

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

What is Trudhesa™ (dihydroergotamine mesylate) nasal spray (0.725 mg per spray)?

- Approved by the U.S. Food and Drug Administration in September 2021 for the acute treatment of migraine with or without aura in adults.
- The first and only therapeutic to use Impel's innovative Precision Olfactory Delivery (POD®) technology to gently deliver dihydroergotamine mesylate (DHE) quickly to the blood stream via the vascular-rich upper nasal space.¹
- Bypasses the gut and potential absorption issues, offering rapid, sustained and consistent symptom relief without injection or infusion, even when administered deep into a migraine attack.²
- Designed to be self-administered.



What is dihydroergotamine mesylate (DHE)?

- DHE is a proven and well-established therapeutic that was approved for the treatment of migraine in 1946 and has more than 70 years of therapeutic use.³
- Migraine treatment with DHE has demonstrated efficacy independent of when the treatment is initiated.⁴
- Unlike other available treatments for migraine, DHE is known to bind to multiple receptors theorized to be implicated in migraine onset and duration.⁵

What is STOP 301?

- The New Drug Application for Trudhesa included the results of the Phase 3, open-label, pivotal safety study, STOP 301, which is the largest longitudinal study ever conducted with DHE using nasal spray delivery. In the study, more than 5,650 migraine attacks were treated over 24 and 52 weeks.¹
- The primary objective of the study was to assess the safety and tolerability of Trudhesa, especially evaluating the safety and tolerability of delivering DHE to the upper nasal space through endoscopic and olfactory functioning examination. In the trial, Trudhesa was generally well tolerated.

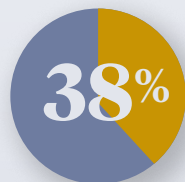
STOP 301 Safety & Tolerability

In STOP 301, Trudhesa was generally well tolerated and there were no serious Trudhesa-related treatment-emergent adverse events (TEAEs) observed and the majority of TEAEs were mild and transient in nature. Some of the most frequently reported Trudhesa-related TEAEs (≥2%) during the entire 52-week study period were nasal congestion (17.8%), nausea (6.8%), nasal discomfort (6.8%), abnormal olfactory test (6.8%) and vomiting (2.7%).*⁶

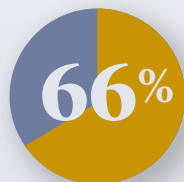
*The percentage of patients who reported these events were at any point during the trial

STOP 301 Exploratory Efficacy*

Exploratory objectives of STOP 301 included efficacy assessments of migraine measures and a patient acceptability questionnaire. Exploratory efficacy findings showed Trudhesa provided rapid, sustained, and consistent symptom relief.



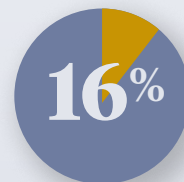
reported pain freedom at two hours after their first dose.⁷



had pain relief within two hours of administration.⁸

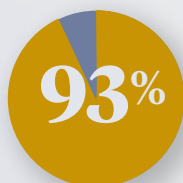


had freedom from their most bothersome migraine symptom at two hours after their first dose of Trudhesa.⁷



of patients noted pain relief started as early as 15 minutes after administration.⁷

Of patients who were pain free at two hours:



were still pain free at 24 hours.⁹



were still pain free through two days during weeks 21-24.⁹

- Unlike some oral acute treatments that need to be taken within one hour of attack onset to be most effective, STOP 301 reported Trudhesa offered consistent efficacy even when taken late into a migraine attack.¹⁰
- The patient acceptability questionnaire reported the patient's impression of Trudhesa usability and effectiveness. The great majority of patients – 84% – reported Trudhesa was easy to use⁶ and preferred it over their current therapy.¹¹

*As exploratory endpoints, there was no placebo control arm and no statistics supporting these exploratory data interpretation

For more information about Trudhesa and Full Prescribing Information, including BOXED WARNING, please visit, www.Trudhesa.com.



Trudhesa[™]
(dihydroergotamine mesylate) nasal spray

0.725 mg per spray

How do you use Trudhesa?

- Trudhesa is a single use, drug-device combination product containing a vial of DHE (4 mg DHE in a 1 mL solution that is clear and colorless to faintly yellow) and a POD[®] device. Prior to initiation of Trudhesa, a cardiovascular assessment is recommended. For patients with risk factors predictive of coronary artery disease who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of Trudhesa take place in the setting of an appropriately equipped healthcare facility, unless the patient has previously received DHE without problem.
- Trudhesa is designed to be self-administered. Once assembled, Trudhesa should be primed before initial use by releasing 4 sprays. A patient should use Trudhesa immediately after priming. The recommended dose of Trudhesa is 1.45 mg administered as two metered sprays into the nose (one spray of 0.725 mg into each nostril). The dose may be repeated, if needed, a minimum of 1 hour after the first dose. A patient should not use more than 2 doses of Trudhesa within a 24-hour period or 3 doses within a 7-day period. A patient should use or discard Trudhesa within 8 hours once the vial has been opened or the product has been assembled. A consumer assembly video is available on www.Trudhesa.com.
- The most common adverse reactions (incidence $\geq 2\%$) to Trudhesa were nasal congestion, nasal discomfort, nausea, product taste abnormal, and product package associated injury.

