihydroergotamine mesylate) Nasal Spray (<i>see CONTRAINDICATIONS</i>).
Impairment of Fertility There was no evidence of impairment of fertility in rats given intranasal doses of MIGRANAL (dihydroergotamine) Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposure [AUC] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg).
Oral Contraceptives The effect of oral contraceptive on the pharmacokinetics of MIGRANAL (dihydroergotamine mesylate) Nasal Spray has not been studied.

REVIEW

PREGNANCY

Migraine and Pregnancy

Migraine is a common condition with an age-adjusted prevalence of 15.9% across all adults in the United States. It is twice as prevalent in women as compared to men.³ Migraine headache often improves during pregnancy. A systematic review suggested that women with migraine may have higher risks for cardiovascular complications during pregnancy, including gestational hypertension, preeclampsia, deep vein thrombosis and ischemic stroke.⁴

Nonclinical Experience

For information on nonclinical data and pregnancy, the reader is referred to the information in the labeling of the relied upon drug, MIGRANAL, under “Current State of the Labeling,” and to the full Pharmacology/Toxicology review by Edmund Nesti, Ph.D. and Lois Freed, Ph.D.

Reviewer Comment:

Pharmacology-toxicology revisions were not finalized at the time this review was completed.

³ Burch R, et al. The prevalence and impact of migraine and severe headache in the United States: Updated age, sex, and socioeconomic-specific estimates from government surveys. *Headache*. 2021;61:60-68.

⁴ Wabnitz A, Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. *Cephalalgia*. 2015;35(2):132-9.

Review of Information from the Phase 3 Safety Study INP104-301

The applicant reports that 4 patients became pregnant during the Phase 3 long-term safety study. All had exposure during the first trimester. Results are noted in the applicant's table below:

Table 11-29 Summary of Pregnancies – 24-Week Full Safety Set

Patient No.	Study Day of First Positive Test	Study Day of Last IP Dose	Total Doses Reported	No. of Doses at time of LMP	No. of Doses Between LMP and Pregnancy Test	Status or Outcome of Pregnancy
(b) (6)	60	26	2	1	1	Spontaneous abortion
	297	284	26	21	5	Spontaneous abortion
	116	115	5	3	2	Full term; live birth; normal infant
	112	111	18	14	4	Full term; live birth

IP = investigational product; LMP = last menstrual period; No. = number.

Study Day = date of assessment – date of enrollment.

Source: [Listing 16.2.1.2](#), [Listing 16.2.5.1](#), [Listing 16.2.8.4](#), and data on file.

Copied from applicant's clinical study report INP104-301, page 185.

Review of Literature

Applicant's Review of the Literature:

The applicant performed a search of the published literature from 1997 through June 30, 2020 using the PubMed database and Google.com with the search terms, "dihydroergotamine and pregnancy."

The applicant reports that of the 14 papers that were located, only two provided clinical cases related to dihydroergotamine exposure during pregnancy.

Applicant's Literature Search*

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Berárd A and Kori, S ⁵ 2012 Canada	Cohort study, Quebec Pregnancy Registry, which is composed of three databases	59,707 pregnant women were included. Of these, there were	Defined as a prescription filled 30 days before the last menstrual period	Major Congenital Malformations (MCMs)- No increased risk with DHE compared to unexposed	Study adjusted for maternal age, area of residence,

⁵ Berárd A, Kori S. Dihydroergotamine (DHE) use during gestation and the risk of adverse pregnancy outcomes. Headache. 2012;52:1085-1093.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
	including prescriptions, diagnoses, hospitalization, demographics, and pregnancy-related information/outcomes	53 exposed to dihydroergotamine (DHE), 139 exposed to triptans and 2990 exposed to NSAIDs during pregnancy	(LMP) or anytime during pregnancy. Dose not described	pregnant women; OR 0.97, 95% CI 0.22-4.28 Spontaneous Abortion- No increased risk with DHE compared to unexposed pregnant women OR 1.97, 95% CI 0.21-18.57 Increased risk for preterm birth with DHE exposure: OR 4.18, 95%CI 1.34-12.99	gestational age at index date maternal medical conditions
Silberstein S, et al. ⁶ 2013 US	Systematic review of the literature	MEDLINE/Pub Med search of the literature from January 1945-October 2011 of cases exposed to DHE or ergotamine during pregnancy	Not described	>350 infant with DHE exposure in utero did not show increased risk of MCMs over background prevalence. Increased risk of prematurity was reported (no statistics were provided in this abstract)	This was an abstract for a poster, with few details provided.

*Reviewer's Table

Reviewer Comment:

The two studies cited by the applicant indicate an increased risk of preterm birth with dihydroergotamine exposure during pregnancy. There was no increased risk for MCMs in either study. Berárd did not find an increased risk for spontaneous abortion; spontaneous abortion was not addressed in the poster by Silberstein.

DPMH Review of the Literature:

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex⁷ using the search terms, “dihydroergotamine” and “pregnancy,” “pregnancy outcomes,” “congenital anomalies,” “stillbirth,” and “spontaneous abortion.”

Micromedex rates dihydroergotamine as, “Fetal risk has been demonstrated.”

Reprotox⁸ states, “Dihydroergotamine decreased fetal weight in guinea pigs. There did not appear to be an increase in malformations in small human studies. Human data suggested a

⁶ Silberstein S, et al. Dihydroergotamine: A review of maternal exposure during pregnancy (P03.108) Neurology. 2013;80(7Suppl):153-154

⁷ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 04/26/2021

⁸ 2021 Reproductive Toxicology Center, accessed 04/26/2021

beneficial effect on placental vascular resistance. An association with preterm birth has been identified; possible confounding by indicated preterm delivery for preeclampsia has been suggested.”

