SYNTOMETRINE®

(OXYTOCIN/ERGOMETRINE MALEATE)

SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Oxytocin, ergometrine maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Syntometrine injection contains synthetic oxytocin 5 IU/mL and ergometrine maleate 500 microgram/mL.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Syntometrine injection is a sterile, clear, colourless solution, faintly bluish fluorescent solution.

It is buffered to pH 3.2.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Active management of third stage of labour:

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.

4.3 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 Section 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy.)
- Severe hypertension, pre-eclampsia, or eclampsia.
- Severe cardiac disorders.
- Severe hepatic or renal impairment.
- Occlusive vascular disease.
- Sepsis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 4.6 Fertility, Pregnancy and Lactation, 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 Section 4.6 Fertility, Pregnancy and Lactation, 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), 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 should be exercised when Syntometrine is used concurrently with other vasoconstrictors or other ergot alkaloids. Concurrent use of vasoconstrictors and Syntometrine after delivery during anaesthesia may lead to severe postpartum hypertension. Methylergometrine may enhance the vasoconstrictor/vasopressor effects of other drugs such as triptans ($5HT_{1B/1D}$ receptor agonists), sympathomimetics (including those in local anaesthetics), beta-blockers or other ergot alkaloids (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Caution is required when using Syntometrine alone or in combination with prostaglandins and their analogues in the treatment of postpartum atonic uterine haemorrhage (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Caution is required in patients with mild or moderate hypertension, cardiac disorders, or hepatic or renal impairment. Severe forms are contraindicated (see Section 4.3 Contraindications and Section 5 Pharmacological Properties). Patients with coronary artery disease may be more susceptible to myocardial ischemia and infarction caused by ergometrine-induced vasospasm (see Section 4.8 Adverse Effects (Undesirable Effects)). Caution is also required in patients with respiratory disease, chronic anaemia and toxaemia 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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 Section 4.9 Overdose).

For oxytocin specific precautions, see Syntocinon® Product Information.

Anaphylaxis in women with latex allergy

There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Due to the existing structural homology between oxytocin and latex, latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions related to both oxytocin and ergometrine administration

Interactions resulting in concomitant use are not recommended (see Section 4.4 Special Warnings and Precautions for Use)

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 Section 4.4 Special Warnings and Precautions for Use).

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 Section 4.4 Special Warnings and Precautions for Use)

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, dalfopristin) 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

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 Section 4.3 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 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.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Taking Syntometrine can start labour. Women having contractions should not drive or use machines.

Adverse effects of Syntometrine include dizziness and low blood pressure (symptoms of which are light-headedness and blurred vision). If affected, you should not drive or use machinery until symptoms have subsided.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

System organ class	Adverse drug reaction
Immune system disorders	Anaphylactic/anaphylactoid reactions associated with dyspnoea, hypotension, collapse or shock
Nervous system disorders	Cerebrovascular accident, headache, dizziness
Cardiac disorders	Myocardial infarction, coronary arteriospasm, bradycardia, cardiac arrhythmias, chest pain (see Section 4.4 Special Warnings and Precautions for Use)
Vascular disorders	Hypertension
Gastrointestinal disorders	Vomiting, nausea, abdominal pain
Skin and subcutaneous tissue disorders	Rash, angioedema

Syntometrine may cause uterine hypertonicity associated with abdominal pain.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 131126 (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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 Section 4.2 Dose and Method of 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Syntometrine Injection contains acetic acid, chlorobutanol hemihydrate, maleic acid, sodium acetate trihydrate, sodium chloride and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG) [1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

Syntometrine Injection is supplied in 1 mL one-point-cut uncoloured glass ampoules with blue colour-code rings.

It is available in packs of 5 x 1 mL ampoules.

Phebra product code – INJ182

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

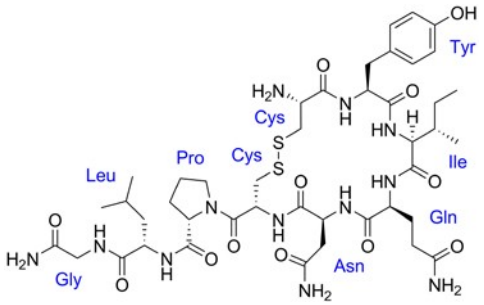
Chemical structure

Oxytocin

Chemical name: l-cysteinyl-l-tyrosyl-l-isoleucyl-l-glutamyl-l-asparaginyl-l-cysteinyl-l-prolyl-l-leucylglycinamide cyclic (1→6)-disulfide

Molecular weight: 1007

Molecular formula: $C_{43}H_{66}N_{12}O_{12}S_2$



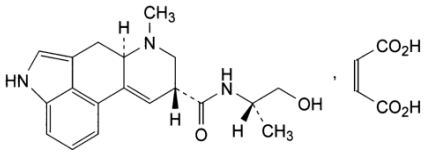
Ergometrine maleate

Chemical name: 6aR,9R)-N-[(S)-2-hydroxy-1-methylethyl]-7-methyl- 4,6,6a,7,8,9-hexahydro-indolo [4,3-fg]quinoline-9-carboxamide (Z)-butenedioate

Molecular weight: 441.5

Molecular formula: $C_{19}H_{23}N_3O_2.C_4H_4O_4$

[1] AUST R 13396



CAS number

Oxytocin: 50-56-6
Ergometrine maleate: 129-51-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Phebra[2] Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

21 Aug 1991

10 DATE OF REVISION

23 May 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	PI reformatted to align with new form
1	Revised the name of medicine
3	Add "Solution for injection" as the pharmaceutical form
4.4	New warning on anaphylaxis for women with latex allergy updated in "4.4 Special warnings and precautions for use"
4.7	Updated the product may impact on ability to drive or use machine
4.8	Minor editorial update
5.2	Minor editorial update

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