SYNTOMETRINE®
(synthetic oxytocin/ergometrine maleate)

NAME OF THE MEDICINE

Active ingredient  oxytocin  ergometrine maleate
Chemical name  l-cysteinyl-l-tyrosyl-l-isoleucyl-l-glutamyl-l-asparaginyl-l-cysteinyl-l-prolyl-l-leucylglycinamide cyclic (1→6)-disulfide
CAS number  50-56-6  129-51-1
Molecular weight  1007  441.5
Molecular formula  C_{43}H_{66}N_{12}O_{12}S_{2}  C_{19}H_{23}N_{3}O_{2}.C_{4}H_{4}O_{4}

DESCRIPTION
Syntometrine injection is a sterile, clear, colourless solution, faintly bluish fluorescent, containing synthetic oxytocin 5 IU/mL and ergometrine maleate 500 micrograms/mL. It contains acetic acid, chlorobutanol hemihydrate, maleic acid, sodium acetate trihydrate, sodium chloride and water for injections and it is buffered to pH 3.2.

PHARMACOLOGY
Pharmacodynamic properties
Pharmacotherapeutic group: Ergot alkaloids and oxytocin incl. analogues, in combination; ATC code: G02AC.

Syntometrine combines the rapid uterine action of oxytocin, a nonapeptide hormone released by the posterior lobe of the pituitary, with the sustained uterotonic effect of ergometrine.

Pharmacokinetics
Following intramuscular administration, the latent period for the occurrence of the uterine response is considerably shorter with Syntometrine (about 2½ min) than with ergometrine given alone (about 7 min) whereas the uterotonic effect of Syntometrine lasts for several hours, compared with only ½-1 hour when oxytocin is given alone.

These properties make Syntometrine i.m. suitable for the active management of the third stage of labour (see DOSAGE AND ADMINISTRATION) and for the prevention or treatment of postpartum haemorrhage, particularly in situations where for any reason the intravenous administration of an uterotonic agent is impracticable.

INDICATIONS
- Active management of the third stage of labour
- Prevention and treatment of post-partum haemorrhage associated with uterine atony
CONTRAINDICATIONS

- Hypersensitivity to oxytocin, ergometrine, or to any of the components in the formulation
- Pregnancy, labour (except in second stage of labour following the delivery of the anterior shoulder) (see Use in Pregnancy)
- Severe hypertension, pre-eclampsia, or eclampsia
- Severe cardiac disorders
- Severe hepatic or renal impairment
- Occlusive vascular disease
- Sepsis.

PRECAUTIONS

In breech presentation and other abnormal presentations, Syntometrine should not be given until after delivery of the child is completed. When Syntometrine is used for the management of the third stage of labour the possibility of multiple pregnancy must be assessed; Syntometrine should not be given until the last child has been delivered (see Use in Pregnancy).

Ergometrine derivatives are excreted in breast milk but in unknown amounts. When mothers are administered with multiple doses of Syntometrine, a higher amount of the drug may be excreted through breast milk. The effects of Syntometrine on breast fed newborns are unknown (see Use in Lactation).

Syntometrine should only be administered under hospital conditions and with qualified medical supervision. Active management of the third stage of labour requires expert obstetric supervision.

In post-partum haemorrhage, if bleeding is not arrested by the injection of Syntometrine, the possibility of retained placental fragments, of soft tissue injury (cervical or vaginal laceration) or of a clotting defect should be considered and appropriate measures taken before a further injection is given.

Ergot alkaloids are substrates of CYP3A4. The concomitant use of Syntometrine with strong 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 elevated exposure to methylergometrine and ergot toxicity (vasospasm and ischemia of the extremities and other tissues). Caution should be exercised when Syntometrine is used concurrently with other vasoconstrictors or other ergot alkaloids. Concurrent use of vasoconstrictors and Syntometrine after delivery during anesthesia may lead to severe postpartum hypertension. Methylergometrine may enhance the vasoconstrictor/vasopressor effects of other drugs such as triptans (5HT1D receptor agonists), sympathomimetics (including those in local anesthetics), beta-blockers or other ergot alkaloids (see INTERACTIONS WITH OTHER MEDICINES).