In *Drugs in Pregnancy and Lactation*,⁹ Briggs rates dihydroergotamine as “Contraindicated” in pregnancy.

A search of the published literature located the following additional report.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre- conception; to what drug/dose	Pregnancy/Infant Outcomes
Kallen B, Lygner PE ¹⁰ 2001 Sweden	Prospective cohort study (Swedish Medical Birth Registry, July 1, 1995 -June 30, 1999)	905 deliveries of women who reported use of drugs for migraine early in pregnancy (dihydroergotamine n=52 (alone), and n=1 in combination with sumatriptan)	First trimester	No increased risk for fetal malformations (3.1% [all migraine medications- DHE not separately analyzed]) compared to the population risk in Sweden (3.6%) No cases of major malformations with DHE exposure. Minor malformations reported with DHE included: One case of a preauricular tag and one case of an infant with an undescended testicle There was “unstable hip” noted with the infant exposed to the DHE/sumatriptan combination There was a non-significant increase in preterm birth and low birth weight in infants exposed to migraine medications overall.

Reviewer comment:

A search of the literature resulted in one additional study not reported by the applicant. The applicant performed an adequate review of the literature. All the studies indicate an increased risk for preterm birth with dihydroergotamine exposure during pregnancy. This is consistent with the oxytocic properties of dihydroergotamine. While the published literature is limited,

⁹ Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 10th Ed. 2015. Online, accessed 11/25/2019 4/26/2021

¹⁰ Kallen B, Lygner PE. Delivery outcomes in women who used drugs for migraine during pregnancy with special reference to sumatriptan. *Headache*. 2001;41:351-356.

dihydroergotamine has been marketed for decades and there does not appear to be an increased risk of fetal malformations.

LACTATION

Nonclinical Experience

Ergot alkaloids are present in animal milk.¹¹

Review of Pharmacovigilance Database

The applicant reports no cases of lactation during the clinical studies.

Review of Literature

Applicant's Review of Literature:

The applicant performed a search of the published literature from 1997 through June 30, 2020, using the PubMed database and Google.com with the search terms, "dihydroergotamine and lactation."

The applicant does not cite any references located in the search.

DPMH Review of the Literature:

DPMH conducted a search of *Medications in Mother's Milk*, the Drugs and Lactation Database (LactMed),¹² Micromedex,¹³ and of the published literature in PubMed and Embase using the search terms "dihydroergotamine" and "lactation" or "breastfeeding."

Micromedex states, "Infant risk has been demonstrated."

Hale¹⁴ rates ergotamine products as, "L-4- Limited Data-Possibly Hazardous," and goes on to state, "Although early reports suggest ergotamine compounds are secreted in breastmilk and cause symptoms of ergotism (vomiting and diarrhea) in infants, other authors suggest that the short term use of ergotamine (0.2 mg postpartum) generally presents no problem to the nursing infant. This is likely, due to the fact that less than 5% of ergotamine is orally absorbed in adults. However excessive dosing and prolonged administration may inhibit prolactin secretion and hence, lactation. Although the initial plasma half-life is only 2 hours, ergotamine is stored for long periods in various tissues producing long-lasting effects (terminal half-life = 21 hours). Prolonged use during lactation should be strongly discouraged. Single use is probably OK due to low oral bioavailability. Major concern is hyperprolactinemia."

¹¹ Iwamura S, Kambegawa A. Determination of methylergometrine and dihydroergotoxine in biological fluids. *J Pharm Dyn.* 1981;4:275-281.

¹² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹³ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 04/26/2021

¹⁴ Hale, Thomas. Hale's Medications and Mother's Milk, online, <https://www.halesmeds.com/monographs/61547?q=lexapro>, accessed 04/26/2021

In *Drugs in Pregnancy and Lactation*,¹⁵ Briggs rates dihydroergotamine as “Contraindicated” in breastfeeding.

Ergotamine is referenced in the LactMed¹⁶ (there is no separate entry for dihydroergotamine) which states, “Because there is limited published experience with ergotamine during breastfeeding and it might cause adverse effects in the infant, most authorities consider ergotamine to be undesirable during nursing.”

A search of the published literature did not produce any additional cases of lactation and dihydroergotamine.

Reviewer comment:

The applicant did not provide any information from their search of the literature. Overall, few cases have been described with ergotamine products and lactation. Most authors do not recommend that dihydroergotamine be used during breastfeeding due to effects on prolactin and potential adverse effects in the breastfed infant. Current labeling states, “It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants.”

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

For information on nonclinical data and fertility, the reader is referred to the information in the labeling of the relied upon drug, MIGRANAL, under “Current State of the Labeling,” and to the full Pharmacology/Toxicology review by Edmund Nesti, Ph.D. and Lois Freed, Ph.D.

Reviewer Comment:

Pharmacology-toxicology revisions were not finalized at the time this review was completed.

Review of Pharmacovigilance Database

The applicant did not report cases of infertility in the clinical studies.

Review of Literature

Applicant’s Review of Literature:

The applicant performed a search of the published literature from 1997 through June 30, 2020 using the PubMed database and Google.com with the search terms, “dihydroergotamine and reproduction.”

The applicant states that there was no new information about reproduction beyond that described in the referenced drug labeling.

