NOVARTIS

Drug Regulatory Affairs

HYDERGINE® / HYDERGINE® SRO / HYDERGINE® FAS / HYDERGIN®

(codergocrine mesilate)

1.0, 1.5, 2.0, 4.5 mg tablets (Hydergine®)

6.0 mg modified-release capsules (Hydergine® SRO)

4.5 mg modified-release tablets (Hydergine® FAS)

1 mg/1mL oral solution / 0.3 mg/1mL solution for injection, (Hydergin®)

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

HYDERGINE® 1.0, 1.5, 2.0, 4.5 mg tablets.

HYDERGINE® SRO 6.0 mg modified-release capsules.

HYDERGINE® FAS 4.5 mg modified-release tablets.

HYDERGIN® 1 mg/mL oral solution.

HYDERGIN® 0.3 mg/mL solution for injection.

2 Qualitative and quantitative composition

The active substance is codergocrine mesilate which is composed of equal parts of the mesilates of dihydroergocornine, dihydroergocristine and dihydroergocryptine (alpha-dihydroergocryptine and beta-dihydroergocryptine in the proportion 2:1).

Quantitative composition for each unit of:

Hydergine tablets: 1.0, 1.5, 2.0 or 4.5 mg

Hydergine SRO modified-release capsules: 6.0 mg

Hydergine FAS modified-release tablets: 4.5 mg

Hydergin oral solution (1 mL = 20 drops): 1.0 mg

Hydergin solution for injection in ampoules (1 mL): 0.3 mg

For excipients, see section 6.1.

3 Pharmaceutical form

Hydergine tablets

Hydergine SRO: modified-release capsules

Hydergine FAS: modified-release tablets

Hydergin oral solution

Hydergin solution for injection

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

- Symptoms and signs of mental deterioration, notably those related to ageing: dizziness, headache, poor concentration, disorientation, impaired memory, lack of initiative, mood depression, unsociability, difficulties with daily living activities and with self-care.
- Acute cerebrovascular disease.

- Migraine and vascular headaches (preventive treatment only).
- Peripheral vascular disorders.
- Subjective symptoms associated with arterial hypertension.

4.2 Posology and method of administration

Oral

3 to 6 mg daily, in divided doses, preferably before meals. For once daily dosage, either one tablet of 4.5 mg, or one Hydergine SRO capsule or one Hydergine FAS tablet, or 1.5 mL (30 drops) of the 3 mg/mL oral solution are recommended before breakfast unless otherwise prescribed by the physician. In patients with mental deterioration or with migraine, alleviation of symptoms is usually gradual and becomes manifest after 3 to 4 weeks. Prolonged therapy (3 months or more) is indicated and the course of treatment may be repeated as required.

Hydergine SRO capsules and Hydergine FAS tablets must be swallowed whole.

Parenteral

- In acute cerebrovascular disorders (especially when associated with hypertension) parenteral therapy is indicated initially in addition to oral treatment: 0.3 mg (1 mL) Hydergine by i.v. drip or slow i.v. injection (in 20 mL dextrose or saline) once or twice daily. Alternatively, 0.3 mg (1 mL) may be given intramuscularly or subcutaneously once to several times daily.
- In severe cases of peripheral vascular disease, 0.3 to 0.6 mg (1 to 2 mL) intramuscularly or subcutaneously once or twice daily, in addition to oral treatment. If necessary, Hydergine may also be given by intra-arterial injection (0.3 to 0.6 mg = 1 to 2 mL), preferably diluted in 10-20 mL saline.

4.3 Contraindications

Known hypersensitivity to codergocrine mesilate or to any of the excipients of Hydergine.

4.4 Special warnings and special precautions for use

Caution is required in patients with severe bradycardia.

Patients with moderate to severe hepatic impairment should be appropriately monitored. A lower starting dose may be considered, and a lower maintenance dose may be required.

Blood pressure may fall, and should therefore be checked following parenteral administration.

Hydergine tablets, SRO modified-release capsules and FAS modified-release tablets contain lactose and are not recommended in patients with rare hereditary problems of galactose intolerance, of lactase deficiency or of glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Components of codergocrine mesilate have been shown to be both, substrates and inhibitors of CYP3A4 (see section 5.2 Pharmacokinetics properties).

Caution is therefore required when codergocrine mesilate is used concomitantly with potent CYP3A4 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) - because exposure to codergocrine may increase, and exaggerated, predominantly dopaminergic, effects may be induced.

4.6 Pregnancy and lactation

Pregnancy

In animals, codergocrine mesilate and the 9-10 dihydrogenated ergot alkaloids have been shown to possess little potential for interfering with embryonic or foetal development and this is correlated with their reduced potential for vasoconstriction in comparison with the unsaturated ergot alkaloids.

The data on the use of codergocrine mesilate in pregnant women are very limited. Isolated cases of foetal malformation have, however, been reported and Hydergine should not be used during pregnancy.

