PRESCRIBING INFORMATION

[Pr]DIHYDROERGOTAMINE (DHE)

(dihydroergotamine mesylate injection USP)

Ampoules (1 mg/mL)

Migraine Therapy

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(dihydroergotamine mesylate injection, USP)

Ampoules (1 mg/mL)

THERAPEUTIC CLASSIFICATION

Migraine Therapy

ACTIONS AND CLINICAL PHARMACOLOGY

Dihydroergotamine displays agonist activity at the 5-HT_{1Da} and 5-$HT_{1Dß}$ receptors, which, by reducing 5-HT neuronal function and/or contracting elements of the cranial vasculature and/or suppressing neurogenic inflammation, is believed to underlie its anti-migraine efficacy. It also displays affinity for the 5-HT_{1A} and 5-HT_{1C} receptors and antagonistic activity at the 5-HT_2 subtype. Dihydroergotamine displays blocking actions at alpha adrenoreceptors, with a direct stimulating effect on the smooth muscle of peripheral blood vessels. Its tonic effect on capacitance vessels (veins) is particularly pronounced, compared to its effects on resistance vessels (arterioles). Dihydroergotamine differs from ergotamine by being more potent with respect to its adrenergic blocking actions and less potent with respect to its capacity to produce arterial vasoconstriction,

but it maintains a marked venoconstrictor effect. Dihydroergotamine reduces the incidence and degree of nausea, photophobia, and phonophobia.

Dihydroergotamine is 93% bound to plasma proteins. Its apparent volume of distribution is about 30 L/kg. The total body clearance is about 1.5 L/min., reflecting mainly the hepatic clearance. Elimination from the plasma is biphasic with an a-phase of 1.5 hours and a ß-phase of 15 hours. The major route of excretion is via the bile in the faeces. Urinary excretion of parent substance and metabolites amounts to about 10% after intravenous administration.

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of cytochrome P450 3A metabolism of the alkaloids by troleandomycin. Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions and rare reports of ergotism have been obtained from patients treated with dihydroergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated with dihydroergotamine and protease inhibitors (e.g. ritonavir), presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine (see **CONTRAINDICATIONS**). No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND CLINICAL USE

Dihydroergotamine (DHE) (dihydroergotamine mesylate injection) is indicated for the treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes, where rapid relief is desired.

CONTRAINDICATIONS

There have been a few reports of serious adverse events associated with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as HIV protease or reverse transcriptase inhibitors, macrolide antibiotics and azole antifungals, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is, therefore contraindicated (See **WARNINGS**: CYP 3A4 Inhibitors).

Dihydroergotamine (DHE) (dihydroergotamine mesylate) is contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids, or to any of the components of Dihydroergotamine (DHE).

Dihydroergotamine (DHE) is contraindicated in patients having conditions predisposing to vasospastic reactions such as known peripheral arterial disease (thromboangitis obliterans, luetic arteritis, severe arteriosclerosis, thrombophlebitis, Reynauld's disease),

coronary heart disease (in particular unstable or vasospastic angina), ischemic heart disease (angina pectoris, history of myocardial infarction or documented silent ischemia), septic conditions, shock, vascular surgery (especially arterial, recent or contemplated), obliterative vascular disease, inadequately controlled hypertension, temporal arteritis, severely impaired hepatic or renal functions, peptic ulcer, severe pruritus, and malnutrition.

Dihydroergotamine (DHE) should not be administered to patients with hemiplegic or basilar migraine.

Dihydroergotmaine (DHE) is contraindicated during pregnancy because it has oxytocic and vasoconstrictive effects on the placenta and umbilical cord. It is likely that dihydroergotamine is excreted in breast milk. Dihydroergotamine (DHE) is therefore contraindicated for nursing mothers.

Dihydroergotamine should not be used with peripheral or central vasoconstrictors (other ergot alkaloids, sumatriptan and other 5-HT_1-receptor agonists) because the combination may result in additive or synergistic elevation of blood pressure.