¹⁵ Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 10th Ed. 2015. Online, accessed 04/26/2021

¹⁶ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

DPMH Review of the Literature:

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, “dihydroergotamine” and “fertility,” “contraception,” “oral contraceptives,” and “infertility.”

No reports of infertility or interactions with hormonal contraception were located in the search.

Reviewer comment:

The DPMH review of the literature aligns with the applicant’s lack of findings related to reproduction and dihydroergotamine. The applicant performed an adequate search of the literature.

DISCUSSION AND CONCLUSIONS

Pregnancy

Dihydroergotamine has been marketed in the United States since 1946. Because of its oxytocic properties, current labeling indicates that it is contraindicated for use during pregnancy. Limited published data indicate that use during pregnancy may be associated with an increased risk for preterm birth and this is consistent with the drug’s potential oxytocic effect. However, the human data do not identify any associations with major congenital malformations. Therefore, labeling changes should be considered (i.e., Warnings and Precautions for preterm birth may be more appropriate than a Contraindication).

Migraine is prevalent in women of reproductive age. However, dihydroergotamine has been marketed for over 60 years, so it is unlikely that a pregnancy registry or complementary study would provide new information. Therefore, postmarketing pregnancy studies are not recommended.

Lactation

Ergotamine compounds are known to be present in human milk, and there are reports of diarrhea vomiting, weak pulse, and unstable blood pressure in breastfed infants. Ergotamine and related compounds are known to decrease prolactin, and therefore, can adversely affect milk production. Current labeling of dihydroergotamine compounds indicate that they are contraindicated during breastfeeding. DPMH recommends removing the breastfeeding contraindication. A breastfeeding contraindication is typically included for drugs that can directly cause harm to the breastfeeding patient. Since dihydroergotamine use is not recommended during lactation due to the potential effects on milk production and adverse effects to the breastfed infant, DPMH recommends including the following language in subsection 8.2:

“Because of the potential for reduced milk supply and serious adverse reaction in the breastfed infant, including diarrhea, vomiting, weak pulse and unstable blood pressure, advise patients not to breastfeed during treatment with TRUDHESA and for XX hours after the last dose.”

Since ergotamine is known to be present in human milk and there is already information about effects of ergotamine on milk production and adverse effects observed in breastfed infants in approved labeling, a clinical lactation study is not recommended at this time.

Reviewer Comment:

Clinical Pharmacology determination of the number of hours to withhold breastfeeding after the last dose of TRUDHESA was pending at the time this review was completed.

Females and Males of Reproductive Potential

Nonclinical data do not indicate an adverse effect of dihydroergotamine on animal reproduction. No data were found indicating an adverse effect on male or female fertility or adverse effects on hormonal contraception. Data do not indicate that dihydroergotamine is a major teratogen, so pregnancy testing and contraception are not required. Nonclinical data can remain in Section 13. Subsection 8.3 will not be included in labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CATHERINE A ROCA
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LYNNE P YAO
07/01/2021 10:17:46 AM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	11/17/2020		
To:	Erica Keafer		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	OPRO/DRBPMI/RBPMB1
From	Michaela Schulman OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Acting Director OPEQ/OHT3/DHT3C		
Subject	NDA 213436 , INP104 (POD-DHE) ICC2000970 Case 00038973		
Recommendation	Filing Recommendation Date: 12/4/2020 ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Mid-Cycle Recommendation Date: 2/1/2021 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☒ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 4/26/2021 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Michaela L. Schulman -S Digitally signed by Michaela L. Schulman -S Date: 2021.04.26 08:56:00 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2021.04.26 09:14:31 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 213436
Sponsor	Impel Neuropharma
Drug/Biologic	INP104 (POD-DHE)
Indications for Use	Acute treatment of migraine headaches with or without aura
Device Constituent	Nasal Spray
Related Files	N/A

Review Team		
Lead Device Reviewer	<i>Michaela Schulman</i>	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
None	None	None

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	4/13/2021
Interim Due Dates	Meeting/Due Date
Filing	12/21/2020
74-Day Letter	1/19/2021
Mid-Cycle	3/29/2021
Primary Review	4/13/2021
Internal Meeting(s)	N/A
Sponsor Meeting(s)	N/A

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☒ Approvable with PMC or PMR, [See Section 2.3](#)
- ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	HF reviewed by DMEPA
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

- ☐ CDRH does not have any further comments to convey to the review team.
- ☒ CDRH has the following comments to convey to the review team:

Comment #1: The sponsor proposed a device constituent shelf life of (b) (4) years (b) (4) months). However, the completed accelerated stability testing only supports a shelf life of (b) (4) months at 25°C ± 2°C/60% RH ± 5%. Additionally, the sponsor proposed only performing (b) (4) months of real-time stability testing. The device constituent parts of the combination product are approvable only for a shelf life of (b) (4) months at 25°C ± 2°C/60% RH ± 5. The sponsor should perform real-time stability testing at 25°C ± 2°C/60% RH ± 5% over the full device constituent shelf-life of (b) (4) months.

CDRH defers to CDER regarding the overall shelf life of the INP104 combination product (includes the vial of DHE) as the sponsor states that the overall INP104 combination product shelf life is (b) (4) months.