Caution is required when using Syntometrine alone or in combination with prostaglandins and their analogues in the treatment of postpartum atonic uterine haemorrhage (see INTERACTIONS WITH OTHER MEDICINES).

Caution is required in patients with mild or moderate hypertension, cardiac disorders, or hepatic or renal impairment. Severe forms are contraindicated (see CONTRAINDICATIONS and PHARMACOLOGY). Patients with coronary artery disease may be more susceptible to myocardial ischemia and infarction caused by ergometrine-induced vasospasm (see ADVERSE EFFECTS). Caution is also required in patients with respiratory disease, chronic anaemia and toxemia of pregnancy.

Oxytocin should be considered as potentially arrhythmogenic. Caution is required when using Syntometrine in patients with other risk factors for torsades de pointes such as drugs which prolong the QT interval or in patients with a history of long QT syndrome (see INTERACTIONS WITH OTHER MEDICINES).

Ergometrine can cause vasoconstriction and should therefore be used with caution in patients with Raynaud’s phenomenon. Treatment should be stopped if signs of vasoconstriction develop.

Accidental administration to the newborn infant has been reported. Treatment should be symptomatic; in most cases respiratory and cardiovascular support has been required (see OVERDOSAGE).

For oxytocin specific precautions, see Syntocinon® Product Information.
Use in Pregnancy: (Category C)
Ergometrine induces uterine contraction and may cause premature or hypertonic labour. Products containing ergometrine must be avoided during pregnancy.

Ergometrine has potent uterotonic activity. Therefore Syntometrine is contraindicated during pregnancy and during induction of labour; first stage labour and second stage labour prior to the delivery of the anterior shoulder (see CONTRAINDICATIONS).

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

Use in Lactation:
There is no specific data available for elimination of ergometrine partitioned in breast-milk. Considering the short half-life (30-120 mins) of ergometrine and the negligible amount of breast milk available during the first 24 hours of immediate post-partum period, a single dose of Syntometrine to the mother during third stage of labour is unlikely to have effects on breast fed newborn. When mothers are administed with multiple doses of Syntometrine, a higher amount of the drug may be excreted through breast milk. The effects of Syntometrine on breast fed newborns are unknown.

Repeated use of Ergometrine can inhibit prolactin secretion and in turn can suppress lactation.

Renal impairment/hepatic impairment
No studies have been performed in patients with renal or hepatic impairment. However considering the metabolic pathway of ergometrine and oxytocin, use is contraindicated in severe hepatic and renal impairment and caution is required in mild or moderate hepatic and renal impairment.

Paediatric Use
No studies have been performed in paediatric patients. Syntometrine is not indicated for use in children.

INTERACTIONS WITH OTHER MEDICINES

Interactions related to both oxytocin and ergometrine administration
Interactions resulting in concomitant use are not recommended (see PRECAUTIONS)
Vasoconstrictors/Sympathomimetics
Syntometrine may enhance the pressor effect of vasoconstrictor drugs and sympathomimetics, even those contained in local anaesthetics.

Prostaglandins and their analogues
Prostaglandins and their analogues facilitate contraction of the myometrium hence Syntometrine can potentiate the uterine action of prostaglandins and analogues and vice versa. Therefore very careful monitoring is recommended in cases of concomitant administration.

Interactions to be considered
Inhalation anaesthetics
Inhalation anaesthetics (e.g. halothane, cyclopropane, sevoflurane, desflurane, isoflurane) have a relaxing effect on uterus and produce a notable inhibition of uterine tone and thereby, anaesthesia may diminish the uterotonic effect of Syntometrine.

Interactions related to oxytocin administration
Interactions resulting in concomitant use not recommended (see PRECAUTIONS)
Drugs prolonging the QT interval
Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for torsades de pointes such as drugs which prolong the QT interval or in patients with history of long QT syndrome.

