The Ohio State University College of Pharmacy
Michael Itschner PharmD Candidate 2022

Dihydroergotamine (Trudhesa®)
Impel NeuroPharma

AHFS THERAPEUTIC CLASS:
Antimigraine agent, ergot derivative

MECHANISM OF ACTION:
For migraines, activation of the 5-HT_{1D} receptor, which is located on the intracranial blood vessels, results in vasoconstriction of the sensory nerve endings of trigeminal system. This inhibits the pro-inflammatory neuropeptide release relieving migraine symptoms.

FDA APPROVED INDICATION(S):
Acute treatment of migraine headache with or without aura, not for prophylactic or management of migraines.

NON-FDA APPROVED (OFF-LABEL) INDICATIONS(S):
- Medication overused headache or intractable migraine (status migranosus)
- Orthostatic hypotension
- Pelvic congestion with pain

CLINICAL EFFICACY:

Reference	Population Criteria	Study Design/Interventions	Results
STOP 301 Phase 3 trial Sponsored by Impel NeuroPharma	Inclusion: • Diagnosis of migraine with or without aura with at least 2 attacks per month in last 6 months • General good health • Childbearing women, and men agree to consent to use effective contraception during the study and 30 days after the last dose Exclusion: • Trigeminal autonomic cephalalgias, hemiplegic migraine, brainstem aura • Chronic migraine, medication induced migraine • Ischemic heart disease, coronary artery vasospasm, coronary artery disease • Use of nicotine,	Study design: Phase 3 open label, single arm assignment study Duration: 24 weeks and 52 weeks Population size: 360 Population characteristics: Mean age ~41-44 years, 82-85% women, ~75% white, ~20% black, ~20-year migraine history Purpose: Determine safety, tolerability, efficacy and patient acceptability for treatment of acute migraine	Endpoint description: Primary Endpoint: Treatment emergent adverse effects, change in nasal mucosa, change in olfactory function Secondary Endpoint: Vital signs, physical examinations electrocardiograms, laboratory evaluations Limitations: • Open label trial with no control group for comparison • Only in the USA for study locations • Patients has long history of migraines, new onset migraine patients not assessed • There were no statistically significant calculations conducted, no p-values

	diabetes, uncontrolled hypertension, artery disease, sepsis, pregnancy • Alcoholism or drug abuse in the last 2 years • >12 days per month of triptan or ergot drugs in 2 months prior to screening		Conclusion: No major safety concerns identified and well tolerated. Most common reported AE were nasal discomfort, nausea, and abnormal taste. Ergot and triptan drugs were not allowed during the trial. Efficacy was determined by pain freedom at 2 hours post dose and most bothersome pain freedom at 2 hours post dose. A higher percentage of patient using Trudhesa had pain freedom at 2 hours post dose compared to standard of care.

The STOP 301 trial was the main trial that was the basis of Trudhesa's FDA approval. There is a Phase 1 trial called STOP 101 trial that included 36 participants of general good health took the Trudhesa (dihydroergotamine in the POD device) nasal spray, IV dihydroergotamine, or a dihydroergotamine traditional pump nasal spray. The purpose of this study was to determine pharmacokinetics between the three different administering techniques. Each participant only had one dose of each with a 7-day washout period. The Trudhesa package insert includes data from 3 other clinical trials (4 total) that support its FDA approval. The details of those studies are not yet published.

PHARMACOKINETICS:

Terminal half-life	9-10 hours
Volume of distribution (Vd)	800 L
Excretion	Primarily fecal, and urinary 6-7% unchanged drug in urine

ADVERSE REACTIONS:

Common:

- Rhinitis
- Local irritation to nose and throat
- Taste disorder
- Dizziness, drowsiness
- Nausea

Rare:

- Pharyngitis
- Muscle stiffness and weakness

SAFETY CONSIDERATIONS:

- Medications with similar names (Look-alike/Sound-alike): bromocriptine, cabergoline, ergoloid mesylates, ergonovine, ergotamine, methylergonovine
- Hazardous Risk Category: Not on the NIOSH list
- Contraindications:
    - Hypersensitivity to dihydroergotamine or any component of the formulation
    - Uncontrolled hypertension
    - Ischemic heart disease
    - Angina pectoris
    - History of MI or after valvular surgery
    - Coronary artery vasospasm

    - Hemiplegic or basilar migraine
    - Peripheral vascular disease
    - Sepsis
    - Severe hepatic or renal dysfunction
    - Recent use of triptan or other ergot medication in the last 24 hours
    - Use of vasoconstricting medication
- Warnings/Precautions:
    - Cardiac valvular fibrosis
    - Cardiovascular effects
    - Myocardial ischemia
    - Medication overuse headache
    - Cerebrovascular event
    - Pleural/retroperitoneal fibrosis
- Boxed Warnings: BBW: Peripheral ischemia with coadministration with a potent CYP3A4 inhibitor including protease inhibitors and macrolide antibiotics. This increases the risk of vasospasm leading to cerebral ischemia of extremities.
- Sentinel Events Advisory: N/A
- REMS Program: No

SPECIAL POPULATIONS:
- Pregnancy: oxytocic and should not be used
- Lactation: inhibit prolactin and excreted in breast milk, do not use
- Geriatrics: monitor cardiac and peripheral effects since there is a higher risk of vascular disease in the elderly
- Pediatrics: may cause nausea
- Renal Dysfunction: do not use, contraindicated
- Hepatic Dysfunction: do not use, contraindicated

DRUG INTERACTIONS:
- CYP3A4 inhibitors increase the vasoconstrictive effects of Trudhesa
- Triptans add to the vasoconstrictive effects of Trudhesa and increase the risk of coronary artery vasospasm
- Beta blockers my potentiate the vasoconstrictive effects of ergotamine drugs by blocking the vasodilatory mechanism of epinephrine
- Nicotine may contribute to vasoconstriction
- SSRIs may cause incoordination, hyperreflexia, and weakness when administered with 5-HT_1 agonist
- Other medications that cause vasoconstriction are not recommended

DOSAGE FORMS AVAILABLE:
Metered nasal spray, 1 spray = 0.725 mg.