2.2. Complete Response Deficiencies

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☒

TABLE OF CONTENTS

1. SUBMISSION OVERVIEW.....	2
2. EXECUTIVE SUMMARY AND RECOMMENDATION.....	3
2.1. Comments to the Review Team.....	3
2.2. Complete Response Deficiencies.....	3
2.3. Recommended Post-Market Commitments/Requirements.....	3
3. PURPOSE/BACKGROUND.....	6
3.1. Scope.....	6
3.2. Prior Interactions.....	6
3.2.1. Related Files.....	6
3.3. Indications for Use.....	6
3.4. Materials Reviewed.....	6
4. DEVICE DESCRIPTION.....	6
4.1. Device Description.....	6
4.2. Steps for Using the Device.....	9
4.3. Device Description Conclusion.....	10
5. FILING REVIEW.....	10
5.1. Filing Review Checklist.....	10
5.2. Facilities Information.....	11
5.3. Quality System Documentation Triage Checklist.....	12
5.4. Filing Review Conclusion.....	13
6. LABELING.....	13
6.1. General Labeling Review.....	13
6.2. Device Specific Labeling Review.....	14
6.3. Clinical Labeling Review.....	17
6.4. Labeling Review Conclusion.....	17
7. DESIGN CONTROL SUMMARY.....	17
7.1. Summary of Design Control Activities.....	17
7.2. Design Inputs and Outputs.....	18
7.3. Applicable Standards and Guidance Documents.....	19
7.4. Design Control Review Conclusion.....	21
8. RISK ANALYSIS.....	21
8.1. Risk Management Plan.....	21
8.2. Hazard Analysis and Risk Summary Report.....	24
8.3. Risk Analysis Review Conclusion.....	24
9. DESIGN VERIFICATION REVIEW.....	26
9.1. Performance/Engineering Verification.....	26
9.1.1. Essential Performance Requirement Evaluation (Verification, Stability & Shipping: 3.2.R document device-dhf-0182; Validation: device-dhf-0183 ;.....	26
9.1.2. Verification of Design Inputs Evaluation.....	28
9.1.3. Evaluation of Test Methods.....	30
9.2. Reliability Verification Review.....	43
9.3. Design Verification Review Conclusion.....	43
9.4. Biocompatibility Review:.....	43
9.5. Discipline Specific Sub-Consulted Review Summary.....	44
10. CLINICAL VALIDATION REVIEW.....	44

10.1.	Review of Clinical Studies Clinical Studies.....	44
10.2.	Clinical Validation Review Conclusion	45
11.	HUMAN FACTORS VALIDATION REVIEW	45
12.	FACILITIES & QUALITY SYSTEMS	45
12.1.	Facility Inspection Report Review	45
12.2.	Quality Systems Documentation Review	45
12.2.1.	Description of the Device Manufacturing Process.....	45
12.2.2.	cGMP Review	46
12.2.3.	Corrective and Preventive Action Review	48
12.3.	Control Strategy Review	49
12.4.	Facilities & Quality Systems Review Conclusion.....	50
13.	APPENDIX A (INFORMATION REQUESTS)	51
13.1.	Filing/74-Day Information Requests	51
13.2.	Mid-Cycle Information Requests	51
13.3.	Interactive Information Requests.....	62
13.3.1.	Interactive Information Requests sent on 3/30/2021.....	62

3. PURPOSE/BACKGROUND

3.1.Scope

Impel Neuropharma is requesting approval of INP104 (POD-DHE). The device constituent of the combination product is a Nasal Spray.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

Technical engineering consult for I123 POD device

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device performance, biocompatibility (non-drug contact components only), clinical study (device components only), quality systems and facilities inspection recommendation
--

This review will not cover the following review areas:

Human Factors (covered by DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2.Prior Interactions

N/A

3.2.1. *Related Files*

N/A

3.3.Indications for Use

Combination Product	Indications for Use
INP104 (POD-DHE) in a vial	Acute treatment of migraine headaches with or without aura
Nasal Spray	Delivery of the Drug Product

3.4.Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	3.2.P.7 Container Closure System
0001	3.2.R Regional Information
0001	3.2.P.5 Control of Drug Product
0001	1.4.2 Statement of Right to Reference
0001	1.14.1.1 Draft Carton and Container Labels
0001	3.2.P.3 Manufacture

4. DEVICE DESCRIPTION

4.1.Device Description

INP104 is a single-use, metered dose nasal DHE (dihydroergotamine mesylate) combination product that is co-packaged with the DHE drug constituent in a vial and the I123 Precision Olfactory Delivery (POD) device. The INP104 drug comes in a 3.5 mL (b) (4) glass vial with a rubber stopper and seal. The vial is packaged with the I123 POD device within a (b) (4) plastic clamshell.

Materials:

Component	Manufacturer/ Address	Type III DMF	Material/ Manufacturer of Construction
Vial	(b) (4)		
Stopper			
Seals			

Table 7: Components, Parts, and Materials of INP104

Component	Part ID	Part Name	Material	Supplier	Fluid Path Yes/No	DMF/ Certifications
Device	(b) (4)					

Table 7: Components, Parts, and Materials of INP104 (Continued)

Component	Part ID	Part Name	Material	Supplier	Fluid Path Yes/No	DMF/ Certifications
Device	(b) (4)					

Table 7: Components, Parts, and Materials of INP104 (Continued)

Component	Part ID	Part Name	Material	Supplier	Fluid Path Yes/No	DMF/ Certifications
Device	(b) (4)					
Drug						

Figure 1: Clam Shell Drawing (b) (4), Packaging, as Molded) (b) (4)



Figure 3: Placement of the Index and Middle Fingers into the Notches and Finger Grips of INP104 with Thumb Located Beneath Drug Vial



3A. INP104 assembled. 3B. INP104 assembled, in use

Figure 4: Diagram of Fluid Path in INP104



Figure 1: INP104 Case (Clamshell) Opened with IFU, DHE DP (Glass Vial), and I123 POD Device

4.2.Steps for Using the Device

1. When ready to dose, the user removes the plastic cover, foil and stopper from the glass vial.

v05.02.2019

2. The user then attaches the drug product containing glass vial to the device.
3. The device is then primed by pumping it 4 times.
4. One complete dose is administered by self-administration as one spray into each nostril.
5. The assembled device is disposed after the dose is given.

