DIHYDERGOT®
(dihydroergotamine mesylate)

NAME OF THE MEDICINE

Active ingredient: dihydroergotamine mesylate
Chemical name: ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-(5'α)-monomethanesulfonate
CAS number: 6190-39-2
Molecular weight: 679.8
Molecular formula: C₃₄H₄₁N₅O₈S
Chemical structure:

[Chemical structure diagram]

DESCRIPTION

Dihydroergotamine mesylate is structurally and pharmacologically related to the other hydrogenated ergot alkaloids of the peptide type. The mesylate is a white to slightly yellowish or grey to pink-tinged powder soluble 0.85% in water, > 2% in methanol and approximately 1% in chloroform.

Dihydergot injection is a clear, colourless solution, pH 3.9-4.9.

Excipients
Tablets: tartaric acid, gelatin, magnesium stearate, stearic acid, talc-purified, starch-maize, lactose.

Ampoules: ethanol 5%, glycerol 15%, and water for injections.

PHARMACOLOGY

Pharmacodynamics
Pharmacotherapeutic group: antimigraine preparations
ATC code: N02CA01

Dihydroergotamine has complex pharmacological effects. It possesses affinity for both alpha-adrenergic and serotonergic receptors with both stimulating and blocking properties.
Dihydergot exerts its effect in orthostatic hypotension by selective constriction of capacitance vessels with no significant effect on resistance vessels. This increase in venous tone leads to a redistribution of blood, preventing excessive venous pooling.

In migraine attacks dihydroergotamine acts primarily by compensating for the decreased 5-HT plasma level. Simulating the effect of 5-HT, it counteracts the loss of tone of the extracranial vasculature.

The uterotonic activity of dihydroergotamine is much weaker than that of ergotamine.

**Pharmacokinetics**

**Absorption:**
Dihydroergotamine is incompletely and variably absorbed after oral administration (20 – 50 %). Peak plasma levels are attained in 1-2 hours and are linear over the range 10 - 30 mg.

The absolute oral bioavailability is low (approx. 1 % when unchanged drug measured) due to a 98 % first pass extraction of absorbed drug. Concomitant oral administration of glyceryl trinitrate has been shown to reduce the extent of first pass extraction in 4 patients by an increase in splanchnic blood flow, but the effect is variable.

After subcutaneous administration, dihydroergotamine is rapidly and completely absorbed. Peak plasma levels are achieved in less than 1 hour and are linear over the range 0.5 - 1.5 mg.

**Distribution:**
The volume of distribution is 8 - 14 L/kg and the drug is 90 – 95 % bound to plasma protein. The maximal venoconstrictor action of dihydroergotamine parallels the peak levels, but the venoconstriction lasts longer than would be expected on the basis of its apparent half-life of elimination, suggesting distribution to a deep compartment.

**Metabolism:**
Dihydroergotamine is extensively metabolised and the major metabolites show significant pharmacological activity. 8'-hydroxy-dihydroergotamine occurs in plasma concentrations in man about 5 – 7 times higher than the parent compound and produces venoconstriction of the same magnitude, duration, and onset of action. The total bioavailability (parent drug plus active metabolites) is, therefore, about 6 – 8 %.

**Excretion:**
Approximately 10 % of dihydroergotamine is excreted in the urine after i.v. administration; only negligible amounts as unchanged drug. The primary route of elimination is presumed to be biliary. The terminal half-life of dihydroergotamine and its metabolites is in the range of 10-30 hours.
INDICATIONS

- Short-term or intermittent treatment of severe disabling orthostatic hypotension associated with autonomic dysfunction, either primary or secondary to metabolic disorder in adult patients.
- Treatment by injection of acute attacks of migraine, cluster headache (Horton's syndrome) and related vascular headaches.

CONTRAINDICATIONS

- Known hypersensitivity to ergot alkaloids or to any other component of the formulation (see DESCRIPTION)
- Concomitant treatment with CYP3A4 inhibitors, including:
  - azole antifungals (ketoconazole, itraconazole)
  - HIV-protease inhibitors or reverse transcriptase inhibitors (ritonavir, nelfinavir, indinavir, delavirdine)
  - macrolide antibiotics (erythromycin, clarithromycin [see “PRECAUTIONS”])
- Concomitant treatment with vasoconstrictive agents, including:
  - ergot alkaloids
  - sumatriptan
  - other 5HT1-receptor agonists
  - nicotine
  - sympathomimetics [see INTERACTIONS WITH OTHER MEDICINES]
- Pregnancy and breast-feeding [see PRECAUTIONS]
- Conditions predisposing to vasospastic reactions:
  - coronary artery disease (particularly in unstable or vasospastic angina)
  - peripheral and obliterative vascular disease
  - severe and/or inadequately controlled hypertension
  - septic conditions
  - shock
- Temporal arteritis
- Hemiplegic or basilar migraine
- Severe hepatic impairment [see PRECAUTIONS]

