NOVARTIS

Drug Regulatory Affairs

METHERGIN®

(methylergometrine)

Coated tablets; oral solution; solution for injection

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.

Author(s): Dr. T. Sergejew, E. Randolph

GPIC approval: 21 April 1998, amended 22 March 2005

Release date: 13 April 2005

Document status: Final

Number of pages: 8

1 Name of the medicinal product

METHERGIN® 0.125 mg coated tablets; 0.25 mg /1 mL oral solution; 0.2 mg / mL solution for injection.

2 Qualitative and quantitative composition

Active substance: 9,10-didehydro-N-[(S)-1-(hydroxymethyl)propyl]-6-methylergoline-8β-carboxamide hydrogen maleate (= methylergometrine hydrogen maleate, methylergonovine hydrogen maleate or methylergobasine hydrogen maleate).

One coated tablet contains 0.125 mg methylergometrine hydrogen maleate.

Oral solution: 1 mL contains 0.25 mg methylergometrine hydrogen maleate.

Solution for injection: 1 mL contains 0.2 mg methylergometrine hydrogen maleate.

For excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Coated tablets and oral solution for oral administration; solution for injection.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Active management of the third stage of labor (as a means to promote separation of the placenta and to reduce blood loss).

Treatment of uterine atony/hemorrhage occurring during and after the third stage of labor, in association with Cesarean section or following abortion.

Treatment of subinvolution of the uterus, lochiometra, puerperal bleeding.

Methergin® is not recommended during breast-feeding (see section 4.6 Use during pregnancy and lactation).

4.2 Posology and method of administration

Active management of the third stage of labor

0.5 to 1 mL (0.1 to 0.2 mg) slowly i.v. (see section 4.4 Special warnings and special precautions for use) following delivery of the anterior shoulder or, at the latest, immediately after delivery of the child. Expulsion of the placenta, usually separated by the first strong contraction following Methergin, should be manually assisted by applying fundal pressure.

For delivery under general anesthesia, the recommended dose is 1 mL (0.2 mg).

Treatment of uterine atony/hemorrhage

1 mL (0.2 mg) i.m. or 0.5 to 1 mL (0.1 to 0.2 mg) slowly i.v. (see section 4.4 Special warnings and special precautions for use). May be repeated every 2 to 4 hours, if necessary, up to five doses within 24 hours.

Treatment of subinvolution, lochiometra, puerperal bleeding

0.125 to 0.25 mg p.o. (1 or 2 tablets or 0.5 to 1 mL of the oral solution), or 0.5 to 1 mL (0.1 to 0.2 mg) s.c. or i.m., up to 3 times daily.

4.3 Contraindications

Pregnancy; first stage of labor; second stage of labor before crowning of the head (Methergin must not be used for induction or enhancement of labor); severe hypertension; pre-eclampsia and eclampsia; occlusive vascular disease (including ischemic heart disease); sepsis; known hypersensitivity to methylergometrine, to other ergot alkaloids or to any excipients of Methergin.

4.4 Special warnings and special precautions for use

In breech presentation and other abnormal presentations Methergin should not be given before delivery of the child is completed, and in multiple birth not before the last child has been delivered.

Active management of the third stage of labor requires obstetric supervision.

Intravenous injections must be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intra- or periarterial injection must be avoided.

Caution should be exercised in the presence of mild or moderate hypertension (severe hypertension is a contraindication) or impaired hepatic or renal function.

Methergin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Methergin tablets.

Methergin oral solution contains ethanol (50 mg per 1 mL). This should be taken into account for those suffering from alcoholism, in children, in pregnant or breast-feeding women and in high-risk groups such as patients with liver disease, or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

Ergot alkaloids have been shown to be inhibitors of CYP3A.

The concomitant use of Methergin with potent 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) should be avoided, since this can result in an elevated exposure to methylergometrine and ergot toxicity (vasospasm and ischemia of the extremities and other tissues).

Caution is required for the concomitant use of Methergin with less potent CYP3A inhibitors.