4.3.Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The device description is adequate		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ Finalize Filing Review Section	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1.Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		

	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

The sponsor provided all information needed to file.

5.2.Facilities Information

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Inspects, assembles and certifies the I123 POD device constituents in packaging clamshell
<u>Inspectional History</u> An analysis of the firm's inspection history over the past 2 years: ☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item.. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☒ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
<u>Inspection Recommendation:</u> ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☒ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.	

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Bioburden testing of I123 POD device, biocompatibility testing
<u>Inspectional History</u> An analysis of the firm's inspection history over the past 2 years: ☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item.. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.	

☒ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

☐ A [choose an item](#) inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,

A recent medical device inspection of the firm [Choose an item](#).

☒ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Firm Name:	Impel NeuroPharma
Address:	201 Elliott Ave W., Suite 260 Seattle, WA 98119 USA
FEI:	N/A
Responsibilities:	I123 POD device component inspection, review of assembly and release. Review of INP104 documentation prior to release

Inspectional History

An analysis of the firm's inspection history over the past 2 years:

☐ Inspection was conducted [Click or tap to enter a date.](#) to [Click or tap to enter a date.](#). The inspection covered [Choose an item](#), and was classified [Choose an item](#).

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☒ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

☐ A [choose an item](#) inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,

A recent medical device inspection of the firm [Choose an item](#).

☒ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Add Additional Facility

5.3.Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☒ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK

Is the final combination product meant for emergency use?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment None.

5.4.Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☒ No Inspection ☐ N/A	
Site(s) needing inspection:	
<u>Reviewer Comments</u> The sponsor provided all information needed to file.	
Refuse to File Deficiencies: ☐ Yes ☐ No ☒ N/A	
74-Day Letter Deficiencies: ☐ Yes ☐ No ☒ N/A	

Add Additional Information Request

6. LABELING

6.1.General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

v05.02.2019

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

All required labeling was included. HF validation study for review by DMEPA is in 5.3.5.4

6.2.Device Specific Labeling Review

The instructions for use are reviewed by the lead reviewer. The instructions for use was taken from 1.14.1.3 labeling-text-ifu.

(b) (4)

Reviewer Comments

The labeling appears adequate. It will be further analyzed as part of the human factors review by DMEPA.

6.3.Clinical Labeling Review

The following Clinical Labeling Review was completed by

☐ Insert Consultant Name ; The full memo is located in [Appendix B.](#)

☐ The Lead Reviewer

Below is a summary of the review & [recommendation](#):

N/A

6.4.Labeling Review Conclusion

LABELING REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☒ No ☐ N/A

Mid-Cycle Deficiencies:

☐ Yes ☒ No ☐ N/A

Final Deficiencies:

☐ Yes ☒ No ☐ N/A

[Reviewer Comments](#)

The device labeling is adequate.

CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No

7. DESIGN CONTROL [SUMMARY](#)

7.1.Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A	Note
Risk analysis conducted on the combination product	X			
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X			
Mitigations are adequate to reduce risk to health		X		

Version history demonstrates risk management throughout design / development activities	X			
Design Inputs/Outputs	Yes	No	N/A	
Design requirements / specifications document present (essential performance requirements included)	X			
Design Verification / Validation Attributes	Yes	No	N/A	
Validation of essential requirements covered by clinical and human factors testing	X			Clinical and HF testing provided. Some EPRs are not validated See MC Deficiency Resolved
To-be-marketed device was used in the pivotal clinical trial	X			It is unclear if the to-be-marketed device was used in both clinical trials. See MC Deficiency Resolved
Bioequivalence Study utilized to-be-marketed device			X	
Verification methods relevant to specific use conditions as described in design documents and labeling	X			
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X			Not an emergency use combination product.
Traceability demonstrated for specifications to performance data	X			3.2.R device-dhf-0100

Reviewer [Comments](#)

Risk Analysis issues are identified in the Risk Analysis section of this review.

dFMEA is missing information. See **MC Deficiency** – The sponsor provided updated dFMEA/risk analysis. **Resolved**

7.2.Design Inputs and Outputs

Essential Performance Requirements

(b) (4)

Reviewer [Comments](#)

Sample sizes in 3.2.R Verification Testing are very small (n=3 to n=14). The sponsor does not identify their statistical methodology for selecting sample sizes. **MC Deficiency** **Resolved**

7.3.Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents: (3.2.R document 32r1p32-device-standards)

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	N – MC Deficiency Resolved
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	N – MC Deficiency Resolved
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y
ISTA 3A:2018 Simulated Shipping Testing	Y

