CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213436Orig1s000

SUMMARY REVIEW

Summary Review

Date	September 2, 2021
From	Heather Fitter, M.D. Nick Kozauer, M.D.
Subject	Summary Review
NDA #	213426
Applicant	Impel NeuroPharma, Incorporated
Date of Submission	November 6, 2020
PDUFA Goal Date	September 6, 2021
Proprietary Name / Established (USAN) names	INP104/ Dihydroergotamine mesylate and Precision Olfactory Delivery device
Dosage forms / Strength	Nasal spray/ 1.45 mg
Proposed Trade Name	Trudhesa
Recommended Indication	Acute treatment of migraine with or without aura in adults
Recommended:	Approval

1. Introduction

The applicant, Impel NeuroPharma, Inc., submitted a 505(b)(2) application for a drug/device combination product for the acute treatment of migraine with and without aura in adults.

The drug product, INP104, is composed of dihydroergotamine (DHE) and I123 Precision Olfactory Delivery (POD) device. The I123 POD device component is designed to administer DHE into the upper nasal space using hydrofluoroalkane-134a (HFA) gas as a propellant. The applicant is using two listed drugs (LDs) to support this application, Migranal (NDA 20148) to support efficacy and DHE 45 injection (NDA 05929) to support safety. The proposed dosing regimen is a single total dose of 1.45 mg DHE nasal spray divided over two sprays (one spray to each nostril), with a maximum of two doses (total of 2.90 mg) over 24 hours, and a maximum of three doses (total of 4.35 mg) over 7 days.

Dosing for Migranal and INP104 are different, since Migranal is administered as four 0.5 mg/0.125 mL sprays with 2 sprays given initially, and then another 2 sprays given fifteen minutes later for a 2 mg total dose. The Migranal label states that no additional benefit has been demonstrated from acute doses greater than 2 mg for a single migraine administration. INP104 is administered as two 0.725 mg/0.181 mL sprays for a total dose of 1.45 mg. The recommended dosage for DHE 45 injection is 1 mg, which may be repeated at 1 hour intervals to a total dose of 3 mL for intramuscular or subcutaneous injection or 2 mL for intravenous delivery in a 24 hour period. The total weekly dosage should not exceed 6 mg.

The applicant submitted data from clinical pharmacology studies to establish a pharmacokinetic (PK) bridge to the listed drugs. The applicant had previously been informed that a long-term local toxicity safety study would be required for approval, and the applicant submitted this study with the current application.

2. Background

DHE is approved under several dosage forms for the acute treatment of migraine and the acute treatment of cluster headache. Migranal is a DHE nasal spray marketed for the treatment of migraine with and without aura in adults. DHE 45 injection is marketed for intramuscular, subcutaneous, or intravenous administration for the acute treatment of migraine with or without aura and the acute treatment of cluster headache episodes.

Two milestone meetings were held for this drug development program. During the pre-IND meeting in May 2016, the Division stated that since the device component of INP104 was a novel nasal spray device that was designed to apply the drug substance higher in the nasal cavity than a typical spray, that results of a long-term safety study to evaluate local toxicity of the product, including an evaluation of smell preservation, would be required as part of any future drug application. In addition, the applicant stated that it planned to rely on a PK bridge of DHE-POD to DHE 45 injection for its planned application. The Division suggested that the applicant also add an additional treatment period in which subjects also receive Migranal nasal spray. In this case, the applicant would need to demonstrate that the plasma concentrations of DHE from INP104 fall between those from Migranal and DHE 45 injection. At the pre-NDA meeting in July 2020, the applicant was informed that its proposed indication of "acute treatment of migraine with and without aura" appeared acceptable based on the proposed package. In addition, the applicant inquired about (b) (4) The Division stated that the applicant could submit this detailed information in the NDA, and it would determine whether the applicant's request was supported following review of the information. (b) (4) .