Lactation

It is not known if codergocrine mesilate passes into the milk but this is likely to be the case since other ergot alkaloids do so. Codergocrine mesilate has dopamine agonistic properties and dihydroergocryptine (one of its constituents) has been shown to inhibit lactation. Hydergine should therefore not be administered to women who elect to breast-feed.

4.7 Effects on ability to drive and use machines

Hydergine may cause dizziness, therefore caution should be exercised when driving or operating machines. Patients experiencing dizziness should not drive or operate machinery.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports.

Table 1

Nervous system disorders

Rare:	Dizziness, headache
Cardiac disorders	
Rare:	Bradycardia
Vascular disorders	
Rare:	Hypotension (particularly after parenteral administration)
Respiratory, thoracic and mediastinal disorders	
Rare:	Nasal stuffiness
Gastrointestinal disorders	
Rare:	Nausea, stomach discomfort, vomiting, diarrhoea
Very rare:	Retroperitoneal fibrosis
Skin and subcutaneous tissue disorders	
Rare:	Rash

4.9 Overdose

There has been only a small number of reports of overdose with Hydergine. Most cases have been asymptomatic, or have involved unspecific, non-serious symptoms. There have been isolated reports of hallucinations.

In the event of overdose, administration of activated charcoal is recommended. Treatment should be symptomatic.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripheral vasodilators, ATC code: C04A E01

Animal studies indicate that Hydergine modifies cerebral neurotransmission, and there is evidence of both a stimulant effect on dopamine and serotonin receptors and for a blocking effect at alpha-adrenoceptor sites. Hydergine improves impaired cerebral metabolic function, an effect which is reflected in changes in the electrical activity of the brain, notably in the power spectra of the electro-encephalogram.

This beneficial effect on the brain function has been confirmed by experimental studies in man. Hydergine has also been found to shorten cerebral circulation time.

Controlled clinical trials have shown that Hydergine is effective in improving many of the symptoms of mental deterioration, especially age-related symptoms in the areas of self-care, social behaviour, emotional state, and mental performance.

Hydergine also has a stabilizing effect on the tone of cranial vessels, which accounts for its prophylactic effect in migraine.

Its beneficial effect in peripheral vascular disorders and on subjective symptoms associated with arterial hypertension attributed both to its dilator effect on precapillary sphincters and its alpha-adrenoceptor blocking activity.

5.2 Pharmacokinetic properties

Absorption

The absorption of Hydergine after oral administration is 25%. Maximum plasma concentrations are reached after 0.5 to 1.5 hours. Due to the first-pass effect, the bioavailability is between 5 and 12%.

Distribution

The volume of distribution is 1100 L (approx. 16 L/kg) and plasma protein binding is 81%.

Biotransformation

In vitro experiments suggest that CYP3A4 is the main cytochrome P450 isoenzyme responsible for the metabolism of the ergopeptide components of codergocrine mesilate [2].

Elimination

The elimination is biphasic, with a short half-life of 1.5 to 2.5 hours (alpha-phase) and a longer one of 13 to 15 hours (beta-phase). Hydergine is mainly excreted with the bile into the faeces. Elimination in the urine accounts for 2% of the unchanged drug and its metabolites and less than 1% of the unchanged substance alone. Total clearance is about 1800 mL/min.

Characteristics in patients

In elderly patients the plasma concentrations are somewhat higher than in younger subjects (in healthy elderly subjects total plasma clearance is reduced by approximately 30% compared with younger adults and there is a 2.5 fold increase in bioavailability, possibly as a result of a reduced extraction ratio).

In patients with renal impairment, dose reduction is rarely necessary because limited amounts of the drug and its metabolites are eliminated by the kidney.

Hydergine SRO

The slow release of codergocrine mesilate from Hydergine SRO capsules leads to a smoother pharmacokinetic profile compared with the equal daily amount of codergocrine mesilate in standard tablets. Hydergine SRO leads to similar minimum plasma concentrations, and lower and delayed maximum plasma concentrations (5-6 hours). The relative bioavailability of the 4.5 mg Hydergine SRO is 100% of that of the standard tablets.

Hydergine FAS

Hydergine FAS is a pharmaceutical formulation that combines the active substance in solid solution with an absorption-promoting excipient; the tablets also have an enteric coating. These features lead to produce high concentrations at the site of absorption, with bioavailability about one third higher with Hydergine FAS than with either Hydergine standard tablets or Hydergine oral solutions. Mean peak plasma concentrations are equal to

those with the conventional dosage forms, but are attained 2.5 to 4 hours later because Hydergine FAS tablets do not dissolve until they have reached the small intestine. The improvement in bioavailability with the FAS tablets is achieved by the persistence of elevated plasma concentrations over a longer period (from approx. 3 hours to a maximum of 24 hours) than with the conventional dosage forms.