Table 1: List of Standards

Standard	Title
ISO 13485: 2016	Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes
ISO 14971: 2012 ^a	Medical Devices – Application of Risk Management to Medical Devices
ISO/TR 24971: 2020	Medical Devices – Guidance on the Application of 14971
EN ISO 10993-1: 2009 ^a	Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process
EN ISO 10993-1: 2016 ^a	Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process
ISO 10993-5: 2009 ^a	Biological Evaluation of Medical Devices – Part 5: Tests for In vitro Cytotoxicity
ISO 10993-10: 2010 ^a	Biological Evaluation of Medical Devices – Part 10: Tests for Irritation and Skin Sensitization
ISO 10993-11: 2006 ^a	Biological Evaluation of Medical Devices – Part 11: Tests for Systemic Toxicity
ISO 10993-12: 2012	Biological Evaluation of Medical Devices – Part 12: Sample Preparation and Reference Materials
ISO 10993-17: 2002 ^a	Biological Evaluation of Medical Devices – Part 17: Establishment of Allowable Limits for Leachable Substances
ISTA 3A	Packaged Products for Parcel Delivery System Shipments 70kg (150 lb) or Less (Standard, Small, Flat or Elongated)
ISTA 3E	Similar Packaged Products in Unitized Loads for Truckload Shipment
ISO 11608-1: 2014	Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-based Injection Systems
IEC 62366-1: 2015 ^a	Medical Devices – Part 1: Application of Usability Engineering to Medical Devices
IEC 62366-2: 2016	Medical Devices – Part 2: Guidance of the Application of Usability Engineering to Medical Devices
ISO/IEC 17025: 2017	General Requirements for the Competence of Testing and Calibration Laboratories
IEC 62366-1: 2015	Medical Devices – Application of Usability Engineering to Medical Devices

Table 1: List of Standards (Continued)

Standard	Title
ASTM F1980-07	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
ICH Q8	Pharmaceutical Development
ICH Q9	Quality Risk Management
USP <87>	Biological Reactivity Tests, In Vitro
USP <88>	Biological Reactivity Tests, In Vivo
USP Class VI	USP Classification of Plastics
USP <788>	Particulate Matter in Injections
USP <232>	Elemental Impurities – Limits
USP <233>	Elemental Impurities – Procedures
USP <1111>	Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use

APPEARS THIS WAY ON ORIGINAL

Table 2: List of FDA Guidances

Title
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation
Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.
Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. Draft Guidance for Industry and FDA Staff
Applying Human Factors and Usability Engineering to Medical Devices. FDA-CDRH Guidance
Guidance on Medical Device Patient Labeling. FDA-CDRH Final Guidance for Industry and FDA Reviewers
Safety Considerations for Product Design to Minimize Medication Errors. FDA CDER
Design Considerations for Devices Intended for Home Use. FDA CDRH Guidance
Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design And Development
Guidance for Industry and FDA Staff: Applying Human Factors and Usability Engineering to Medical Devices

Reviewer Comments

- For ASTM D4169-09, the sponsor performed testing using ISTA 3A Simulated Shipping Testing. They provided a thorough comparison to demonstrate how the two are equivalent. This is reasonable.
- The sponsor clarified that they used cGMP. This is reasonable.
- ISO 14971: Sponsor states conformance with 2012 version, not FDA recognized. However, the sponsor conforms to the recognized 2019 version in their Risk Management Plan.

7.4.Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer <u>Comments</u> See MC Deficiencies.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

8. RISK ANALYSIS

8.1.Risk Management Plan



Reviewer Comments

See above.

8.3.Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

ICC2000970
NDA 213436 ,INP104 (POD-DHE)
Impel Neuropharma

Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments See MC Deficiencies		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

9. DESIGN VERIFICATION REVIEW

9.1.Performance/Engineering Verification

9.1.1. *Essential Performance Requirement Evaluation* (Verification, Stability & Shipping: 3.2.R document device-dhf-0182; Validation: device-dhf-0183 ;

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Spray Content Uniformity	The product shall deliver a dose of 1.45 mg (b) (4) of DHE. (b) (4) For acceptance: a) 18 of 20 doses shall fall within 1.45mg DHE (b) (4) with none outside of 1.45mg DHE (b) (4) b) Of the 20 samples tested, the mean of the SCU results for the 6 products testing from the beginning of the batch, the mean of the results for the 8 products tested from the middle and the mean of the 6 products tested from the end shall fall within 1.45mg DHE (b) (4) If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside (b) (4) dose label claim but none are outside of (b) (4) of dose label claim and the means for each of the beginning, middle, and end determination are not outside of (b) (4) of dose label claim, a second tier of batch testing will occur.	Y	Y**	Y	Y***
Spray Pattern	For each sample, the results of the spray pattern testing at 6cm for spray 5 and spray 6 shall be averaged, the resulting mean shall conform to the following: Dmax: (b) (4) Ratio (Dmax/Dmin): (b) (4) Shape: (b) (4)	Y	Y**	Y	Y***

Droplet Size Distribution	For each sample, the results of the droplet size distribution testing at 6cm for spray 5 and spray 6 shall be averaged, the resulting mean shall be characterized for typical performance	Y*	Y	Y	Y***
Actuation Force	For each sample, the force to actuate the product during the actuation of spray 5 and spray 6 shall be averaged, the resulting mean shall be within (b) (4)	Y	Y**	Y	Y***
Plume Geometry	For each sample, the results of the plume geometry testing at 6cm for spray 5 and spray 6 shall be averaged, the resulting mean shall be characterized for typical performance.	Y*	Y	Y	Y***
Spray Actuation Content (Valve Delivery/Delivered Dose)	(b) (4)	Y*	Y	Y	N

Aging/Stability Testing: 32p81-stability-summary-conclusion & 3.2.P.8.1 device-rpt-080275-01-06

- ^Shelf Life of device constituents: (b) (4) months at 25°C ± 2°C/60% RH ± 5%

(b) (4)