WARNINGS

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 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 these medications is contraindicated. (See also CONTRAINDICATIONS)

Dihydroergotamine (DHE) should only be used where a clear diagnosis of migraine headache has been established.

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

There have been rare reports of serious adverse events in connection with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as HIV protease and reverse transcriptase inhibitors, azole antifungals, and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or and ischemia of the extremities. The use of potent CYP 3A4 inhibitors with dihydroergotamine should therefore be avoided (see **CONTRAINDICATIONS**). Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir, and indinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors

should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with dihydroergotamine.

Fibrotic Complications

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Rarely, prolonged daily use of other ergot alkaloid drugs has been associated with cardiac valvular fibrosis. Rare cases have also been reported in association with the use of injectable dihydroergotamine mesylate; however, in those cases, patients also received drugs known to be associated with cardiac valvular fibrosis.

Administration of Dihydroergotamine (DHE) (dihydroergotamine mesylate injection), should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events

Dihydroergotamine (DHE) should not be used by patients with documented ischemic or vasospastic coronary artery disease. It is strongly recommended that Dihydroergotamine

(DHE) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g. hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, females who are surgically or physiologically postmenopausal, or males who are over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, Dihydroergotamine (DHE) should not be administered. For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of Dihydroergotamine (DHE) take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received dihydroergotamine mesylate. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining, on the first occasion of use, an electrocardiogram (ECG) during the interval immediately following Dihydroergotamine (DHE), in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of Dihydroergotamine (DHE) and who have or acquire risk factors predictive of CAD, as

described above, undergo periodic interval cardiovascular evaluation as they continue to use Dihydroergotamine (DHE).

The systematic approach described above is currently recommended as a method to identify patients in who Dihydroergotamine (DHE) may be used to treat migraine headaches with an acceptable margin of cardiovascular safety.

Cardiovascular Events and Fatalities

The potential for adverse cardiac events exists. Serious adverse cardiac events including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported to have occurred following the administration of dihydroergotamine mesylate injection. A causal relationship has not been established. In this context, it is important that the contraindications of coronary heart disease and uncontrolled hypertension are strictly followed. Considering the extent of use of dihydroergotamine in patients with migraine, the incidence of these events is extremely low.

Drug-Associated Cerebrovascular Events and Fatalities

Cerebral hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate injection, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the DHE injection having been administered in the incorrect belief that the

symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g. stroke, hemorrhage, transient ischemic attack).

Other Vasospasm Related Events

Dihydroergotamine could cause vasospastic reactions, including angina, although it seems to do so less frequently than ergotamine. This action appears to be dose-related. These reactions are manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia (e.g., muscle pains, numbness, coldness and pallor or cyanosis of the digits), angina or unusual syndromes, such as mesenteric ischemia. Consequently, Dihydroergotamine (DHE) should be discontinued immediately if signs or symptoms of vasoconstriction develop.

Increase in Blood Pressure

Significant elevation in blood pressure has been reported on rare occasions in patients with and without a history of hypertension treated with Dihydroergotamine (DHE). Dihydroergotamine (DHE) is contraindicated in patients with uncontrolled hypertension.

Intra-arterial injection of DHE injectable must be strictly avoided. Should this occur accidentally, an alpha-blocker such as phentolamine should be administered.

Caution should be exercised when DHE is administered to patients with severe renal disease, unless they are receiving dialysis. In such cases the dosage should be reduced.

If excessive or prolonged dosage is contemplated, patients should be closely monitored for peripheral vascular complications.

PRECAUTIONS

Dihydroergotamine (DHE) is only indicated for the treatment of acute migraine attacks and cluster headaches and not for prevention.

Drug Interactions:

Although formal studies have not been done, the concomitant use of oral contraceptives by female patients does not appear to influence the disposition of Dihydroergotamine (DHE) (dihydroergotamine mesylate nasal spray).