3. Chemistry, Manufacturing and Controls/Device

The technical lead on the Office of Pharmaceutical Quality (OPQ) review was Dr. Martha Heimann (refer to her review for the entire OPQ list of participants in the review of this application). Dr. Heimann states that DHE was initially developed by Sandoz Pharmaceuticals for the treatment of migraine. The active moiety, DHE, is a semi-synthetic derivative of the ergot alkaloid ergotamine. Sandoz developed two products, DHE 45 injection and Migranal . The current application is for an alternative DHE NS using the applicant's POD device. The formulations for Migranal and INP104 are identical, and the drug component has the same manufacturer. While Migranal uses a conventional (b) (4) , the current product uses a hydrofluoroalkane-134a (HFA) pressurized, disposable actuator. The applicant states that HFA propels the DHE drug product in a targeted plume to pass through the nasal valves and into the upper nasal space (olfactory region) resulting in a more consistent deposition and uptake into systemic circulation relative to standard nasal pumps.

The OPQ team recommends approval of the proposed INP104 product. From a quality perspective, the application provides adequate information to ensure that the applicant can consistently manufacture this product and that it is suitable for use by the intended patients.

Drug Substance

The applicant cross-referenced Chemistry, Manufacturing, and Controls (CMC) information for the drug substance, dihydroergotamine mesylate to Type II drug master files (DMF) (b) (4) for the manufacture and control, and characterization of the drug substance. The DMF has been reviewed and deemed adequate.

OPQ states that information provided in the NDA regarding drug substance, general properties, impurities, specification and analytical methods, and batch analyses is consistent with information in the DMF. The DMF holder has assigned a retest period of (b) (4) months for drug substance stored at (b) (4) degrees Celsius, and the retest period is supported by stability data in the DMF.

Drug Product

OPQ states that the drug product solution contains DHE mesylate 4 mg/1 mL compendial excipients that include caffeine, dextrose, water, and carbon dioxide. The drug product solution is stored in a glass vial with a (b) (4) stopper and a plastic/aluminum flip-tear seal cap.

The test methods used for control of the drug product are adequately detailed and validated for quality control purposes. The proposed acceptance criteria are adequate with one exception. The proposed shelf-life limit of not more than (NMT) (b) (4)% for a principal degradation product, (b) (4) was not qualified adequately by either toxicology studies or by testing versus the innovator. The applicant was asked to revise the limit for this impurity to a threshold of NMT 1.0%. The applicant agreed and has provided release results demonstrating that all batches met the proposed specification. The Center for Devices and Radiological Health (CDRH) deemed the controls critical quality attributes (CQAs) for the drug constituent and essential performance requirements for the device adequate.

Stability studies on three batches of the combination product in commercial packaging are being conducted. Due to the lower limit for (b) (4) the maximum shelf life that can be granted is 12 months when stored at 20-25 degrees Celsius. The device has an allowable shelf life of (b) (4) months. A longer shelf life may be granted for the combination product if the applicant is able to qualify the higher limit for the (b) (4) impurity.

Manufacturing

The manufacturing process involves (b) (4). The product must be protected from light and oxygen since it is sensitive to these two things.

The device constituent is assembled at a separate facility. Drug vials are placed in a clam shell package with the device. The commercial trade package is a 4-count carton of four complete single use kits. OPQ states that all facilities involved in the manufacture and testing of DHE

USP, the DHE drug formulation, POD nasal spray device, and finished combination product are currently acceptable.

The applicant claimed a categorical exclusion for submission of an environmental assessment and provided adequate information to justify this claim.

Product Quality Microbiology Review

The drug and device constituents were tested for viable bioburden. The microbial limits acceptance criteria are consistent with requirements for nonsterile aqueous preparations for nasal use. Total yeast and mold count and specified microorganism are adequately validated and suitable for quality control. The container closure is designed to maintain product microbiological quality and the product is a single dose container. Since the product is a single dose, antimicrobial effectiveness testing is not needed.

CDRH

Ms. Michaela Schulman was the primary reviewer and Dr. Rumi Young was the team leader for the review of the nasal spray device for this application. As already stated, INP104 is a single-use, metered dose nasal DHE combination product that is co-packaged with the DHE drug constituent in a vial and the I123 POD device (see Figure 1 below).

Ms. Schulman states that this review includes a review of the essential performance requirements, design verification, design validation, stability, shipping validation, risk analysis, biocompatibility, and finished product specification. This review does not involve human factors (HF) (see Section 12 of this review). CDRH concludes that the device constituent parts of the combination product are approvable.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) primary reviewer for this application was Dr. Xiaohan Cai; the secondary review was conducted by Dr. Gopichand Gottipati. This application relies on the results of a single-dose pivotal relative bioavailability study (INP104-

101) conducted in healthy volunteers and a long-term safety study (INP104-301) evaluating the chronic intermittent use of INP104 in patients with acute migraine with and without aura.