Reviewer Comment

- Spray Actuation Content (Valve Delivery/Delivered Dose) are verified by the HFA manufacturer (b) (4) as part of lot release. Per CDER Nasal Spray Guidance, “Acceptance testing for pump delivery on incoming pump lots can substitute for the release testing of pump delivery for the drug product, if justified. However, the acceptance criteria for pump delivery should be included in the drug product specification.” This is sufficient and can substitute release testing. Note: Spray Actuation Content (Valve Delivery/Delivered Dose) verification testing was performed by supplier (b) (4). – see 32p2-pharmaceutical-development and device-dhf-0199 and is verified on-release.
- ^The proposed shelf life changes (b) (4)

Will convey in response to sponsor and CDER. IR#2 – Sponsor confirmed a shelf-life of (b) (4) months for the device constituents. Resolved

- *The sponsor only provided method/testing summaries for droplet size distribution, plume geometry and spray actuation content. No full test methods or protocol. **MC Deficiency** – Full methods were provided. **Resolved**
- For verification testing and release testing, sponsor doesn't support sample sizes with confidence/reliability calculations. **MC Deficiency** – Updated **Resolved**
- **The sponsor does not conform to ASTM D4169-16. They only perform drop testing – their drop testing was performed per ISO 11608-1:2014 (this is a needle ISO that they translated for nasal spray). They also did not perform shipping testing on all EPRs. **MC Deficiency** – The sponsor provided a sufficient comparison of ASTM D4169-16 and ISTA 3A 2018. **Resolved**
- ***Validation is using INP104-101 and INP104-301 clinical studies. The sponsor hasn't verified that the final finished device was used in INP104-101 to support validation of the device. **MC Deficiency** – Updated **Resolved**
- Droplet Size Distribution, Plume Geometry and Spray Actuation Content (Delivered Dose) are not included in the validation plan or validation report. **MC Deficiency** – Updated **Resolved**
- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

9.1.2. *Verification of Design Inputs Evaluation*



9.2.Reliability Verification Review

Since this device is not an emergency use device, reliability testing is not required.

9.3.Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments See MC Deficiencies		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

9.4.Biocompatibility Review:

CDER is responsible for the device components that are part of the fluid path. Under this review, the mucosal/skin contacting devices were evaluated per ISO 10993-1 for biocompatibility testing for medical devices.

4.1.6.5. Biocompatibility / Toxicology

Impel has performed a biocompatibility assessment for the INP104 product in accordance with the FDA guidance document, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (2016, CDRH). The I123 POD device constituent is classified as a surface device, mucosal membrane contact, (A) ≤ 24 hours. This classification identifies three tests as required per Table A.1 of the standard: cytotoxicity, irritation, and sensitization testing. A summary of the study results are provided in Section 4.1.6.5.1, Section 4.1.6.5.2, and Section 4.1.6.5.3 for cytotoxicity, irritation, and sensitization, respectively, with references to the full study reports.

In addition to the biocompatibility testing performed on the clamshells, biocompatibility testing was performed on the two colorants that have been used for the finger grip component in the clinical and commercial configurations of the product (b) (4). These colorants are identified by their supplier, (b) (4). Both colorants were tested following the requirements in USP <1031> and were found to meet the requirements of a Class VI product. Please refer to DMF (b) (4) for details of the testing for the (b) (4).

Given the amount of contact that the patient will be using the device, a contact duration of less than 24 hours was used. The sponsor identifies the I123 POD as the mucosa membrane contacting device; therefore, they state that Cytotoxicity, Sensitization, and Irritation testing was completed. However, the sponsor provided biocompatibility testing performed on the I123 POD clamshell exterior, not on the I123 POD device. They state that the clamshell components are the only patient-contacting components.

Biocompatibility information is provided in 32p2-pharmaceutical-development. The biocompatibility testing performed on the two colorants used for the finger grip component is provided in DMF (b) (4). The acceptability of the finger grip components (including colorants) should be addressed in the I123 POD biocompatibility testing.

Reviewer Comment

- The sponsor does not provide the biocompatibility testing performed on the I123 POD actuator device. They only perform testing on the clamshell casing. **MC Deficiency** – The sponsor provided biocompatibility testing on the patient contacting component. **Resolved**

9.5.Discipline Specific Sub-Consulted Review Summary

- ☒ No Additional Discipline Specific Sub-Consults were requested
- ☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
- ☒ There are clinical studies for review

This information was obtained from the following [documents](#): 276-synopses-individual studies in 2.7.6.

Two clinical studies were performed:

- A Phase 1 comparative bioavailability study in healthy adult subjects (Study INP104-101)
 - *INP104 was self-administered, with a single dose achieved through 2 actuations, 1 to each nostril, to deliver a total target dose of 1.45 mg DHE. Batch Number for DHE product: 0011705; PPP.17.1198. Batch Number for I123 POD device: 72399*
- A Phase 3 open-label long-term safety and tolerability study in patients with migraine headaches with or without aura (Study INP104-301)
 - *The IP used in this study was INP104. INP104, provided as a co-packaged drug-device combination product that includes a drug constituent (DHE drug product) and a device constituent (I123 POD device), was self-administered by patients. INP104 (co-packaged) labeled lot numbers: N185091.01, N185091.02, N185091.03, N185091.05, N185091.06, N185091.07, N185091.08, N185091.09, N185091.10, and N185091.13.*