DOSING AND ADMINISTRATION:
Recommended dose of 1.45 mg at migraine onset, 1 spray in each nostril at onset of migraine. The dose can be repeated once in 1 hour if needed, but no more than 2 doses in a 24 hour period or 3 doses in a 7 day period.

COST/USAGE COMPARISON:

Drug	*Dosage Form(s)*	*Unit Cost*	*Daily Dose*	*Daily Cost*	*Treatment Cost*
Trudhesa	4 mg/ml Nasal	$255	1 mg	$510	$510-1020
Sumatriptan	100 mg tablet	$26	100 mg	$26	$26-52
Ubrogepant	100 mg tablet	$107	100 mg	$107	$107-214

MEDICATION MONITORING PLAN:
This medication carries increased risk to those who have cardiovascular disease, the easiest way for patients to monitor their blood pressure at home after taking a dose of Trudhesa. For clinicians monitoring of hypertension and cardiac and peripheral vasculature effects (elderly especially) if they have cardiovascular risk factors or CVD (diabetes, peripheral vascular disease).

CONCLUSION:
The approval of Trudhesa offers an alternative delivery route of medication to the patient for migraine relief. The intranasal formulation bypasses first pass metabolism and dependance on GI motility for absorption of the mediation. Some patents with migraine experience nausea and GI disruption which further hinders absorption of oral formulation products, slowing the response time and increasing the total migraine time the patient experiences.

STOP 301 was the pivotal phase 3 study that granted Trudhesa FDA approval. There are four other studies that are listed in the package insert that support safety and efficacy for this medication. In all 4 placebo-controlled studies, a greater percentage of participants experienced migraine relief at the 2 hour and 4-hour mark after a single 2 mg dose. These results were found to be statistically significant with a p-value of <0.01. Two of the studies had a population of ~100 participants in each group and the other two had 50 in each group. During these studies none of the participants had other migraine medication 8 hours before or during the 4-hour study period.

Currently, use of triptan and other ergot medications are not recommended with Trudhesa due to increased vasoconstrictive effects leading to a higher risk of a cardiovascular event. Trudhesa is used as an abortive migraine medication and not for prophylaxis at this point due to the lack of data in this regard. Other abortive medications should not be used at the same time as Trudhesa due to increased risk of adverse events and increased cost to the patient for these medications. Trudhesa does provide an alternative route of administration to patients suffering from migraines, especially those to have nausea and increases GI motility symptoms due to the migraine itself.

REFERENCES:

1. Trudhesa [package insert]. Seattle, WA; Impel NeuroPharma; Revised September 2021.
2. Smith TR, Winner P, Aurora SK, Jeleva M, Hocevar-Trnka J, Shrewsbury SB. STOP 301: A Phase 3, open-label study of safety, tolerability, and exploratory efficacy of INP104, Precision Olfactory Delivery (POD®) of dihydroergotamine mesylate, over 24/52 weeks in acute treatment of migraine attacks in adult patients. *Headache*. 2021;61(8):1214-1226. doi:10.1111/head.14184
3. Dihydroergotamine. Lexi-Drugs. Lexicomp. Wolters Kluwer. Hudson, Oh. Available at https://online.lexi.com. Accessed September 27, 2021.
4. ClinicalTrials.gov: Safety and Tolerability of POD-DHE (INP104) in Migraine (STOP 301) https://clinicaltrials.gov/ct2/show/NCT03557333?term=stop+301&draw=2&rank=1. Published June 15th, 2018. Accessed September 27, 2021.
5. ClinicalTrials.gov: Bioavailability of DHE Administered by I123 POD Device, IV Injection, and Marginal Nasal Spray in Healthy Adults https://clinicaltrials.gov/ct2/show/NCT03401346?term=INP104&draw=2&rank=2. Published January 17th, 2018. Accessed September 27, 2021.

6. Ubrelvy. Micromedex Solutions. Truven Health Analtics Inc. Greenwood Village, CO. Available at http://www.micromedexsolutions.com. Accessed September 27, 2021.
7. Sumatriptan. Micromedex Solutions. Truven Health Analtics Inc. Greenwood Village, CO. Available at http://www.micromedexsolutions.com. Accessed September 27, 2021.
8. Trudhesa. Micromedex Solutions. Truven Health Analtics Inc. Greenwood Village, CO. Available at http://www.micromedexsolutions.com. Accessed September 27, 2021.
9. ClinicalTrials.gov: A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine https://clinicaltrials.gov/ct2/show/NCT04940390?term=Dihydroergotamine+nasal&draw=2&rank=2. Published June 25th, 2021. Accessed September 27, 2021.
10. ClinicalTrials.gov: EMERGE: A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Single Doses of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine https://clinicaltrials.gov/ct2/show/NCT03901482. Published April 3rd, 2019. Accessed September 27, 2021.