1 PRODUCT NAME

SYNTOMETRINE®

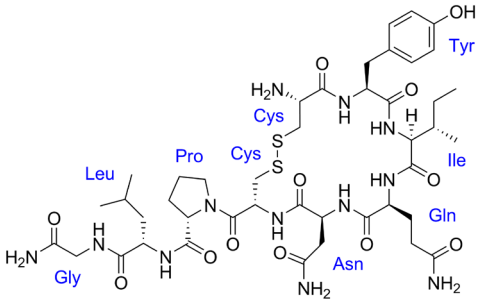
2 QUALITATIVE AND QUANTITATIVE COMPOSITION

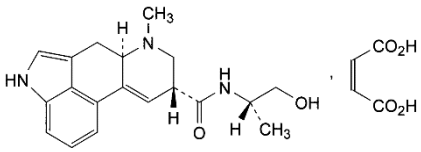
Name and strength of the active substances:

Each 1 mL ampoule of injectable solution contains:
Synthetic Oxytocin 5 IU/mL ((8.5 µg) added as 200 IU/mL solution) and
Ergometrine maleate 0.5 mg/mL

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	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
CAS number	50-56-6	129-51-1
Molecular weight	1007	441.5
Molecular formula	$C_{43}H_{66}N_{12}O_{12}S_2$	$C_{19}H_{23}N_3O_2.C_4H_4O_4$

Chemical structures





Excipient(s) with known effect

For the full list of excipients, refer section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

Description

SYNTOMETRINE® injection is a sterile, clear, colourless solution, faintly bluish fluorescent. It is buffered to pH 3.2.
The ampoules have two blue identification rings.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Active management of the third stage of labour (as a means to promote separation of the placenta and to reduce blood loss).
- Prevention and treatment of postpartum 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 postpartum haemorrhage:
1 mL i.m. following expulsion of the placenta, or when bleeding occurs.
If necessary, the injection of 1 mL may be repeated after an interval of not less than 2 hours. The total dose given within 24 hours should not exceed 3 mL.
Intravenous administration of Syntometrine® (0.5 to 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 any of the components
- Pregnancy and labour (induction of labour, first stage labour and second stage labour prior to the delivery of the anterior shoulder) due to the risk of uterine hypertonus and associated foetal complications (Use in Pregnancy – refer Section 4.6)
- Severe hypertension, pre-eclampsia, 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 (Use in Pregnancy – refer Section 4.6).

Ergometrine derivatives are excreted in breast milk but in unknown amounts. It can also suppress lactation, so repeated use should be avoided (Use in Lactation – refer

Section 4.6).

Active management of the third stage of labour requires expert obstetric supervision. If in the treatment of postpartum haemorrhage, bleeding is not arrested by the injection of Syntometrine®, the possibility of a retained placental fragment, or 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 anesthesia may lead to severe postpartum hypertension. Methylergometrine may enhance the vasoconstrictor/vasopressor effects of other drugs such as triptans (5HT1B/1D receptor agonists), sympathomimetics (including those in local anesthetics), beta-blockers or other ergot alkaloids (INTERACTIONS WITH OTHER MEDICINES – refer Section 4.5).

Caution is required when using Syntometrine® alone or in combination with prostaglandins and their analogues in the treatment of postpartum atonic uterine haemorrhage (INTERACTIONS WITH OTHER MEDICINES – refer Section 4.5).

Caution is required in patients with mild or moderate hypertension, cardiac disorders, or hepatic or renal impairment. Severe forms are contraindicated (CONTRAINDICATIONS refer Section 4.3 and PHARMACOLOGICAL PROPERTIES – refer Section 5.0). Patients with coronary artery disease may be more susceptible to myocardial ischemia and infarction caused by ergometrine-induced vasospasm (UNDESIRABLE EFFECTS – refer Section 4.8). 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 (INTERACTIONS WITH OTHER MEDICINES – refer Section 4.5).

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.

Ergometrine can cause vasoconstriction and should therefore be used with caution in patients with Raynauds Phenomenon. Treatment should be stopped if signs of

vasoconstriction develops.

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

4.5 Interaction with other medicines and other forms of interaction

Interactions related to both oxytocin and ergometrine administration

Interactions resulting in concomitant use are not recommended (Special warnings and precautions for use – refer Section 4.4)

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.

