

Dihydroergotamine Nasal Spray (TRUDHESA)

Abbreviated National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Introduction

The purposes of this abbreviated monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating Dihydroergotamine Nasal Spray (TRUDHESA) [DHET] and its VA National Formulary status; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics¹

Dihydroergotamine acts as an agonist at 5-HT_{1B}, 1D receptors on cranial blood vessels, resulting in vasoconstriction. Its efficacy for treatment of migraine may also be due to inhibition of pro-inflammatory neuropeptide release following activation of 5-HT_{1D} receptors on sensory nerve endings of the trigeminal system.

In a randomized, open-label, crossover study evaluating comparative bioavailability, healthy adults received single doses of DHET 1.45 mg, IV dihydroergotamine 1 mg, or Migranal 2 mg over 3 treatment periods with a 7-day washout between treatments. From 30 minutes to 48 hours after a dose, DHET produced plasma levels of dihydroergotamine that were comparable to IV dihydroergotamine. Peak concentrations occurred 10 minutes earlier and were 4-fold higher with DHET compared to Migranal.

FDA Approved Indication(s)¹

Dihydroergotamine Nasal Spray (TRUDHESA) is an ergotamine derivative indicated for the acute treatment of migraine with or without aura in adults.

Current VA National Formulary Alternatives

Dihydroergotamine Nasal Spray (Migranal)
Dihydroergotamine injection

Dosage and Administration¹

The recommended dose of Dihydroergotamine Nasal Spray (TRUDHESA) is 1.45 mg (administered as one metered spray of 0.725 mg into each nostril). The dose may be repeated, if needed, a minimum of 1 hour after the first dose. Do not use more than 2 doses within a 24-hour period or 3 doses within 7 days. The device must be discarded after one complete dose (ie, 1 spray in each nostril.)

Efficacy²⁻⁵

No new efficacy trials were required for FDA approval of DHET. Approval was based on the relative bioavailability of DHET compared to Dihydroergotamine Nasal Spray (MIGRANAL) and on the results of previous randomized, placebo-controlled trials with Migranal. In four

clinical trials, Migranal nasal spray relieved migraine headache pain after 2 hours in 30-61% of patients.

STOP 101² was a Phase 1, open-label, randomized, single-dose, 3-period, 3-way crossover study. Subjects received a single dose of A) INP104 1.45 mg (a drug-device combination product composed of DHE and the I123 POD device); B) DHE 45® Injection (IV) 1.0 mg; and C) DHE by Migranal® Nasal Spray 2.0 mg in 38 . Plasma levels of DHE and the major bioactive metabolite, were measured. INP104 provides a PK profile of DHE that is comparable to IV DHE, except for a lower peak concentration, and it demonstrated a Tmax of 30 minutes, which is faster than Migranal. Additionally, a shorter time to reach Cmax and at 4 times the plasma concentration of DHE in comparison to Migranal, INP104 met the predefined statistical criteria for comparative bioavailability with IV DHE and Migranal. The incidence of adverse events with INP104 1.45 mg was lower than with IV DHE 1.0 mg and generally comparable to Migranal.

In STOP 301,³ an open-label, single-group assignment study, the safety and tolerability of DHET was assessed in 354 adults with migraine. Patients self-administered DHET at least once during a 24-week period. The treatment period was preceded by a 28-day screening period in which patients treated migraine attacks with best usual care (mainly acetaminophen, NSAIDs, or triptans). An exploratory efficacy endpoint compared the results for the last migraine attack treated with best usual care to those for the first migraine attack treated with DHET. The self-reported outcomes for pain freedom and most bothersome symptom (MBS) freedom at 2 hours after a dose were 38.0% and 52.1%, respectively, with DHET, and 30.1% and 46.4%, respectively, with best usual care. Among patients who reported pain freedom at 2 hours after their first DHET-treated attack, the incidence of migraine recurrence was 7.1% and 14.3% at 24 and 48 hours, respectively. Throughout the initial 24-week treatment period and the full 52-week treatment period, DHET demonstrated meaningful improvement with a favorable tolerability profile.

Adverse Events (Safety Data)^{1,2}

Common Adverse Events

Most common adverse reactions (greater than 1%) were rhinitis, nausea, altered sense of taste, application site reactions, dizziness, vomiting, somnolence, pharyngitis, and diarrhea.

Contraindications

- Concomitant use of strong CYP3A4 inhibitors
- Patients with ischemic heart disease or coronary artery vasospasm
- Patients with uncontrolled hypertension, peripheral arterial diseases, sepsis, following vascular surgery, or severe hepatic or renal impairment
- Patients with hypersensitivity to ergot alkaloids
- Recent use of other 5-HT₁ agonists (e.g., sumatriptan) or ergotamine containing or ergot-type medications within 24 hours
- Concomitant use of peripheral and central vasoconstrictors

Warnings and Precautions

- In patients with risk factors, consider 1st dose administration under medical supervision with electrocardiogram.

- Cerebral hemorrhage, subarachnoid hemorrhage and stroke have been reported; discontinue DHET if suspected.
- DHET may cause vasospasm or elevation in blood pressure. Discontinue if signs or symptoms of vasoconstriction develop.
- Medication Overuse Headache: Detoxification may be necessary.
- Preterm Labor: Advise pregnant women of the risk.
- Pleural and retroperitoneal fibrosis have been reported following prolonged daily use of dihydroergotamine mesylate.
- Administration of DHET should not exceed the dosing guidelines or be used for chronic daily administration.
- If severe local irritation occurs for no other attributable reasons, suspend DHET until resolution.

Special Populations

- Pregnancy: Based on animal data, may cause fetal harm
- Lactation: Advise not to use during breastfeeding.

Drug Interactions - Same as with Migranal

Beta Blockers/Nicotine: May potentiate/provoke vasoconstriction

Selective Serotonin Reuptake Inhibitors: Weakness, hyperreflexia, and incoordination may occur with coadministration.

Conclusions

DHET is a new dihydroergotamine nasal spray FDA-approved for acute treatment of migraine. It utilizes a device that delivers the drug to the upper nasal cavity, resulting in greater bioavailability with a lower dose compared to Migranal nasal spray. Peak concentrations occurred 10 minutes earlier and were 4-fold higher with DHET compared to Migranal.

DHET demonstrates a pharmacokinetic profile similar to DHE given intravenously. In a comparative study with Migranal, DHET demonstrated improved responses for pain freedom and most bothersome symptom (MBS) freedom at 2 hours. Common adverse effects include nasal congestion and discomfort, nausea, and abnormal taste. Patient acceptance and adherence may be improved with DHET as a single dose requires 2 sprays (1 spray per nostril) in comparison to Migranal which requires 4 sprays (1 spray per nostril, repeated 15 minutes later).

References

1. Trudhesa prescribing information. Impel NeuroPharma, Inc. September 2021
2. SB Shrewsbury et al. 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; 59:394.
3. TR Smith et al. 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; 61:1214.

4. A new dihydroergotamine nasal spray (Trudhesa) for migraine. *Med Lett Drugs Ther.* 2021 Dec 27;63(1640):204-207
5. Silberstein SD, Shrewsbury SB, Hoekman J. Dihydroergotamine (DHE) - Then and Now: A Narrative Review. *Headache.* 2020 Jan;60(1):40-57.

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