Trudhesa™
(dihydroergotamine mesylate) nasal spray
0.725 mg per spray

NATIONWIDE AVAILABILITY ONLY THROUGH PHIL AND CAREPOINT PHARMACY

YEARS OF DHE RESULTS DON'T LIE

NOW THEY DON'T LIE IN WAIT[1,2]

For over 70 years, DHE (dihydroergotamine mesylate) has been recognized as a highly effective treatment for migraine[2-4]

The efficacy of intravenous (IV) DHE is well-regarded by physicians because of its[4,5]:

- ✓ Rapid onset and sustained effects lasting up to 48 hours
- ✓ Efficacy irrespective of the time of treatment—from within 2 hours to beyond 4 hours, post migraine attack onset
- ✓ Efficacy against a full range of migraine symptoms, including pain, allodynia, photophobia, and phonophobia

DHE may alleviate migraine symptoms across the different phases of migraine[5]

- ✓ Targets multiple receptors
- ✓ May prevent progression from peripheral to central sensitization
- ✓ Can potentially reverse established central sensitization in patients treated later in migraine attacks

Well-established safety and tolerability profile of DHE[1]

In US and foreign clinical studies:

- Of the 1796 patients and subjects treated with DHE nasal spray ≤2 mg, only 1.4% discontinued due to adverse events

In studies of traditional DHE nasal spray versus placebo (N=1228):

- The most common adverse reactions reported by ≥1% of patients taking DHE and occurred more frequently than in the placebo group were rhinitis (26% vs 7%), nausea (10% vs 4%), altered sense of taste (8% vs 1%), application site reaction (6% vs 2%), vomiting (4% vs 1%), dizziness (4% vs 2%), pharyngitis (3% vs 1%), somnolence (3% vs 2%), diarrhea (2% vs <1%), hot flashes (1% vs <1%), asthenia (1% vs 0%), and stiffness (1% vs <1%)

Important Safety Information

Indication

Trudhesa is an ergotamine derivative indicated for the acute treatment of migraine with or without aura in adults.

WARNING: PERIPHERAL ISCHEMIA FOLLOWING COADMINISTRATION WITH POTENT CYP3A4 INHIBITORS

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with strong CYP3A4 inhibitors. 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 Trudhesa with strong CYP3A4 inhibitors is contraindicated.

Please see the enclosed Trudhesa Prescribing Information, including **Boxed Warning** and Medication Guide.

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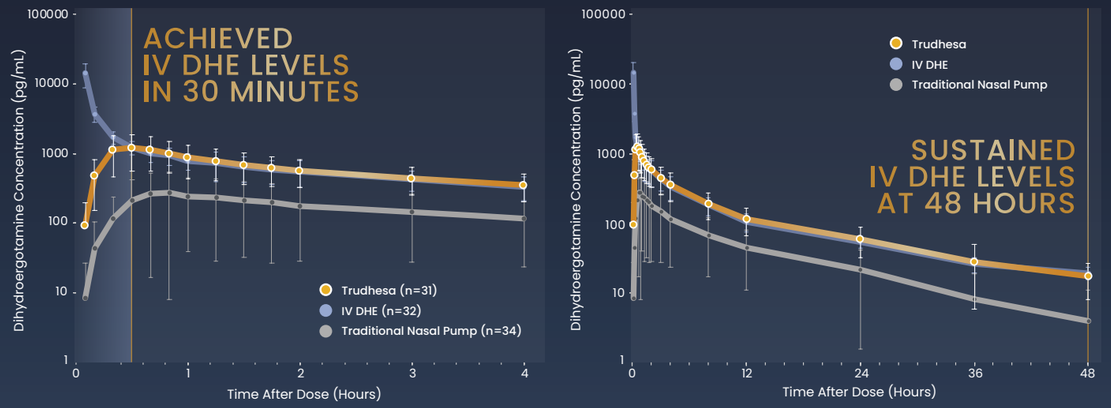
PROVEN DHE EFFICACY + HIGH-TECH DELIVERY