Caution should be exercised when Methergin is used concurrently with other vasoconstrictors or other ergot alkaloids. Methylergometrine may enhance the vasoconstrictor/vasopressor effects of other drugs such as triptans ($5HT_{1B/1D}$ receptor agonists), sympathomimetics (including those in local anesthetics) or other ergot alkaloids.

The concomitant use of bromocriptine and Methergin in the puerperium is not recommended.

No adverse interactions are known to occur with the concurrent administration of Methergin and oxytocin. For prevention and treatment of uterine hemorrhage by i.m. injection, it may be advantageous to combine the two uterotonic principles, since oxytocin has a very short latent period whereas Methergin possesses a prolonged duration of action.

Anesthetics like halothan and methoxyfluran may reduce the oxytocic potency of Methergin.

4.6 Pregnancy and lactation

Pregnancy

The use of Methergin in pregnancy is contraindicated because of its potent uterotonic activity.

Lactation

Methergin has been reported to reduce milk secretion and to be excreted in the breast milk (see section 5.2 Pharmacokinetic properties). There have been isolated reports of intoxication in breast-fed infants whose mothers were receiving the drug for several days. One or more of the following symptoms were observed (and disappeared upon withdrawal of the medication): elevated blood pressure, bradycardia or tachycardia, vomiting, diarrhea, restlessness, clonic cramps.

In view of the possible side effects for the child and the reduction of the milk yield Methergin is not recommended for use during breast-feeding.

4.7 Effects on ability to drive and use machines

Methylergometrine may cause dizziness and convulsions. Therefore, caution should be exercised when driving or operating machines, especially at the start of treatment.

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

Immune system disorders		
	Very rare	Anaphylactic reactions.
Nervous system disorders		
	Common	Headache.
	Uncommon	Dizziness, convulsions.
	Very rare	Hallucinations.
Ear and labyrinth disorders		
	Very rare	Tinnitus.
Cardiac disorders		
	Uncommon	Chest pain.
	Rare	Bradycardia, tachycardia, palpitations.
	Very rare	Myocardial infarction, arteriospasm coronary.
Vascular disorders		

Common	Hypertension.
Uncommon	Hypotension.
Rare	Arterial spasm (peripheral).
Very rare	Thrombophlebitis.
Respiratory, thoracic and mediastinal disorders	
Very rare	Nasal congestion.
Gastrointestinal disorders	
Uncommon	Nausea, vomiting.
Very rare	Diarrhoea.
Skin and subcutaneous tissue disorders	
Common	Skin eruptions.
Uncommon	Hyperhidrosis.
Musculoskeletal and connective tissue disorders	
Very rare	Muscle cramp.
Pregnancy, puerperium and perinatal conditions	
Common	Abdominal pain (caused by uterine contractions).

4.9 Overdose

Symptoms

Nausea; vomiting; hypertension or hypotension; numbness; tingling and pain in the extremities; respiratory depression; convulsions; coma.

Treatment

Elimination of orally ingested drug by administration of high doses of activated charcoal.

Symptomatic treatment under close monitoring of the cardiovascular and the respiratory system.

If sedation is required, benzodiazepines may be used.

In case of severe arteriospasm, vasodilators should be administered, e.g. sodium nitroprusside, phentolamine or dihydralazine. In the event of coronary constriction, appropriate antianginal treatment should be provided (e.g. nitrates).

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: oxytocics (ATC code G02A B01)

Methylergometrine, a semi-synthetic derivative of the naturally occurring alkaloid ergometrine, is a potent and specific uterotonic agent. It acts directly on the smooth muscle of the uterus and increases the basal tone, frequency and amplitude of rythmic contractions. Compared with other ergot alkaloids, its effects on cardiovascular and central nervous system are less pronounced. The strong and selective oxytocic effect of methylergometrine results from its specific pattern of actions as partial agonist and antagonist at serotoninergic, dopaminergic and α-adrenergic receptors. Neverthless, this does not totally preclude from vasoconstrictory complications (see section 4.8 Undesirable effects).

5.2 Pharmacokinetic properties

The onset of action of Methergin occurs 30 to 60 seconds after i.v., 2 to 5 minutes after i.m., and 5 to 10 minutes after oral administration, and lasts for 4 to 6 hours.