PRECAUTIONS

CYP3A4 inhibitors:
There have been rare reports of serious adverse events in connection with the co-administration of ergot alkaloids and potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischaemia and/or ischaemia of the extremities. Examples of some of the more potent CYP3A4 inhibitors include the antifungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir and indinavir, and the macrolide antibiotics erythromycin and clarithromycin. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine and
The use of CYP3A4 inhibitors with Dihydergot should be avoided (see CONTRAINDICATIONS). These lists are not exhaustive and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with Dihydergot.

**Fibrotic Disorders:**
Patients with history of drug induced fibrotic disorders such as retroperitoneal and pleural fibrosis, should be monitored with caution. There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of ergot alkaloids, including prolonged daily use of injectable dihydroergotamine mesylate. Rarely, prolonged use of ergot alkaloids has also 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 (see ADVERSE REACTIONS).

**Orthostatic hypotension:**
In view of the limited experience with high oral doses (above 10 mg per day), particular caution should be experienced when Dihydergot is given to patients suffering from severe, disabling orthostatic hypotension.

**Inter-arterial injection:**
Intra-arterial injection of dihydroergotamine must be strictly avoided. In case of accidental i.a. administration, measures should be taken to prevent vasospasm (see ADVERSE REACTIONS - Serious or life-threatening reactions).

**Peripheral vascular disease:**
Due to the vasoconstrictor activity of dihydroergotamine, peripheral vascular disease may be worsened (see CONTRAINDICATIONS).

**Coronary artery disease:**
Dihydergot must not be used by injection or in high oral doses in patients with coronary artery disease, particularly in unstable or vasospastic angina (see CONTRAINDICATIONS).

**Hypertension:**
Caution must be exercised in patients with hypertension. Dihydergot must not be used by injection in patients with inadequately controlled hypertension (see CONTRAINDICATIONS).

**Renal impairment:**
Caution is indicated and the dosage should be reduced where Dihydergot is being given on a long-term basis to patients with severe renal impairment.

**Hepatic impairment:**
Dihydroergotamine is extensively metabolised and excreted mainly in the bile. In patients with pre-existing liver disease the dosage should be reduced. Patients with mild to moderate hepatic impairment, especially cholestatic patients, should be appropriately monitored.
Severe hepatic impairment is contraindicated.

**Long-term use:**
No carcinogenicity studies have been performed with dihydroergotamine. Furthermore, data on the long-term safety of the drug at higher doses are incomplete. For this reason long-term use in severe, disabling orthostatic hypotension is not recommended (see "INDICATIONS").

**Ergot poisoning:**
Prolonged use may lead to habituation and ergot poisoning (see OVERDOSAGE). A symptom resembling reversible dementia has been described in chronic ergotamine intoxication.

Continued daily use of Dihydergot solution for injection or its use in excess of the recommended doses must be avoided since it may cause vasospasm.

**Drug Dependence**
Prolonged use of Dihydergot must be avoided since it may cause drug dependence.

**Women of child-bearing potential**
Women planning to become pregnant should not take Dihydergot. Also see PRECAUTIONS - Use in Pregnancy, and CONTRAINDICATIONS.

**Use in Pregnancy (Category C)**
Dihydroergotamine induces uterine contraction and may, therefore, cause premature parturition or hypertonic labour. Therefore products containing ergotamine or dihydroergotamine should be discontinued immediately when a pregnancy is confirmed (see CONTRAINDICATIONS).

**Use in Lactation**
It is likely that dihydroergotamine is excreted in the breast milk. Dihydergot is, therefore, contraindicated in nursing mothers (see CONTRAINDICATIONS).