Dihydroergotamine (DHE) should not be used with vasoconstrictors because the combination may cause a further elevation of blood pressure.

Concurrent use of vasoconstrictor agents including ergotamine or other ergot alkaloids, sumatriptan and other 5-HT_1-receptor agonists, and nicotine may enhance the risk of vasoconstriction. Twenty four hours should elapse before taking sumatriptan following

administration of Dihydroergotamine (DHE). This will avoid additive vasospastic effects. Conversely, Dihydroergotamine (DHE) can be taken six hours following the administration of sumatriptan.

Although there have been reports that propranolol may potentiate the vasoconstrictive action of ergotamine by synergism upon ß-blockade, the results of a limited clinical study (n=8) did not indicate a safety problem associated with the administration of Dihydroergotamine (DHE) in subjects already receiving propranolol. Caution is required with the combination of a ß-adrenergic blocking agent and dihydroergotamine in patients with impaired peripheral circulation.

CYP 3A4 Inhibitors (see also **CONTRAINDICATIONS and WARNINGS**)

The concomitant use of cytochrome P450 3A (CYP3A) inhibitors such as macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g. ketoconazole, itraconazole, voriconazole) and DHE must be avoided (see CONTRAINDICATIONS), since this can result in an elevated exposure to dihydroergotamine and ergot toxicity (vasospasm and ischemia of the extremities and other tissues). Dihydroergotamine has also been shown to be an inhibitor of CYP3A. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Weakness, hyperreflexia and incoordination have been reported rarely when 5-HT_1 agonists have been co-administered with SSRI's (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no reported cases from spontaneous reports of drug interaction between SSRI's and Dihydroergotamine (DHE) injection.

Use in pregnancy: (see **CONTRAINDICATIONS**)

Nursing Mothers:

It is likely that dihydroergotamine is excreted in human milk, although it is not known at which concentration, while it is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse and unstable blood pressure in breastfed infants. Because of the potential for these serious adverse events in breastfed infants, nursing mothers should not use Dihydroergotamine (DHE) (dihydroergotamine mesylate injection) [See **CONTRAINDICATIONS**].

Pediatric Use:

Safety and efficacy in pediatric patients have not been established.

Fibrotic Complications:

Patients with a history of drug induced fibrotic disorders such as retroperitoneal and pleural fibrosis, should be monitored with caution (see also WARNINGS: Fibrotic Complications).

Information for Patients

Administration of Dihydroergotamine (DHE) (dihydroergotamine mesylate injection), should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Nausea and vomiting (not migraine related) may occasionally occur but they are less frequent and less prolonged than with ergotamine tartrate. Other adverse reactions include hypersensitivity reactions (such as skin rash, face oedema, urticaria and dyspnea), increase in blood pressure, dizziness, abdominal pain and diarrhea. Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, myocardial ischemia, transient tachycardia or bradycardia, localized edema and itching have also been reported. Extremely rare cases of myocardial infarction and stroke have been reported in postmarketing experience. A causal relationship has not been established.

In a few patients who have taken oral dihydroergotamine continuously over years, development of fibrotic changes, in particular of the pleura and the retroperitoneum, has been observed. Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate (see **WARNINGS:** Fibrotic Complications).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of acute overdosage with this drug. The symptoms of an acute oral dihydroergotamine overdose are similar to those of an ergotamine overdose, although there is less pronounced nausea and vomiting with dihydroergotamine. These symptoms include the following: peripheral signs and symptoms of vasospasm (e.g. numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses); respiratory depression; an increase and/or decrease in blood pressure usually in that order; confusion, delirium, convulsions and coma; and/or some degree of nausea, vomiting and abdominal pain.

The treatment of an overdosage is symptomatic under close monitoring of the cardiovascular and respiratory systems. Treatment includes discontinuation of the drug, local application of warmth to the affected area and nursing care to prevent tissue damage; in case of severe vasospasms, vasodilators should be administered (e.g. Sodium nitroprusside, phentolamine or dihydralazine). In the case of coronary constriction, appropriate treatment such as nitroglycerin should be initiated.