Absorption

Studies conducted in fasted healthy female volunteers have shown that oral absorption of a 0.2 mg Methergin tablet was fairly rapid with a mean peak plasma concentration (C_{max}) of 3243 ± 1308 picogram/mL observed at 1.12 ± 0.82 hours (t_{max}). For a 0.2 mg i.m. injection, C_{max} was 5918 ± 1952 picogram/mL and t_{max} 0.41 ± 0.21 hours. The bioavailability of the tablet was equivalent to that of the i.m. solution given orally and dose proportional following administration of 0.1, 0.2 and 0.4 mg. After i.m. injection, the extent of absorption was about 25% greater than after oral administration. A delayed gastrointestinal absorption (t_{max} about 3 hours) was observed in postpartum women during continuous treatment with Methergin tablets.

Distribution

Following i.v. injection, methylergometrine is rapidly distributed from plasma to peripheral tissues within 2 to 3 minutes or less. In healthy female volunteers the distribution volume is 56.1 ± 17.0 liters. It is unknown whether the drug crosses the blood-brain barrier.

Biotransformation

Methylergometrine is metabolised mainly in the liver. The metabolic pathway has not been investigated in humans. *In vitro* studies showed N-demethylation and hydroxylation of the phenyl ring.

Elimination

In healthy female volunteers the plasma clearance is 14.4 ± 4.5 liters per hour and the mean elimination half-live 3.29 ± 1.31 hours. A study in male volunteers has shown that only about 3% of an oral dose is eliminated as parent drug in the urine. The drug is mainly eliminated with the bile into the feces. During continuous treatment the drug is also secreted into the milk. A milk-plasma ratio of about 0.3 was found.

5.3 Preclinical safety data

Acute toxicity

The LD_{50} values determined after single oral treatments were 140 and 93 mg/kg in the mouse and the rat. After single i.v. treatments the LD_{50} values were 85, 23, 2 and 45 mg/kg in the mouse, rat, rabbit and guinea pig.

Subacute/chronic toxicity

No results from long-term toxicity studies with Methergin are available.

Reproduction toxicity

No studies have been performed to assess the reproduction toxicity of Methergin.

Mutagenic and carcinogenic potential

The effect of Methergin on mutagenesis and carcinogenesis has not been determined.

6 Pharmaceutical particulars

6.1 List of excipients

Methergin coated tablets: maleic acid; stearic acid; gelatin; talc; maize starch; lactose; iron oxide red (E172);silica, colloidal anhydrous; acacia; sucrose; cetyl palmitate.

Methergin oral solution: propyl parahydroxybenzoate (E216); methyl parahydroxybenzoate (E218); maleic acid; disodium maleate dihydrate; ethanol 96% v/v; propylene glycol; water, purified.

Methergin solution for injection: maleic acid; sodium chloride; water for injection.

Information might differ in some countries.

6.2 Incompatibilities

None known.

6.3 Shelf life

Methergin coated tablets: 5 years.

Methergin oral solution: 2 years.

Methergin solution for injection: 4 years if stored at 2-8°C; the ampoules may be stored for 14 days out of a refrigerator but not above 25°C.

Information might differ in some countries.

6.4 Special precautions for storage

Methergin coated tablets: store below 30 °C.

Methergin oral solution: protect from light; store in a refrigerator (2-8°C); 3 months after opening the bottle, the solution has to be discarded if not used.

Methergin solution for injection: protect from light; store in a refrigerator (2-8°C); protect from freezing; the ampoules may be stored for 14 days out of a refrigerator but not above 25°C.

Methergin must be kept out of the reach and sight of children.

Information might differ in some countries.

6.5 Nature and contents of container

Methergin coated tablets: Alu/PVC/PVDC blister pack.

Methergin oral solution: bottle made of amber glass with a rubber stopper kept in place with an aluminium seal cap. For the period of use, the closure is a screw cap with dosing pipette.

Methergin solution for injection: ampoules made of colorless borosilicate glass.

Information might differ in some countries.

6.6 Instructions for use and handling

Methergin oral solution: 3 months after opening the bottle, the solution has to be discarded if not used.

Methergin solution for injection: the ampoules may be stored for 14 days out of a refrigerator but not above 25°C.