**INDICATIONS AND USAGE**

Dihydroergotamine mesylate injection is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes.

**CONTRAINDICATIONS**

There have been a few reports of serious adverse events associated with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors (e.g., ritonavir). Therefore, concomitant use of dihydroergotamine mesylate and protease inhibitors (e.g., ritonavir, indinavir, saquinavir, nelfinavir) is contraindicated. CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics have been reported to elevate the serum levels of dihydroergotamine mesylate. 

**WARNINGS**

- **Cardiac**
  - Predisposition to ischemic heart disease, including Prinzmetal’s variant angina.
  - Patients with a history of CAD, or with strong family history of CAD, females who are surgically or physiologically postmenopausal, or males who are over 40 years of age. 
  - These patients should undergo periodic interval cardiovascular evaluation as they continue to use dihydroergotamine mesylate injection. (See CLINICAL PHARMACOLOGY). 
- **Adults**
  - Dihydroergotamine mesylate injection should not be used with peripheral vasoconstrictors because the combination may cause synergistic elevation of blood pressure. 

**Pharmacokinetics**

Following intranasal administration, dihydroergotamine mesylate is rapidly absorbed, becomes protein-bound, and is extensively metabolized. 

**CONTRAINdications**

Dihydroergotamine mesylate injection should only be used where a clear diagnosis of migraine headache has been established. 

**CYP 3A4 Inhibitors**

Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, indinavir, saquinavir, nelfinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors include: fluconazole, fluoxetine, ritonavir, saquinavir, and ritonavir. 

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT 1 agonist in a study evaluating subjects with pulmonary hypertension. 

**CYP 3A4 Inhibitors**

The systematic approach described above is currently recommended as a method to identify patients in whom dihydroergotamine mesylate injection should not be used with peripheral vasoconstrictors because the combination may cause synergistic elevation of blood pressure.

**STORAGE**

The text of a patient information sheet is printed at the end of this insert. To assure safe and effective use of dihydroergotamine mesylate injection, the patient information sheet should be given to the patient as provided. (See CONTRAINDICATIONS).

**DOSAGE AND ADMINISTRATION**

- **DOSAGE**
  - The usual adult dosage is 1 mg administered subcutaneously. 
  - In patients with renal impairment, the dosage should be reduced to 0.5 mg. 

**WARNINGS**

Sedatives and/or the-thresholding peripheral ischemia has been associated with the coadministration of DHE with potent CYP 3A4 inhibitors. Dihydroergotamine mesylate injection elevates the serum levels of dihydroergotamine mesylate, the risk for vasoconstriction leading to ischemic and/or oxidative stress is increased. Hence, concurrent use of these medications is contraindicated. (See CLINICAL PHARMACOLOGY and WARNINGS).

**DESCRIPTION**

Dihydroergotamine mesylate is ergotamine hydrated in the 9, 10 position as the mesylate salt. Dihydroergotamine mesylate is known clinically as DHE or DHE-P03. In chemical terms, its molecular formula is C_21 H_27 NO_4 _2CH_3 SO_3 H, and its structural formula is:

**CLINICAL PHARMACOLOGY**

Dihydroergotamine mesylate injection is a sterile, clear, colorless solution in saline for IM or subcutaneous administration. Each mL contains dihydroergotamine mesylate USP 1 mg, methanesulfonic acid, and/or sodium hydroxide added to adjust pH to a range of 3.4 to 4.3.

**Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergotamine).**

**Mechanism of Action**

Dihydroergotamine binds with high affinity to 5-HT_1D, 5-HT_1F, and 5-HT_1C receptors. It also binds with high affinity to serotonin 5-HT_1A, 5-HT_1D, and 5-HT_1F receptors, noradrenaline _α_1D and _α_1F receptors, and dopamine D_2 and D_3 receptors. The therapeutic activity of dihydroergotamine in migraine is generally attributed to its agonist effect at 5-HT_1D receptors. Three current theories have been proposed to explain the efficacy of 5-HT_1D receptor agonists in migraine: one theory suggests that activation of 5-HT_1D receptors located on intracranial blood vessels, including those in arteries ensues anadromous leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT_1D receptors on sensory nerve endings of the trigeminal system results in a central inhibition of pain. In addition, dihydroergotamine possesses opioid properties. (See CONTRAINDICATIONS).
Dihydroergotamine Mesylate Injection USP is supplied as a clear, colorless solution in single 1 mL vials, each vial containing 1 mg of dihydroergotamine mesylate, in cartons of 15 (NDC 0036-0310-15). 

Dosage

Dihydroergotamine mesylate should be administered as a dose of 1 mL intravenously, intramuscularly or subcutaneously. Your doctor will have told you what dose to use for each migraine attack. Should you get another migraine attack in the same day as the attack you treated, you must not treat it with dihydroergotamine mesylate injection unless at least 6 hours have elapsed since your last injection. If you have an injection of dihydroergotamine mesylate injection should be injected during a one-week period. Dihydroergotamine mesylate injection is not intended to be used on a prolonged daily basis.

How to use the dihydroergotamine mesylate injection

1. Use available training materials.
2. Read and follow the instructions in the patient instruction leaflet which is provided with the dihydroergotamine injection package before attempting to use the product.
3. If there are any questions concerning the use of your dihydroergotamine mesylate injection, ask your doctor or pharmacist.
4. Check the expiration date printed on the vial containing medication. If the expiration date has passed, do not use it.
5. Do not use the dihydroergotamine mesylate injection if there are any air bubbles, cloudy, discolored, or excessively darkened.
6. Check the dose of the medication. If the dose is incorrect, repeat steps above until you draw up the right dose.
7. While holding the syringe with your left hand, use your right hand to draw back slightly on the plunger.
8. With your left hand, firmly grasp about a 1-inch fold of skin at the injection site.
9. While holding the syringe in your right hand, take the needle off the syringe and rub.
10. Push the needle shaft, level up, all the way into the fold of skin at a 45° to 90° angle, then remove the needle of the syringe.
11. If you do not see any blood coming back into the syringe, inject the medication by pushing down on the plunger. If you see blood in the syringe, that means the needle has penetrated a vessel. If this happens, the needle/syringe off the skin and discard safely and sterilely and seek medical advice.
12. Use right hand to pull the needle out of skin your quickly at the same angle you injected. Immediately press the end of the injection site with your fingers, using firm pressure.

Answers to patients’ questions about dihydroergotamine mesylate injection

What if I need help in using my dihydroergotamine mesylate injection? If you have any questions or if you need help in opening, pulling off the needle of the syringe, or injecting the medication, call your pharmacist or doctor.

How much medication should I use and how often?

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Questions about the use of dihydroergotamine mesylate injection

Dihydroergotamine mesylate injection should be administered as a dose of 1 mL intravenously, intramuscularly or subcutaneously. The dose is repeated, as needed, at 1 hour intervals to a total dose of 3 mL for infusion or subcutaneous/dermal delivery or 2 mL for intravenous delivery in a 24 hour period. The total weekly dosage should not exceed 6 mL. Dihydroergotamine mesylate injection should not be used for chronic daily administration.

Parenteral drugs should be inspected visually for particulate matter and discoloration, whenever solution and container permit.