Trudhesa is now available through Trudhesa Direct™, a streamlined, customized, end-to-end process that provides hassle-free prescribing, savings, and home delivery. The digital pharmacy partners, Carepoint Pharmacy and Phil Inc., facilitate the process beginning with e-prescribing and automatic enrollment of eligible, commercially-insured patients in the Trudhesa Direct Savings Program.

References

¹ On file at Impel.

² Impel NeuroPharma. (2020). INP104-301. Table 3.8.2.

³ The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache: The Journal of Head and Face Pain, 59: 1-18. <https://doi.org/10.1111/head.13456>

⁴ Tepper SJ, et al. Mayo Clin Proc. 2011;86(10):948-955.

⁵ Silberstein SD, et al. Headache. 2020;60:40-57.

⁶ Impel Neuropharma. (2020). Clinical Study Report, Protocol No. INP104-301. Version 1.0. Table 14.3.1.1.3b

⁷ Impel Neuropharma. (2020). INP104-301. Table 3.3.4.

⁸ Impel Neuropharma. (2020). INP104-301. Table 3.3.1.

⁹ Impel Neuropharma. (2020). INP104-301. Table 3.3.6.

¹⁰ 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; 00: 1- 13. <https://doi.org/10.1111/head.14184>

¹¹ Shrewsbury SB, Hoekman J, Jeleva M, Hocevar-Trnka J, Hoekman J, Shrewsbury SB, A long term, open label study of Safety and Tolerability Of Precision olfactory delivery of DHE in acute migraine (STOP 301): Clinical Results, PainWEEK Live Virtual Conference Sept 11-13, 2020

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Indication and Important Safety Information

Indication

Trudhesa is used to treat an active migraine headache with or without aura in adults. Do not use Trudhesa to prevent migraine when you have no symptoms. It is not known if Trudhesa is safe and effective in children.

Important Safety Information

Serious or potentially life-threatening reductions in blood flow to the brain or extremities due to interactions between dihydroergotamine (the active ingredient in Trudhesa) and strong CYP3A4 inhibitors (such as protease inhibitors and macrolide antibiotics) have been reported rarely. As a result, these medications should not be taken together.

Do not use Trudhesa if you:

- Have any disease affecting your heart, arteries, or blood circulation
- Are taking certain anti-HIV medications known as protease inhibitors (such as ritonavir or nelfinavir)
- Are taking a macrolide antibiotic such as clarithromycin or erythromycin
- Are taking certain antifungals such as ketoconazole or itraconazole
- Have taken certain medications such as triptans or ergot-type medications for the treatment or prevention of migraine within the last 24 hours
- Have taken any medications that constrict your blood vessels or raise your blood pressure
- Have severe liver or kidney disease
- Are allergic to ergotamine or dihydroergotamine

Before taking Trudhesa, tell your doctor if:

- You have high blood pressure, chest pain, shortness of breath, heart disease; or risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease or you are postmenopausal, or male over 40); or problems with blood circulation in your arms, legs, fingers, or toes.
- You have or had any disease of the liver or kidney.
- You are taking any prescription or over-the-counter medications, including vitamins or herbal supplements.
- You are pregnant, planning to become pregnant or are nursing, or have ever stopped medication due to an allergy or bad reaction.
- This headache is different from your usual migraine attacks.

The use of Trudhesa should not exceed dosing guidelines and should not be used on a daily basis.

Serious cardiac (heart) events, including some that have been fatal, have occurred following the use of dihydroergotamine mesylate, particularly with dihydroergotamine for injection, but are extremely rare.

You may experience some nasal congestion or irritation, altered sense of taste, sore throat, nausea, vomiting, dizziness, and fatigue after using Trudhesa.

Contact your doctor immediately if you experience:

- Numbness or tingling in your fingers and toes
- Severe tightness, pain, pressure, heaviness, or discomfort in your chest
- Muscle pain or cramps in your arms or legs
- Cold feeling or color changes in 1 or both legs or feet
- Sudden weakness
- Slurred speech
- Swelling or itching

The risk information provided here is not comprehensive. To learn more, talk about Trudhesa with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at www.trudhesa.com or 1-800-555-DRUG. You can also call 1-833-TRUDHESA (1-833-878-3437) for additional information.

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