The pivotal relative bioavailability study was an open-label, randomized, single-dose, three period, six-sequence, three-way crossover study conducted in healthy subjects to evaluate the PK, safety, and PK bridge between the proposed product (INP104 1.45 mg) and each of the two LDs, DHE 45 injection (1 mg) and Migranal (2 mg) to enable reliance of FDA's previous findings for safety and efficacy, respectively. Dr. Cai states that the results from study INP104-101 demonstrated that the upper bound of the 90% confidence interval for the geometric mean ratios for AUC ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and C_{max} of DHE between INP104 and DHE 45 injection was ≤ 125%, suggesting that it is appropriate to bridge safety information from DHE 45 injection; and the lower bound of the 90% confidence interval for the geometric mean ratios for AUC ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and C_{max} of DHE between INP104 and Migranal was ≥ 80%, suggesting that it is appropriate to bridge efficacy information from Migranal (refer to Table 1 below). Dr. Cai concludes that the relative bioavailability study conducted by the applicant provides an adequate scientific bridge (i.e., the exposure from INP104 is bracketed by those from the two LDs) for this 505(b)(2) application.

Table 1: Study INP104-101- Summary of Plasma PK Parameters of DHE (source: Dr. Cai's review)

	Treatment					
	1.45 mg INP104		**1 mg D.H.E. 45 for injection (IV)**		**2 mg Migranal**	
Parameters	**N**	**Mean (CV%)**	**N**	**Mean (CV%)**	**N**	**Mean (CV%)**
T_{max} (h)[#]	30	0.5 (0.33-2.05)	27	0.08 (0.07-0.1)	30	0.73 (0.5-3.08)
C_{max} (pg/mL)	30	1277 (52.2%)	27	14491.48 (34.4%)	30	329.26 (84.9%)
$AUC_{0\text{-last}}$ (h*pg/mL)	30	5951.89 (42.8%)	27	8424.03 (56.1%)	30	2057.2 (79.7%)
$AUC_{0\text{-inf}}$ (h*pg/mL)	30	6247.04 (42.1%)	27	8798.72 (53.7%)	28	2381.15 (70.6%)
$t_{½}$ (h)	30	11.69 (24.2%)	27	14.52	28	10.73 (27.9%)

(b) (4)

A consult request for clinical and bioanalytical site inspections for the pivotal bioavailability study was sent to the Office of Study Integrity and Surveillance (OSIS). OSIS recommended accepting the data without an on-site inspection because both sites were inspected previously.

OCP recommends approval of this application based on an adequate PK bridge demonstrated between INP104 (1.45 mg) and the listed drugs, DHE 45 IV injection (1 mg) and Migranal (2 mg) for the acute treatment of migraine with or without aura in adults.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The relative bioavailability study conducted by the applicant provides an adequate scientific bridge (i.e., the exposures from INP104 is bracketed by those from the two LDs) for this 505(b)(2) application. Therefore, the applicant can rely on the FDA's previous finding of efficacy of Migranal for the treatment of (b) (4) migraine with and without aura in adults, as described in the Migranal label, to support the efficacy of INP104.

8. Safety

Dr. Ryan Kau reviewed the clinical safety data from the pivotal clinical pharmacology study (INP104-101) and the Phase 3 open-label, single-group assignment, long-term safety study (INP104-301).

Study INP104-101 was a 3-period, 6-sequence, 3-way, randomized, open-label, single-dose, crossover comparative bioavailability study. Subjects were given a single dose of either 1.45 mg intranasal INP104, 1 mg IV DHE. 45 injection, or 2 mg intranasal Migranal over three periods. There were no nasal specific exams performed in this study.

Study INP401-301 was an open-label, single-group assignment, long-term safety and tolerability study lasting up to 52 weeks. Adult migraine patients were to self-administer one spray in each nostril of INP104 when they experienced a migraine. No more than 2 doses were to be taken in a 24-hour period and no more than 3 doses were to be taken in a 7-day period. Patients who enrolled would complete at least a 24-week treatment period, with a subset continuing treatment to 52 weeks.