Interactions related to ergometrine administration
Interactions resulting in concomitant use not recommended (see PRECAUTIONS)
CYP3A4 inhibitors
Strong CYP3A4 inhibitors such as protease inhibitors, macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine), azole
antifungals (e.g. ketoconazole, itraconazole, voriconazole), quinolones might raise the levels of ergot derivatives, which may lead to ergotism. Combined use with Syntometrine should be avoided. Other weaker CYP3A4 inhibitors (e.g. cimetidine, delavirdine, grapefruit juice, quinupristin, dallopristin) might interact similarly, although possibly to a lesser extent.

Ergot alkaloids/ergot derivatives
Concurrent use of other ergot alkaloids (e.g. methysergide) and other ergot derivatives can increase the risk of severe and persistent spasm of major arteries in some patients.

Triptans
Additive vasoconstriction may occur when ergometrine is concomitantly given with triptans (e.g. sumatriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan).

Beta-blockers
Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

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

Interactions to be considered
CYP3A4 inducers
CYP3A4 inducers (e.g. nevirapine, rifampicin) may reduce the clinical effect of ergometrine.

ADVERSE EFFECTS
The following adverse drug reactions have been reported during post-approval use of Syntometrine via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size and subject to confounding factors, it is not possible to reliably estimate their frequency which is therefore quoted as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system class organ class, ADRs are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse drug reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic/anaphylactoid reactions associated with dyspnoea, hypotension, collapse or shock</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Cerebrovascular accident, headache, dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial infarction, coronary arteriospasm, bradycardia, cardiac arrhythmias, chest pain (see PRECAUTIONS)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting, nausea, abdominal pain</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, angioedema</td>
</tr>
</tbody>
</table>

Syntometrine may cause uterine hypertonicity associated with abdominal pain.

DOSAGE AND ADMINISTRATION
Active management of third stage:
1 mL intramuscularly following delivery of the anterior shoulder, or immediately after delivery of the child. Expulsion of the placenta, which is normally separated by the first strong uterine contraction following the injection of Syntometrine should be assisted by controlled cord traction.
Prevention and treatment of post-partum haemorrhage:
1 mL intramuscularly following expulsion of the placenta, or when bleeding occurs.

If necessary, the injection of 1 mL may be repeated after an interval of no less than two hours. The total dose given within 24 hours should not exceed 3 mL.

Intravenous administration of Syntometrine (0.5 - 1 mL by slow injection) is possible, but not generally recommended. It is advisable to monitor blood pressure during intravenous administration.

OVERDOSAGE
For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia).

Accidental administration to the newborn infant has been reported and has proved fatal. In these accidental neonatal overdosage cases, symptoms such as respiratory depression, convulsions, cyanosis, oliguria, hypertonia, and arrhythmia have been reported. Treatment should be symptomatic; in most cases respiratory and cardiovascular support has been required.

Symptoms
The symptoms most likely to occur would be those of acute ergometrine intoxication: nausea, vomiting, hypertension or hypotension, vasospastic reactions, respiratory depression, convulsions, coma.

Treatment
Treatment would have to be symptomatic

In cases of oral ingestion, activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

In both acute and chronic poisoning by all routes, attempts must be made to maintain an adequate circulation to the affected parts of the body in order to prevent the onset of gangrene. In severe arterial vasospasm vasodilators such as sodium nitroprusside by intravenous infusion have been given; heparin and dextran 40 have also been advocated to minimise the risk of thrombosis. Analgesics may be required for severe ischaemic pain.

Inadvertent administration to the newborn infant has proved fatal. Other than general resuscitative measures, no treatment is available.

PRESENTATION AND STORAGE CONDITIONS
Presentation
Ampoules: 1 mL one-point-cut uncoloured glass with blue colour-code rings, containing a clear, colourless, faintly bluish, fluorescent solution. Packs of 5 x 1 mL ampoules.

Storage
Store at 2° to 8°C. Refrigerate. Do not freeze. Protect from light. Keep out of the reach of children.

NAME AND ADDRESS OF THE SPONSOR
Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW, 2066, Australia
Telephone: 1800 720 020

POISON SCHEDULE OF THE MEDICINE
Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)
21 August 1991

Date of most recent amendment: 16th April 2018