NOVARTIS

METHERGIN®
(methylergometrine)

0.125 mg Sugar Coated Tablets & 0.2 mg/mL Solution for Injection

LEAFLET

Trade name
METHERGIN® 0.125 mg sugar coated tablets; 0.2 mg/mL solution for injection.

Description and composition
Pharmaceutical form
Sugar coated tablets for oral administration; solution for injection.

Active substance(s)
Active substance: methylergometrine hydrogen maleate, or methylergonovine hydrogen maleate
One sugar coated tablet contains 0.125 mg methylergometrine hydrogen maleate.
Solution for injection: 1 mL contains 0.2 mg methylergometrine hydrogen maleate.

Active moiety
Methylergometrine

Excipients
Methergin sugar coated tablets: maleic acid; stearic acid; gelatin; talc; maize starch; lactose; iron oxide red; acacia; sucrose.
Methergin solution for injection: maleic acid; sodium chloride; water for injection.

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
  - following abortion.
- Treatment of subinvolution of the uterus, lochiometra, puerperal bleeding.

Dosage and administration
Dosage
General target population
Active management of the third stage of labor
Intramuscular injection (i.m.) is the recommended route of administration. When administered intravenously (i.v.) the dose must be administered slowly over a period of no less than 60 seconds (see section Warnings and precautions)
The recommended dosage of Methergin is: 1 ml (0.2 mg) i.m. or 0.5 to 1 mL (0.1 to 0.2 mg) slowly i.v. 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) by slow intravenous injection.

Treatment of uterine atony/hemorrhage
Intramuscular injection (i.m.) is the recommended route of administration. When administered intravenously (i.v.) the dose must be administered slowly over a period of no less than 60 seconds (see section Warnings and precautions)

The recommended dosage of Methergin is: 1 mL (0.2 mg) i.m. or 0.5 to 1 mL (0.1 to 0.2 mg) slowly i.v. The dose may be repeated as required at intervals of no less than 2 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 i.m., up to 3 times daily; in lactating women preferably for no longer than 3 days.

Special populations
Renal impairment / Hepatic impairment
Caution should be exercised in the presence of impaired hepatic or renal function (see section Warnings and precautions).

Contraindications

- Pregnancy
- First stage of labor
- Second stage of labor before delivery of the anterior shoulder (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.

Warnings and precautions

General recommendation on administration
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.

Breast-feeding
Due to the possible side effects for the child and the reduction of the milk yield, Methergin is not recommended for use during breast-feeding. Women should not breast-feed during treatment with Methergin and at least 12 hours after administration of the last dose. Milk secreted during this period should be discarded (see section Women of child-bearing potential, pregnancy, breast-feeding and fertility).

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

Coronary artery disease
Patients with coronary artery disease or with risk factors for coronary artery disease (e.g. smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergometrine-induced vasospasm (see section Adverse drug reactions)

Medication errors
Accidental administration to the newborn infant has been reported. In these accidental neonatal overdosage cases, symptoms such as respiratory depression, convulsions, cyanosis, oliguria, have been reported. Furthermore, encephalopathy has been reported in infants presenting with signs and symptoms such as irritability, agitation and lethargy. Treatment should be symptomatic; in severe cases respiratory and cardiovascular support have been required. Fatal cases have been reported in the absence of adequate treatment (see section Overdosage)

Interactions
Ergot alkaloids are substrates of CYP3A4. The concomitant use of Methergin 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) 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) (see section Interactions).
The concomitant use of Methergin with bromocriptine in the puerperium, or with prostaglandins is not recommended (see section Interactions).
Caution is required when using Methergin with drugs with less potent CYP3A4 inhibitors (e.g. cimetidine, delavirdine, grapefruit juice, quinupristin, dalfopristin) or with drugs with vasoconstrictor/vasopressor effects such as triptans ($5HT_{1B/1D}$ receptor agonists), sympathomimetics, other ergot alkaloids or beta-blockers (see section Interactions).

Adverse drug reactions
Adverse reactions (Table 1) are listed by MedDRA system organ classare ranked by frequency, with the most frequent first;. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS II): 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).

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	Vasoconstriction, vasospasm, arterial spasm
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 spasms
Pregnancy, puerperium and perinatal conditions	
Common	Abdominal pain (caused by uterine contractions).

Adverse drug reactions from post-marketing spontaneous reports and literature cases (frequency not known)
The following adverse drug reactions have been derived from post-marketing experience with Methergin 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.