To evaluate local toxicity, nasal endoscopy and the University of Pennsylvania Smell Identification Test (UPSIT) were conducted in Study INP104-301. The UPSIT is a clinical outcome assessment tool used in clinical practice to assess olfactory function. It includes a 40-item scratch and sniff test with four multiple choice options for each item; the range of scores is 0-40. A higher score indicates better smell function. Based on the overall score, patients are categorized as having normal smell, mild microsmia, moderate microsmia, severe microsmia, or anosmia.

Nasal endoscopy was performed at screening, week 4, week 8, week 12, and week 24. The UPSIT was administered at screening, baseline, week 12, and week 24. The subset of patients that participated in the additional 28-week portion of the trial also completed the UPSIT and nasal endoscopy at weeks 36 and 52. If there was any clinically significant change on nasal

endoscopy, a repeat nasal endoscopy was completed at 2-week intervals until resolution or trial period completion. If during the study there was a reduction in the UPSIT score of ≥5 points, INP104 was to be stopped and 4 weeks later another UPSIT would be administered, with continued scheduled visits until olfaction returned or study participation was completed.

The applicant was asked to provide safety data on at least 150 patients that treated on average at least 2 migraines per month for 6 months, and if a signal was seen in the 6-month safety database, then additional safety data on at least 50 patients at 1 year should be obtained. The applicant chose to collect safety data up to 1 year on a subset of patients. The applicant provided safety data on 385 patients that received at least one dose of INP104 and on 185 patients that treated on average at least 2 migraines a month for 6 months and 55 patients that treated on average at least 2 migraines a month for 12 months. Dr. Kau deemed this long-term safety database acceptable. Dr. Kau reviewed the systemic adverse events in this application, but focused his safety review on local irritative adverse events. He notes that of the 385 patients that received at least one dose of study drug, 185 (52%) experienced local irritative adverse events.

Dr. Kau notes that there were no reports of death. There were 10 serious adverse events (SAEs) in Study INP104-301, specifically spontaneous abortion, status migranosis, ovarian mass, pulmonary embolism, visual impairment, clavicle fracture, rib fracture, and intestinal obstruction. All of these events occurred in one patient each, except for spontaneous abortion which occurred in two patients. One patient experienced intestinal obstruction twice separated by 7 days after resolution of the first event. There were no SAEs related to local toxicity; however, there was a patient that developed a septal perforation and another that developed anosmia, but both events were considered notable by Dr. Kau and are described in greater detail below:

1. A 49-year-old patient status post sinus and septal surgery with a history of seasonal allergies presented with a nasal septal perforation (designated as mild) and moderate sinusitis 11 days post receiving a second dose of INP104 and 25 days since the first dose. There was no documentation of the perforation on the screening exam. Dr. Kau's impression is that it is unlikely that this event is related to study drug administration for the following reasons: 1) The patient only had two doses of this medication, and in general septal perforations due to medication are due to chronic frequent nasal spray use, 2) there were no reported symptoms, such as pain or epistaxis, and 3) septal surgery would be more likely the cause of a septal perforation when compared to drug induced septal perforations. The applicant suggests that this finding may have been overlooked at the time of the screening visit and Dr. Kau agrees with this assertion based on the reasons outlined above.

2. A 44-year-old female with a history of baseline average UPSIT score of 36.5, a normal baseline upper and lower nasal endoscopy, presented with anosmia the same day as study drug administration, which resolved later the same day. Ten days later the patient took a second dose, and had an UPSIT score of 34 the same day (which is considered normal). Although the patient's subjective decrease in olfaction resolved the same day after the first dose, and the patient had a normal UPSIT score after the

second dose and the patient reportedly decided to withdraw from the study due to lack of efficacy. Dr. Kau reports that a relationship to study drug cannot be ruled out, but given that the event resolved the same day and that there were no UPSIT testing results at that time Dr. Kau classifies this event as "not serious".

Dr. Kau notes that the overall systemic safety profile was comparable to that of the LD intended to support the safety of the proposed product, DHE 45 injection.