Table 1: Listing of Clinical Studies

Type of Study	Study Number	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1	INP104-101 Protocol SAP	Module 5.3.1.2	Compare the BA of dihydroergotamine following a single dose administration of INP104 (nasal) to that of the LDs (D.H.E. 45 Injection and Migranal Nasal Spray)	3-period, 6-sequence, 3-way, randomized, open-label, single-dose, crossover comparative BA study Comparators: D.H.E. 45 Injection (IV) and Migranal Nasal Spray (nasal)	INP104 One spray per nostril (total 1.45 mg DHE); Nasal D.H.E. 45 Injection 1 mg DHE (1-minute IV injection of 1 mL) Migranal Nasal Spray One spray to each nostril, followed by an additional spray in each nostril 15 minutes later for a total of 4 sprays; Nasal	36	Healthy adult volunteers	A single dose	Completed; final CSR
Phase 3	INP104-301 Protocol SAP	Module 5.3.5.2	Assess the safety and tolerability of INP104, including changes in nasal mucosa and olfactory function	Open-label, long-term safety study Single arm	INP104 One spray per nostril (total 1.45 mg DHE); maximum of 2 doses in a 24-hour period and 3 doses in a 7-day period Nasal	354	Adult patients with migraine headaches with or without aura	Up to 52 weeks	Completed; final CSR

BA = bioavailability; CSR = clinical study report; DHE = dihydroergotamine mesylate; LD = listed drug; IV = intravenous; SAP = statistical analysis plan.

Reviewer Comment:

For the Phase 1 study (Study INP104-101), it is unclear if the final finished product was used. **MC Deficiency** – The sponsor confirmed that the final finished product was used in the clinical study. **Resolved**

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments See MC Deficiencies		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☒

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

(b) (4)

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☒ Yes

☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☒ N/A

Mid-Cycle Deficiencies:

☒ Yes ☐ No ☐ N/A

Final Deficiencies:

☐ Yes ☒ No ☐ N/A

Reviewer Comments

See MC Deficiencies

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No

<<END OF REVIEW>>

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/s/

ERICA F KEAFER
04/26/2021 12:57:37 PM



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 24, 2021

To: Nicholas Kozauer, MD, Director (Acting)
Division of Neurology 2

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: **Product:** Dihydroergotamine mesylate nasal spray (DHE; INP104) trade name: Trudhesa
NDA number: 213436
Indication: Treatment of migraine, with or without aura
Dosages: 1.45 mg DHE in two sprays, one spray in each nostril, up to twice a day
Sponsor: Impel NeuroPharma

Materials reviewed: NDA for Trudhesa (November 6, 2020)

I. Background

The Division of Neurology II (DN2) consulted CSS regarding NDA 213436 for dihydroergotamine mesylate (DHE) nasal spray (utilizing the I123 Precision Olfactory Delivery device), which was submitted on November 6, 2020, by Impel NeuroPharma.

Trudhesa is proposed for the treatment of migraine headaches, with or without aura. The NDA for Trudhesa was submitted under the 505(b)(2) pathway, referencing DHE45 Injection (NDA 05929) for safety and Migranal Nasal Spray (NDA 20148) for efficacy. Each bottle of Trudhesa will contain 4 mg DHE, 10 mg caffeine, and 50 mg dextrose in 1 mL of water.

DHE is an ergot alkaloid that has been marketed as a treatment for migraine since 1946. It is currently marketed as Migranal and DHE45 for acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes. DHE is currently available in these products as a nasal spray and in ampules for subcutaneous, intramuscular, and intravenous injection.

Adverse events described in the drug label for the marketed DHE products include “vasospasm, paraesthesia, hypertension, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, and increased sweating.”

The Sponsor conducted a bioavailability study with Trudhesa but did not conduct a bioequivalency study. Local safety was assessed from a Phase 3 clinical safety study in patients with migraine. The Sponsor claims that the novel device allows for a more consistent drug uptake but lower systemic exposure due to delivery of DHE to the upper nasal passages. The NDA states that, “The drug formulation of DHE Nasal Spray solution in INP104 is the same as that of the commercially available Migranal Nasal Spray and is manufactured by the same contract manufacturing organization (Mipharm).”

The therapeutic effects of DHE are thought to occur as the result of its agonist activity at serotonin 5HT_{1B} and 5HT_{1D} receptors. Neither of these receptors are associated with abuse potential. Dihydroergotamine is not a scheduled drug under the Controlled Substances Act.

II. Conclusions

DHE has been marketed since 1946 and is not controlled under the Controlled Substances Act as a drug of abuse. Its mechanism of action as a serotonin 5HT_{1B} and 5HT_{1D} agonist is not associated with abuse potential.

III. Recommendation

CSS has determined that there is no need for an abuse potential assessment to be conducted on NDA 213436 for Trudhesa. Should any abuse-related questions or concerns arise during the review cycle, DN2 may contact us again to address them.

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/s/

KATHERINE R BONSON
03/24/2021 10:55:47 AM

CHAD REISSIG
03/25/2021 09:20:21 AM

DOMINIC CHIAPPERINO
03/25/2021 10:20:31 AM

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 1/27/2021

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 213436

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: NDA (b) (4)

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation:

(b) (4)

After receiving a written response from the site, OSIS determined that the site's response adequately addressed the observed concern and that the data from the audited study (b) (4) are reliable ([OSIS Final EIR Review - \(b\) \(4\) Inspection](#)).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
01/27/2021 10:22:47 AM

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 1/26/2021

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 213436

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in December 2017. The inspection was conducted under the following submission: BLA 761073.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale provided above, an inspection not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Nucleus Network, Ltd.	The Centre for Clinical Studies, 5 th Floor, Burnet Tower, AMREP Precinct, 89 Commercial Road, Melbourne, Victoria, Australia

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/s/

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