TREATING MIGRAINE MAY NEVER BE THE SAME[1]

Trudhesa™ delivered IV-like DHE levels with no initial C_{max} spike[6,7]:



pod® TECHNOLOGY

Trudhesa is the only migraine treatment that uses advanced Precision Olfactory Delivery (POD®) technology to consistently deliver DHE to the vascular-rich upper nasal space.[1,6,7]

Limitations of Use
Trudhesa is not indicated for the preventive treatment of migraine or for the management of hemiplegic or basilar migraine.

Contraindications
Trudhesa is not recommended in patients with:
- Concomitant use of strong CYP3A4 inhibitors such as protease inhibitors (eg, ritonavir, nelfinavir, or indinavir) and macrolide antibiotics (eg, erythromycin or clarithromycin)
- Ischemic heart disease or coronary artery vasospasm
- Uncontrolled hypertension, known peripheral arterial diseases, sepsis, following vascular surgery, or severe hepatic or renal impairment
- Hypersensitivity to ergot alkaloids
- Concomitant use of other 5-HT_1 agonists (eg, sumatriptan) or ergotamine-containing or ergot-type medications within 24 hours
- Concomitant use of peripheral and central vasoconstrictors

Trudhesa demonstrated a well-established safety profile in a Phase 3 trial that included cardiovascular (CV) assessment[7,8]

The Trudhesa safety study was the largest longitudinal study ever conducted with DHE using nasal spray delivery[9]*

- Over 6300 doses of Trudhesa were self-administered over the course of the 52-week study, and only 0.6% of doses resulted in nausea[10]
- Although nasal safety was the primary focus, information on treatment-emergent adverse events (TEAEs) such as CV effects (vital signs and electrocardiograms [ECGs]) were regularly collected and reviewed against concomitant medication use[8]
- 5.1% (18/354) of study patients had cardiac disorders[11]
- Patients were excluded if they had a history of CV events or presented with significant risk factors for CV disease. Patients with a history of hypertension could enroll if hypertension was stable and well-controlled on current therapies for >6 months, provided no other risks were present[1,8]

Local irritative symptoms[1†]

- The most common local irritative symptoms reported by ≥1% of patients taking Trudhesa during the 6- or 12-month study were 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

CV-related effects[8]

CV assessments were among secondary endpoints. Vital signs, including blood pressure, were collected every 4 weeks and ECGs were performed during the screening period, at baseline, Week 24, and Week 52[8]

- No treatment-related cardiac events
- Minimal changes from baseline in systolic and diastolic blood pressure and median heart rate over 24 weeks
- No clinically significant ECG changes or TEAEs associated with an abnormal ECG
- Over 24 weeks, 1.4% (5/354) of patients experienced adverse vascular events
  - 0.3% (1/354) of patients experienced adverse vascular events (ie, mild hypertension) related to Trudhesa

Today, with POD® technology, patients can have the proven efficacy of DHE on demand for rapid, sustained, consistent relief, with no dosing window.[1,5,12]

*A Phase 3, interventional, open-label, single-group assignment study (STOP 301) assessing the safety, tolerability, and exploratory efficacy of INP104 over 24 and 52 weeks.[7]
†52% of patients experienced any local irritative symptom.[1]

Please see the enclosed Trudhesa Prescribing Information, including **Boxed Warning** and Medication Guide.