Dr. Kau reports that of the 354 patients that received at least one dose of INP104, 52% reported local irritative adverse events. The most common local irritative treatment emergent adverse events (at least 1% of patients) were nasopharyngitis (21%), rhinitis (19%), nasal discomfort (7%), product taste abnormal/dysgeusia (6%), sinusitis (6%), sinus discomfort (4%), olfactory test abnormal (defined based on a change in score at the prespecified threshold on the UPSIT) (4%), epistaxis (3%), pharyngitis (3%), nasal mucosal disorder (2%), change in smell (1%), ear discomfort (1%), and rhinorrhea (1%). One local irritative treatment emergent adverse event (TEAE) was reported to be severe, which was nasal congestion, but this TEAE resolved without treatment on the same day of onset. Dr. Kau recommends that the local irritative TEAEs that occurred in at least 1% of patients should be described in labeling.

Since the LD that is being relied on for safety, DHE 45 injection, allows for a second dose to be taken 1 hour after the initial dose, systemic safety is available to support the use of a second dose of INP104 one hour following the initial dose. Dr. Kau also evaluated the local toxicity safety data provided in the application for patients that received a second dose of INP104 within 24 hours (in the following time windows: 0-1 hour, greater than 1-2 hours, and greater than 2 -24 hours) and compared this to the local toxicity safety data of patients that received a single dose within 24 hours. One hundred and seventy eight patients took one dose within 24 hours and 175 patients took 2 doses within 24 hours. Of the patients that took 2 doses within 24 hours, 40 patients took this dose within two hours after the first dose and 135 patients took a second dose greater than 2 hours to 24 hours post the first dose. Dr. Kau notes that patients that took a second dose 0-2 hours after the initial dose did not show increased local toxicity events when compared to those that took a second dose in the greater than 2 to 24 hour timeframe, or than patients that took only one dose in 24 hours. Therefore, he suggests that labeling should be consistent with that of the LD regarding the timing of a second dose and allow for an option of taking a second dose a minimum of 1 hour after the initial dose.

Dr. Kau notes that the applicant conducted the UPSIT on patients in the study and prespecified that a 5-point decrease or greater would represent an abnormal olfactory test. Of the 354 patients that received at least one dose of INP104, twenty five patients met this criteria, and of those only 2 noted a subjective smell change. These cases of hyposmia are described below.

1. A 50-year-old female with a history of recent onset of menopause and a normal baseline UPSIT score (36.5) , experienced mild hyposmia one day after the 45th dose, at which time no UPSIT score was reported. Subsequent to this event, the patient had an UPSIT scores of 34 (mild microsmia) 54 days later and another UPSIT score of 31 (mild microsmia) 172 days following the initial event. The event resolved 228 days after onset. Dr. Kau reports that this case is confounded by the fact that the patient had

a recent onset of menopause since olfactory dysfunction could be associated with menopause. Given that this event began in close proximity to dosing, and resolved, although the patient continued to be in menopause, Dr. Kau concludes that it is likely that study drug administration is related to this event.

2. A 44-year-old female with a normal baseline UPSIT score (35.5) reported hyposmia on study day 169, nine days after her 34th dose. At this time the patient had an UPSIT score of 30 (moderate microsmia). Nineteen days later (study day 188) the patient had an UPSIT score of 29 (moderate microsmia). The patient did not take another dose following this event, and at the time of the last patient contact, the event was ongoing. Dr. Kau states that since the onset of the hyposmia was 9 days following administration of the last dose, he considers that an association between study drug and hyposmia is unlikely, but states that a relationship between study drug and this event cannot be definitively ruled out.

In addition, there were two patients that reported smell changes as adverse events of parosmia and anosmia, that did not have an UPSIT assessment at the time of symptoms. Both patients had resolution of these symptoms on the same day as onset.

Dr. Kau conducted a safety analysis by sex, age (less than or equal to 40 years, and over 40 year) and race (Black and White) and noted that abnormal product taste tended to occur more often in females and patients 40 years and under, but noted that the number of patients in the male and over 40 years subgroups are small and therefore no conclusions can be drawn regarding meaningful differences.

Safety Conclusions
There are no safety issues that preclude approval.

The safety profile of INP104 described in labeling will predominately be derived from the DHE 45 injection labeling with the addition of local toxicity findings of nasopharyngitis, rhinitis, nasal discomfort, product taste abnormal/dysgeusia, sinusitis, sinus discomfort, olfactory test abnormal, epistaxis, pharyngitis, nasal mucosal disorder, change in smell, ear discomfort, and rhinorrhea, identified in the long-term safety study conducted with INP104. The DHE 45 injection labeling includes a boxed Warning describing a drug interaction of DHE and strong CYP3A4 inhibitors, and this will remain in the labeling for the current product.