**Use in the Elderly**
No studies have been performed in geriatric patients.

**Effects on Ability to Drive or Operate Machinery**
Patients experiencing dizziness or other central nervous system disturbances should not drive or operate machinery.
INTERACTIONS WITH OTHER MEDICINES

Anticipated interactions resulting in a contraindication

CYP3A4 inhibitors:
Pharmacokinetic interactions have been reported in patients treated orally with ergot alkaloids (e.g. increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of CYP3A4 metabolism of the alkaloids by troleandomycin. Ergot alkaloids have also been shown to be inhibitors of CYP3A4 catalysed reactions and rare reports of ergotism have been obtained from patients treated with ergot alkaloids and macrolide antibiotics (e.g. troleandomycin, clarithromycin, erythromycin) and patients treated with ergot alkaloids and HIV protease inhibitors or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, or delavirdine), or azole antifungals (e.g. ketoconazole, itraconazole, or voriconazole). presumably due to inhibition of CYP3A4 metabolism of ergotamine (see CONTRAINDICATIONS and PRECAUTIONS - CYP3A4 inhibitors). These interactions can result in elevated exposure to dihydroergotamine and ergot toxicity (vasospasm and ischemia of the extremeties and other tissues).

Vasoconstrictors:
Dihydroergotamine should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. Nicotine (e.g. smoking) may provoke vasoconstriction in some patients, predisposing to a greater ischaemic response to ergot therapy.

Concurrent use of dihydroergotamine with other ergot alkaloids, sumatriptan and other 5-HT1 receptor agonists must also be avoided since this may result in enhanced vasoconstriction [see CONTRAINDICATIONS]. An interval of at least 24 hours should be observed before treating any further migraine attack with parenteral dihydroergotamine, any ergotamine-containing preparations, sumatriptan or other 5-HT1 receptor agonists.

Observed interactions to be considered

Beta-blockers
The beta-blocker propranolol has been reported to potentiate the vasoconstrictive action of ergot alkaloids by blocking the vasodilating property of epinephrine. Although the combination of beta-adrenergic blocking agents (e.g. propranolol) and Dihydergot is usually well tolerated, caution is required in patients with impaired peripheral circulation.

Serotonin reuptake inhibitors:
Concurrent use of Dihydergot with Serotonin reuptake inhibitors (e.g. amitriptyline) including selective agents (e.g. sertraline) can lead to serotonin like syndrome and need to be used with caution.

Glyceryl trinitrate:
The bioavailability of oral dihydroergotamine has been shown to be increased by 50-360 % in 4 patients following concomitant oral administration of glyceryl trinitrate due to an increase in splanchnic blood flow.
Anticipated interactions to be considered

CYP3A4 inducers

Drugs inducing CYP3A4 (e.g. nevirapine, rifampicin) can lead to a decrease in pharmacological action of dihydroergotamine.

Absence of interaction

No pharmacokinetic interactions involving other CYP450 isoenzymes are known.

ADVERSE REACTIONS

More common reactions:

Nausea and vomiting (not migraine-related) may occasionally occur.

Less common reactions:

Cardiovascular:

Vasospasms due to dihydroergotamine have been reported with a low frequency when administered by injection to patients at risk (peripheral vascular disease, multiple trauma, sepsis) and with macrolide antibiotics after oral administration. These reactions include cold extremities, peripheral paraesthesia (numbness and tingling in the fingers and toes), muscle cramps/pain, myocardial ischaemia (see also "Serious or life-threatening reactions").

Other cardiovascular reactions reported include myocardial ischaemia, hypertension, palpitation/tachycardia, bradycardia, extrasystoles. A few cases of myocardial infarction have been reported.

Central nervous system:

Convulsions (rare).

Reproductive:

Uterine contractions in pregnant women, neonatal asphyxia.

Dermatological:

Skin rash, pruritus.

Miscellaneous:

Diarrhoea, leg pain, abdominal pain, headache, dizziness, vertigo, tremor, restlessness/anxiety, hot flushes, dry mouth and hypersensitivity reactions (such as skin rash, face oedema, urticaria and dyspnoea).

In a few patients who have taken oral or injectable dihydroergotamine continuously over years, development of fibrotic changes, in particular of the pleura and retroperitoneum, has been observed. There have been isolated reports of fibrotic changes of the pericardium and cardiac valves (see “PRECAUTIONS – Fibrotic complications”).
Muscle spasms, peripheral ischemia and gangrene have been reported during post-marketing use. Headache primarily occurring at start of therapy in patients treated for headache/migraine has been reported with the i.v. formulation.

**Serious or life-threatening reactions:**

Although severe vasospasm is more likely to occur with ergotamine than with dihydroergotamine, parenteral administration of higher than usual doses of dihydroergotamine may cause severe vasospasm. The possibility of severe vasospasm from dihydroergotamine should be considered, especially if muscle pains in the extremities, numbness and tingling in fingers and toes, or precordial distress and pain occur. Renal artery spasm, peripheral ischaemia, intermittent claudication, Raynaud's phenomenon and gangrene have been described in isolated cases. Management of severe vasospasm should include discontinuing the drug, keeping the extremities warm, supportive care to prevent tissue damage and, if necessary, administering vasodilators (e.g. sodium nitroprusside, phentolamine or hydralazine).