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Want to learn more about the efficacy of proven DHE with POD® technology?[1] Scan the QR code or visit trudhesaHCP.com

Warnings and Precautions
Trudhesa may cause:

- **Cardiac events:** Cardiac events in patients with risk factors of coronary artery diseases: Consider administration of the first dose of Trudhesa under medical supervision (including the use of an electrocardiogram)
- **Cerebrovascular events:** Cerebrovascular events (eg, cerebral hemorrhage, subarachnoid hemorrhage, and stroke) have been reported, particularly with dihydroergotamine mesylate injection
- **Vasospasm/elevated blood pressure:** Dihydroergotamine may cause vasospasm or elevation in blood pressure
- **Fibrotic complications:** Rare cases have been reported following prolonged daily use of dihydroergotamine mesylate. Administration of Trudhesa should not exceed the dosing guidelines or be used for chronic daily administration
- **Medication overuse headache:** Detoxification may be necessary
- **Preterm labor:** Advise pregnant women of the risk
- **Local irritation:** Local irritation has been reported following administration of Trudhesa

Most Common Adverse Reactions
Most common adverse reactions (incidence >1%) were rhinitis, nausea, altered sense of taste, application site reactions, dizziness, vomiting, somnolence, pharyngitis, and diarrhea.

Use in Special Populations
Pregnancy: Available data from published literature indicate an increased risk of preterm delivery with Trudhesa use during pregnancy.
Lactation: Patients should not breastfeed during treatment with Trudhesa and for 3 days after the last dose.

Please see the Trudhesa Full Prescribing Information, including **Boxed Warning** and Medication Guide.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.trudhesaHCP.com or 1-800-555-DRUG. You can also call 1-833-TRUDHESA (1-833-878-3437) for additional information.

References: 1. Trudhesa. Prescribing information. Impel NeuroPharma; 2021. **2.** Saper JR, Silberstein S, Dodick D, Rapoport A. DHE in the pharmacotherapy of migraine: potential for a larger role. *Headache*. 2006;46(suppl 4):S212-S220. **3.** US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed August 24, 2021. **4.** Silberstein SD, Shrewsbury SB, Hoekman J. Dihydroergotamine (DHE) - then and now: a narrative review. *Headache*. 2020;60(1):40-57. **5.** Aurora SK, Ray S, Satterly K, Shrewsbury SB, Hoekman J. Does dihydroergotamine treat the "whole migraine"? Poster presented at: American Headache Society Virtual Annual Scientific Meeting, June 2020. **6.** Shrewsbury SB, Jeleva M, Satterly KH, Lickliter J, Hoekman J. STOP 101: a phase 1, randomized, open-label, comparative bioavailability study of INP104, dihydroergotamine mesylate (DHE) administered intranasally by a I123 Precision Olfactory Delivery (POD®) Device, in healthy adult subjects. *Headache*. 2019;59(3):394-409. **7.** 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 [published online ahead of print, 2021 Aug 7]. *Headache*. 2021;10.1111/head.14184. doi:10.1111/head.14184. **8.** Craig K, Jeleva M, Hocevar-Trnka J. Cardiovascular safety results of INP104 (POD-DHE) from the STOP 301 phase 3 study. Poster presented at: American Headache Society Virtual Annual Scientific Meeting, June 3-6, 2021. **9.** Impel NeuroPharma announces U.S. Food & Drug Administration acceptance of new drug application for INP104 for the acute treatment of migraine [press release]. Impel NeuroPharma; January 20, 2021. https://impelnp.com/2021/01/20/impel-neuropharma-announces-u-s-food-drug-administration-acceptance-of-new-drug-application-for-inp104-for-the-acute-treatment-of-migraine/. Accessed September 10, 2021. **10.** Randle L, Aurora SK, Hocevar-Trnka J, et al. Reduced nausea when dihydroergotamine mesylate is delivered by INP104. Poster presented at: American Headache Society Virtual Annual Scientific Meeting, June 3-6, 2021. **11.** Data on File. Impel NeuroPharma. 2020. **12.** Smith TR, Aurora S, Hocevar-Trnka J, Shrewsbury S. Acute treatment of migraine with INP104: exploratory efficacy from the phase 3 STOP 301 study. Poster presented at: American Headache Society Virtual Annual Scientific Meeting, June 3-6, 2021.

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