Nervous system disorders
Cerebrovascular accident, paraesthesia

Cardiac disorders
Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block

Interactions
Ergot alkaloids are substrates of CYP3A4

Interactions resulting in concomitant use not being recommended
CYP3A4 inhibitors
The concomitant use of Methergin 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) 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) (see section Warnings and precautions)

Bromocriptine
The concomitant use of bromocriptine and Methergin in the puerperium is not recommended as methylergometrine may enhance the vasoconstrictor effect of other ergot alkaloids (see section Warnings and precautions)
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.

Prostaglandins
Prostaglandins (e.g. sulprostone, dinoprostone, misoprostol) facilitate contraction of the myometrium hence, Methergin can potentiate the uterine action of prostaglandins and vice versa. Concomitant use with these drugs is not recommended (see section Warnings and precautions).

Interactions to be considered

Less potent CYP3A4 inhibitors
Caution is required for the concomitant use of Methergin with less potent CYP3A4 inhibitors since this may result in an elevated exposure to methylergometrine (e.g. cimetidine, delavirdine, grapefruit juice, quinupristin, dalfopristin)

Vasoconstrictors, triptans, sympathomimetics and other ergot alkaloids
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 (see section Warnings and precautions).

Beta-blockers
Caution should be exercised when Methergin is used concurrently with beta-blockers. Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids (see section Warnings and precautions).

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

CYP3A4 inducers
Drugs (e.g. nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of Methergin.

Glyceryl trinitrate and other antianginal drugs
Methylergometrine produces vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential
Not applicable for Methergin due to the targeted indications.

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

Breast-feeding
Methergin has been reported to reduce milk secretion and to be excreted in the breast milk (see section 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, convulsion. 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. Women should not breast-feed during treatment

with Methergin and at least 12 hours after administration of the last dose. Milk secreted during this period should be discarded. (see section Warnings and precautions)

Fertility
Not applicable for Methergin due to the targeted indications.

Driving and using machines
Methylergometrine may cause dizziness and convulsions. Therefore, caution should be exercised when driving or operating machines.

Overdosage

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).

Medication errors
Accidental administration to the newborn infant has been reported. In these accidental neonatal overdosage cases, symptoms such as respiratory depression, convulsions, cyanosis, oliguria, have been reported. Furthermore, encephalopathy has been reported in infants presenting with signs and symptoms such as irritability, agitation and lethargy. Treatment should be symptomatic; in severe cases respiratory and cardiovascular support have been required. Fatal cases have been reported in the absence of adequate treatment (see section Overdosage)

Clinical pharmacology

ATC Code
Pharmacotherapeutic group: oxytocics (ATC code G02A B01).

Mechanism of action (MOA)
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.

Pharmacodynamics
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. Nevertheless, this does not totally preclude from vasoconstrictory complications (see section Adverse drug reactions).

For prevention and treatment of uterine hemorrhage by i.m. injection, the concurrent administration of Methergin and oxytocin can be considered as oxytocin has a very short latent period whereas methylergometrine possesses a prolonged duration of action.

Pharmacokinetics
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.
In healthy female volunteers, following oral administration, 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. Methylergometrine is also secreted into the breast milk.
After 1 h of single oral administration of 250 microgram of methylergometrine, the milk / plasma concentration ratio was 0.18±0.03. The half-life of methylergometrine reported in milk is 2.3 ± 0.3 h

Linearity / non-linearity
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

Bioavailability / bioequivalence studies
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

Clinical studies
Methergin is an established product. There are no recent clinical data regarding the approved indications for Methergin.

Non-clinical safety data
The genotoxic potential of methylergometrine has not been determined. No studies are available which evaluated the carcinogenic potential of methylergometrine. Standard animal studies on fertility and reproduction toxicity have not been performed with methylergometrine.

Pharmaceutical information
Incompatibilities
None known.

Shelf life
Methergin sugar coated tablets: 3 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.

Special precautions for storage
Methergin sugar coated tablets: do not store above 25°C.
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.

Nature and contents of container
Methergin sugar coated tablets: strip : PT/PE/Al/PE.
Methergin solution for injection: ampoules made of colorless borosilicate glass.

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

Packing and Registration Number
Methergin® solution for injection :
Box of 10 ampoules @ 1 mL — Reg. No.DKI9667501543A1
Methergin® sugar coated tablets :
Box of 10 strips @ 10 Sugar Coated Tablets — Reg. No.DKL8630402916A1

HARUS DENGAN RESEP DOKTER
To be dispensed only on the prescription of a physician

Methergin® solution for injection:
Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.
Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Methergin® sugar coated tablets :
Manufactured by PT Novartis Indonesia, Jakarta, Indonesia, under license and control of Novartis Pharma AG, Basel, Switzerland.

Leaflet based on CDS 28-Jan-2015