5.3 Preclinical safety data

Preclinical data for Hydergine, Hydergine FAS as well as the excipient polyoxyethylene(24)-cholesterol ether (referred to as Solulan®) reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, mutageniciy, carcinogenic potential, toxicity to reproduction or local tolerance.

Effects in preclinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Adverse reactions were observed in preclinical studies at high dosages only. They were attributed to the pharmacodynamic activity of Hydergine or to the species-specific sensitivity of the test animals.

Acute toxicity

LD50 values after single intravenous injection of co-dergocrine mesylate (Hydergine) were found to be 180 mg/kg in mouse; 86 mg/kg in rat and 18.5 mg/kg in rabbit.

Specific to Hydergine FAS:

Acute toxicity of the excipient polyoxyethylene(24)-cholesterol ether (referred to as Solulan®) after single dose intravenous injection was 364 mg/kg in mice, 234 mg/kg in rats, and over 100 mg/kg in rabbits.

Acute toxicity of the Hydergine (1 part) and Solulan (4 parts) mixture after single intravenous injection was 335 mg/kg in mice, 232 mg/kg in rats, and over 100 mg/kg in rabbits. Consequently, the mixture, was of equal or lower acute toxicity than Hydergine alone. The mixture administered caused similar clinical symptoms as the individual components.

Subchronic and chronic toxicity

Hydergine, Hydergine FAS as well as the excipient polyoxyethylene(24)-cholesterol ether (referred to as Solulan) are devoid of a specific acute or chronic toxicity potential after oral or parenteral administration. There was no specific organ toxicity. Adverse effects, recorded at high dosages, were attributed to the pharmacodynamic activity of Hydergine or species-specific sensitivity of the test animals. In general, 9-10 dehydrogenated ergot derivatives are less toxic than natural alkaloids and exert a reduced potential for vasoconstriction and embryotoxicity.

Sufficient safety margins exist between the no-toxic-effect levels in animal experiments and the human therapeutic doses (about 0.1 mg/kg/day per os or 0.02 mg/kg/day i.v.).

Mutagenicity and carcinogenic potential

There was no evidence that Hydergine or the excipient Solulan had a mutagenic, or carcinogenic potential.

Reproduction toxicity

There has been no evidence that Hydergine or the excipient Solulan had a teratogenic potential in rats and rabbits. In rats, treated with 10 mg/kg/day (about 100 times the intended oral therapeutic dose in humans) borderline litter effects were noted. Maternal toxicity and fetotoxic effects such as reduced weight gain in dams, reduced weight of fetuses, and increased number of fetuses with retarded ossification were noted at 30 and 100 mg/kg/day.

Codergocrine mesilate and the 9-10 dihydrogenated ergot alkaloids have been shown to possess little potential for interfering with embryonic or fetal development and this is correlated with their reduced potential for vasoconstriction in comparison with the unsaturated ergot alkaloids.

Local tolerance

A local tolerance study was conducted in rabbits. Injection sites were examined macroscopically and microscopically 24 and 48 hours after the injections. Hydergine ampoule solution was well tolerated intramuscularly. The initial, concentration-dependent, slight irritation of the Hydergine ampoule solution was reduced after 24 hours considerably.

6 Pharmaceutical particulars

6.1 List of excipients

Hydergine 1.0 and 1.5 mg tablets:

Lactose, monohydrate; maize starch; povidone; talc; stearic acid.

Hydergine 2.0 and 4.5 mg tablets:

Lactose, monohydrate; maize starch; povidone; talc; magnesium stearate.

Hydergine SRO 6 mg modified-release capsule:

Capsule content: magnesium stearate; cetyl palmitate; hypromellose; lactose, monohydrate.

Capsule shell: gelatin, indigotine (E 132); erythrosine (E 127); iron oxide, black (E 172); titanium dioxide (E 171).

Printing ink: iron oxide, black (E 172); shellac.

Hydergine FAS 4.5 mg modified-release tablets:

Core tablet content: Povidone; lactose, anhydrous; cellulose, microcrystalline; pregelatinized starch; polyoxyethylene(24)-cholesterol ether; silica, colloidal anhydrous; magnesium stearate.

Coating content: hypromellose phthalate; glycerol triacetate; titanium dioxide (E 171); iron oxide yellow (E 172).

Hydergin 1 mg/mL oral solution:

Glycerol ; ethanol 96% v/v ; propylene glycol ; water, purified.

Hydergin 0.3 mg/mL solution for injection:

Ethanol 96% v/v; sodium chloride; methanesulphonic acid; water for injections.

Information might differ in some countries.

6.2 Incompatibilities

Not applicable for tablets, capsules and oral solution.

In the absence of compatibility studies, Hydergin solution for injection should not be mixed with other drugs.

6.3 Shelf life

Country-specific.

6.4 Special precautions for storage

Country-specific.

Hydergine / Hydergin should be kept out of the reach and sight of children.

6.5 Nature and contents of container

Country-specific.

6.6 Instructions for use and handling

No specific instruction for use.