DOSAGE AND ADMINISTRATION

Optimal results are obtained by titrating the dose for several headaches to find the minimal effective dose for each patient and this dose should then be employed at onset of subsequent attacks.

Onset of action occurs in 15 to 30 minutes following I.M. administration and persists for 3 to 4 hours. Repeated dosage at 1 hour intervals up to a total of 3 mL may be required to obtain maximal effect.

The total weekly dosage should not exceed 6 mL (6 mg).

Pretreatment with an antiemetic may be considered when DHE is administered by the I.V. route.

Acute migraine attack:

1 mL (1 mg) by intramuscular or subcutaneous injection at the first sign of headache; in refractory cases, a further 1 mL may be administered after 30 to 60 minutes.

Do not exceed a total of 3 mL per attack or per day.

When more rapid effect is desired, the intravenous route may be employed: 1 mL (1 mg) by **slow intravenous injection** at the onset of the attack, followed in an hour by 1 mL (1 mg) if necessary. Do not exceed a total of 2 mL (2 mg) per migraine attack.

Cluster Headache (Horton Syndrome):

0.5 mL (0.5 mg) by slow intravenous injection.

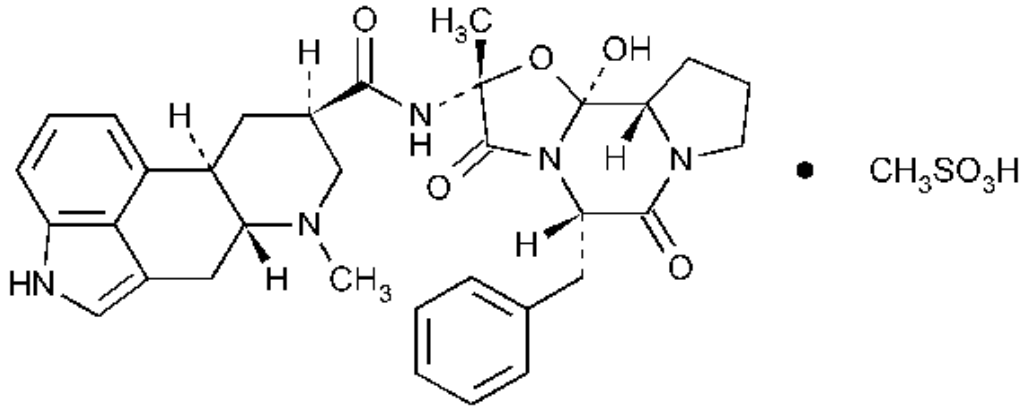
PHARMACEUTICAL INFORMATION

Drug substance:

Trade Name: Dihydroergotamine (DHE)

Common Name: 9,10-dihydro-12'-hydroxy-2'-methyl-5'a (phenyl-methyl) ergotaman-3', 6', 18-trione methanesulfonate

Structural Formula:



Molecular Formula: $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$

Molecular Weight: 679.8

Description: White or off-white, fine, crystalline, hygroscopic powder.

Moderately soluble in water.

pKa in ethanol-water (1:1) = 6.35 ± 0.05

pH in solution = 4.4 - 5.4

Dihydroergotamine mesylate melts with strong decomposition

between 220°C and 240°C

Composition of Dihydroergotamine (DHE) Ampoules:

Each 1 mL ampoule of Dihydroergotamine (DHE) contains:

Dihydroergotamine mesylate	1 mg
Ethanol 96%	50 mg
Glycerol	150 mg
Water for injection q.s.	1 mL

Storage requirements:

Protect ampoules from light. Store below 25°C. If the solution becomes discoloured, do not use.

AVAILABILITY

Boxes of 5 ampoules of 1 mL each.

REFERENCES

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