9. Controlled Substance Staff (CSS)

Dr. Katherine Bonson was the primary reviewer for the controlled substance review and Dr. Chad Reissig was the team leader. Dr. Bonson states that DHE has been marketed since 1946 and is not controlled under the Controlled Substances Act as a drug of abuse. It's mechanism of action as a serotonin (5-HT$_{1B}$ and 5-HT$_{1D)}$ agonist is not associated with abuse potential. However, other forms of ergot therapy have been associated with abuse and/or dependence. Therefore, Section 9 of the DHE 45 injection label describes cases of drug abuse or psychological dependence in patients on other forms of ergot therapy. Dr. Bonson recommends that the current product label mirror that of the listed drug, and recommends

updated wording for consistency with Physician Labeling Rule (PLR) formatting. These recommendations have been incorporated into the final labeling.

10. Advisory Committee Meeting

Not applicable

11. Pediatrics

INP104 was discussed at a Pediatric Review Committee (PeRC) meeting on July 27, 2021. Agreement was reached with the applicant's plan for requesting a partial waiver of clinical trials in patients 0 to less than 6 years of age (on the basis that such studies are highly impracticable) and a post-approval deferral of such trials in patients 6 to 17 years of age. Please refer to Section 14 of this memo for the required pediatric postmarketing studies.

12. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis (DMEPA)

Dr. Murewa Oguntimein was the primary reviewer for the DMEPA review, and Dr. Colleen Little conducted the secondary review. Their review focused on the evaluation of a HF validation study and labeling submitted for this application.

Following review of the HF validation study, DMEPA identified additional mitigations that could be implemented to address one identified use error that occurred with a critical task. In addition, review of labeling identified areas of vulnerability that may lead to medication errors. DMEPA made recommendations to address these areas. The applicant submitted revised labeling which was deemed acceptable by DMEPA.

Division of Pediatrics and Maternal Health (DPMH)

Dr. Catherine Roca conducted the primary review for DPMH and Dr. Miriam Dinatale with the team leader. DPMH was consulted to assist with the labeling review since both LDs were not in PLR formatting or Pregnancy and Lactation Labeling Rule (PLLR) formatting. Dr. Roca notes that DHE has been marketed in the US since 1946. Regarding pregnancy labeling, due to its oxytocic properties the LD labeling indicated that it is contraindicated for use during pregnancy. The limited published data that she reviewed indicated that use during pregnancy may be associated with an increased risk of preterm birth; however, the human data did not identify any association with major congenital malformations. Therefore, DPMH recommends that labeling changes be considered to remove the Contraindication for pregnancy and instead include a Warning and Precaution for preterm birth. In addition, DPMH does not recommend a postmarketing pregnancy registry since this product has been marketed for 60 years and it is unlikely that such a registry study would provide new information.

Regarding lactation, Dr. Roca states that ergotamine compounds are known to be present in human milk, and that 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 can reduce milk production. Current labeling of DHE compounds indicate that they are contraindicated during breastfeeding. DPMH recommends removing this contraindication since this is normally included for drugs that directly cause harm to the breastfeeding patients. DPMH recommends including the following language in section 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." DPMH is also not recommending a clinical lactation study since ergotamine is known to be present in human milk, and there is already information about the effects of ergotamine on milk production and the adverse effects observed with breastfed infants in approved labeling.

13. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

14. Postmarketing Recommendations

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

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

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

15. Recommendations/Risk Benefit Assessment

This application is approvable based on the finding from the relative bioavailability study that there is an adequate scientific bridge (i.e., the exposure from INP104 is bracketed by those from the two LDs) for this 505(b)(2) application. Therefore, INP104 can rely on DHE 45 injection and Migranal and borrow relevant information to support systemic safety and efficacy from their respective labels. In addition, safety data from the long-term safety study conducted with INP104 provides adequate local toxicity safety data to support chronic intermittent use of this product in migraine patients. This study identified irritative adverse events with chronic intermittent use of INP104, which will be described in labeling. Overall, the risk/benefit assessment is acceptable and similar to that of previously approved DHE products.

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/s/

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