Healthcare Provider and Pharmacist Alert: Supply Disruption of METHERGIN® (methylergometrine maleate) tablets 0.125 mg

Dear Healthcare Professional,

This is to inform you regarding an emerging supply disruption of Methergin (methylergometrine maleate) Tablets 0.125 mg, distributed in Israel. METHERGIN® is licensed for use in prevention or treatment of uterine haemorrhage. It is expected that the shortage will become effective as of September 2017, after which time we are unable to guarantee the supply of METHERGIN® tablets.

Considerations for you and your patients:

Substitution of METHERGIN® (methylergometrine maleate) tablets with a generic version of methylergometrine should be considered, if available. If other methylergometrine products are not available in Israel, we recommend you to use any other suitable alternatives treatment available. Please refer to the prescribing information enclosed for further information on the approved indications and other information.

We have informed local Health Authorities of this supply disruption. Novartis places the highest priority on patient health and access to our medicines. We acknowledge the impact of this supply disruption that may have on the patients.

Should you have any questions, please do not hesitate to contact Novartis Israel Ltd. at:

e-mail: il.medinfo@novartis.com
Fax no.: 03-9231817

We will keep you informed as further information becomes available.

Yours sincerely,

Osnat Meron Ozeri (Appointed Pharmacist) and Hagar Salman (medical advisor)
METHERGIN®

(methylergometrine)

Coated tablets

Prescribing Information

1 Trade name

METHERGIN® 0.125 mg tablets.

2 Description and composition

Pharmaceutical form

Coated tablets for oral administration.

Active substance

Active substance: methylergometrine hydrogen maleate or methylergonovine maleate.

One coated tablet contains 0.125 mg methylergometrine hydrogen maleate.

Active moiety

Methylergometrine

Excipients

Methergin coated tablets: Lactose, monohydrate, Sucrose; crystalline (Saccharose), Talc, Maize starch, Acacia (Gum accacia, Acacia spray-dried), Gelatin, Iron oxide pigment red, Stearic acid, Silica; colloidal anhydrous (Silicic acid colloidal), Maleic acid, Cetylpalmitate; atomized.

3 Indications

Prevention or treatment of uterine haemorrhage.
4 Dosage and administration

Dosage

General target population

The recommended dosage of Methergin is: 1 or 2 tablets (0.125 to 0.25 mg) orally, up to 3 times daily and usually for up to 5 days.

Special populations

Renal impairment / Hepatic impairment

Caution should be exercised in the presence of impaired hepatic or renal function (see section 6 Warnings and precautions).

5 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

6 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.

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

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 9 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 7 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 10 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 8 Interactions).

The concomitant use of Methergin with bromocriptine in the puerperium, or with prostaglandins is not recommended (see section 8 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<sub>1B/1D</sub> receptor agonists), sympathomimetics, other ergot alkaloids or beta-blockers (see section 8 Interactions).

**Driving and using machines**

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

**7 Adverse drug reactions**

Adverse reactions (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are 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 III): 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 7-1 Adverse drug reactions**

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Very rare</th>
<th>Anaphylactic reactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dizziness, convulsions.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hallucinations.</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Very rare</td>
<td>Tinnitus.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Chest pain.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Bradycardia, tachycardia, palpitations.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Myocardial infarction, arteriospasm coronary.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hypertension.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypotension.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Vasoconstriction, vasospasm, arterial spasm.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Thrombophlebitis.</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very rare</td>
<td>Nasal congestion.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
<td>Vomiting, nausea.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Diarrhoea.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
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<tr>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin eruptions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
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<tr>
<td>Hyperhidrosis.</td>
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</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Muscle spasms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy, puerperium and perinatal conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Abdominal pain (caused by uterine contractions)</td>
</tr>
</tbody>
</table>

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. Since 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form [http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il](http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

8 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), orazole antifungals (e.g. ketoconazole,itraconazole, voriconazole) should be avoided, since this can result in an
increased exposure to methylergometrine and ergot toxicity (vasospasm and ischemia of the extremities and other tissues) (see section 6 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 6 Warnings and precautions).

**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 6 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 increased 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<sub>1B/1D</sub> receptor agonists), sympathomimetics (including those in local anesthetics) or other ergot alkaloids (see section 6 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 6 Warnings and precautions).

**Anesthetics**

Anesthetics like halothan and methoxyflurane may reduce the oxytocic potency of Methergin (see section 2 Dosage and administration).

**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 induces vasoconstriction and may reduce the effect of glyceryl trinitrate and other antianginal drugs.
9 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 11 Clinical pharmacology / Pharmacokinetics). 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 and 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 6 Warnings and precautions).

Fertility
Not applicable for Methergin due to the targeted indication.

10 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 anti-anginal 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 6 Warnings and precautions).

11 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 rhythmic contractions. Compared with other ergot alkaloids, its effects on the 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 \(\alpha\)-adrenergic receptors. Nevertheless, this does not totally preclude from vasoconstrictory complications (see section 7 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 has a prolonged duration of action.

Pharmacokinetics

The onset of action of Methergin occurs 5 to 10 minutes after oral administration, and lasts for 4 to 6 hours.

Absorption

Studies conducted in fasting healthy female volunteers have shown that oral absorption of a 0.2 mg Methergin tablet was fairly rapid with a mean peak plasma concentration \((C_{\text{max}})\) of 3243 ± 1308 picogram/mL observed at 1.12 ± 0.82 hours \((t_{\text{max}})\). For a 0.2 mg i.m. injection, \(C_{\text{max}}\) was 5918 ± 1952 picogram/mL and \(t_{\text{max}}\) 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 ($t_{\text{max}}$ 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 / Metabolism**

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, following oral administration, the plasma clearance is 14.4 ± 4.5 liters per hour and the mean elimination half-life 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 one hour 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 dose proportional following administration of 0.1, 0.2 and 0.4 mg.

**12 Clinical studies**

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

**13 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.
14 Pharmaceutical information

Incompatibilities
None known.

Special precautions for storage
Store below 25 °C.
Protect from moisture.
Methergin must be kept out of the reach and sight of children.

Manufacturer:
Novartis Pharma Produktions GmbH, Wehr, Germany
For: Novartis Pharma AG, Basel, Switzerland

Registration Holder:
Novartis Israel Ltd.
36 Shacham street, Petach-Tikva.