The following adverse drug reactions (Table 1) have been derived from post-marketing experience with Dihydergot via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 1: Adverse drug reactions (frequency not known)**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity, Face oedema, Urticaria, Dyspnoea, Skin rash</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paraesthesia*, Numbness in fingers and toes*, Tingling feet/ hand*, Dizziness, Headache*</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial infarction*, Myocardial ischaemia*, Endocardial fibrosis***</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension, Vascular spasms**, Peripheral ischaemia, Gangrene</td>
</tr>
<tr>
<td>Respiratory, thoracic &amp; mediastinal disorders</td>
<td>Pleural fibrosis***</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, Vomiting, Abdominal pain, Diarrhoea, Retroperitoneal fibrosis***</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
</tr>
</tbody>
</table>

*Following parenteral administration, paraesthesia (e.g. numbness, tingling) in the fingers and toes, myocardial ischaemia and a few cases of myocardial infarction have been reported. With oral use such effects are extremely rare. Headache primarily occurring at start of therapy in patients treated for headache/migraine has been reported with the i.v. formulation.*
**Vascular spasms:** If signs of vascular spasms are observed, Dihydergot should be discontinued and treatment with a peripheral vasodilator initiated (see OVERDOSAGE).

***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. There have been isolated reports of fibrotic changes of the cardiac valves.

**DOSAGE AND ADMINISTRATION**

**Severe disabling orthostatic hypotension:**
It is preferable to first establish the extent of response by slow intravenous administration of 10 microgram/kg. Oral therapy should be commenced at half to one tablet three times a day, and the dose titrated by weekly increments until a satisfactory response is achieved. Due to extensive first pass metabolism, the effective dosage may vary considerably from individual to individual. Doses of up to 40-60 mg may be required in some cases. With prolonged treatment it may be possible to reduce the dosage.

**Acute migraine attack:**
1 mg (1 mL) i.m. or s.c. at the first sign of headache; in refractory cases a further 1 mg may be given at 30 to 60 minute intervals, to a total of 3 mg (3 mL). The following restriction must be observed: if supplementary antimigraine medication is required, the use of intranasal dihydroergotamine, any ergotamine-containing preparations or sumatriptan must be avoided [see CONTRAINDICATIONS and PRECAUTIONS – INTERACTIONS WITH OTHER MEDICINES]. Total weekly dosage should not exceed 6 mg (6 mL).

**Cluster headache (Horton's syndrome):** 0.5 mg (0.5 mL) by slow i.v. injection.

**Children under 12 years of age:** one-third to two-thirds of the adult dosage according to age.

Oral dihydroergotamine is not recommended for acute migraine attack because efficacy has not been demonstrated.

**OVERDOSE**

**Symptoms:**
Nausea, vomiting, headache, tachycardia, vertigo, peripheral signs and symptoms of vasospasm (e.g. numbness, tingling, peripheral ischemia, gangrene, and pain in the extremities), ergot poisoning, (initial signs may include dizziness, frontal headache, depression, leg and low back pain; more severe poisoning results in formication, severe cyanosis of the extremities, muscular twitching, tonic spasms, convulsions, delirium and death ) and coma.

**Treatment:**
In the case of orally ingested drug, administration of activated charcoal is advised.
Symptomatic treatment, including monitoring of the cardiovascular and respiratory systems. See ADVERSE REACTIONS - Serious or life-threatening reactions for the management of vasospasm.

In the event of severe vasospastic reactions, i.v. administration of a peripheral vasodilator such as nitroprusside, phentolamine or dihydralazine, local application of warmth to the affected area and nursing care to prevent tissue damage are recommended. In case of coronary constriction, appropriate treatment such as glyceryl trinitrate should be initiated.

PRESENTATION AND STORAGE CONDITIONS

Presentation
Tablets: 2.5 mg dihydroergotamine mesylate - whitish, scored and coded ZI on one side, SANDOZ on the other side; packs of 100 (no longer supplied).
Ampoules: 1 mg dihydroergotamine mesylate in 1 mL; packs of 5.

Storage
Ampoules: Store below 25°C. Protect from heat and light.
Tablets: Store below 30°C (no longer supplied)

SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Ltd
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE, NSW 2113
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