Interactions to be considered

Inhalation anesthetics

Inhalation anesthetics (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 (Special warnings and precautions for use – refer Section 4.4)

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 (Special warnings and precautions for use – refer Section 4.4)

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

Use in Pregnancy: (Category C)

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 (CONTRAINDICATIONS – refer Section 4.3).

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

Use in Lactation:

Ergometrine derivatives are excreted in breast milk but in unknown amounts. There is no specific data available for elimination of ergometrine partitioned in breast-milk. Ergometrine can inhibit prolactin secretion and in turn can suppress lactation, so its repeated use should be avoided.

4.7 Effects on ability to drive and use machines

There is no information available.

4.8 Undesirable effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 (see PRECAUTIONS) bradycardia, cardiac arrhythmias, chest pain
Vascular disorders	Hypertension
Gastrointestinal disorders	Vomiting, nausea, abdominal pain
Skin and subcutaneous tissue disorders	Rash, angioedema

4.9 Overdose

Accidental administration to the newborn infant has been reported. In these accidental neonatal over dosage 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. Fatal cases have been reported in the absence of adequate treatment.

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

In cases of oral ingestion, although the benefit of gastric decontamination is uncertain, activated charcoal may be given to patients who present within 1 hour of ingesting a toxic dose (more than 125 micrograms/kg in adults) or any amount in a child or in adults with peripheral vascular disease, ischaemic heart disease, severe infection, or hepatic or renal impairment. Alternatively, gastric lavage may be considered in adults within 1 hour of ingesting a potentially life-threatening overdose.

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.

For further information on the management of overdose, contact the National Poisons Centre (telephone 0800 POISON or 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 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. Following intramuscular administration, the latent period for the

occurrence of the uterine response is considerably shorter with Syntometrine® (about 2.5 minutes) than with ergometrine given alone (about 7 minutes), whereas the uterotonic effect of Syntometrine® lasts for several hours compared with only 0.5 to 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 for the prevention or treatment of postpartum haemorrhage, particularly in situations where for any reason the intravenous administration of an uterotonic agent is impracticable.

Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labour. Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased. The oxytocin receptors are G-proteins coupled receptors. Activation of receptor by oxytocin triggers release of calcium from intracellular stores and thus leads to myometrial contraction Oxytocin elicits rhythmic contractions in the upper segment of the uterus, similar in frequency, force and duration to those observed during labour. Being synthetic, oxytocin in Syntometrine® does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Ergometrine produces sustained tonic uterine contraction via agonist or partial agonist effects at myometrial 5-HT2 receptors and alpha-adrenergic receptors. Both upper and lower uterine segments are stimulated to contract in a tetanic manner. Unlike oxytocin ergometrine has an effect on the non-pregnant uterus. Ergometrine inhibits prolactin secretion and in turn can reduce lactation. Compared with other ergot alkaloids, effects of ergometrine on cardiovascular and central nervous system are less pronounced.

5.2 Pharmacokinetic properties

Oxytocin

Absorption
Oxytocin is rapidly absorbed from the IM site.

Distribution
The steady-state volume of distribution determined in 6 healthy men after IV injection is 12.2 L or 0.17 L/kg. Plasma protein binding is negligible for oxytocin. It crosses the placenta in both directions. Oxytocin may be found in small quantities in mother's breast milk.

Biotransformation / Metabolism
Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy. It is capable of degrading oxytocin. It is produced both by the mother and the foetus. The liver and kidney play a major role in metabolizing and clearing oxytocin from the

plasma. Thus, the liver, kidney and systemic circulation contribute to the biotransformation of oxytocin.

Elimination
The plasma half life of oxytocin ranges from 3 minutes to 20 minutes. The metabolites are excreted in urine whereas less than 1 % of the oxytocin is excreted unchanged in urine. The metabolic clearance rate amounts to 20 mL/kg/min in the pregnant woman

Ergometrine

Absorption
Ergometrine is absorbed rapidly after IM injection. The latent period for occurrence of the uterine response is about 7 minutes.

Distribution
The average steady state volume of distribution of ergometrine in healthy man is reported to be 1.04 L/kg. The plasma protein binding of ergometrine is unknown. Ergometrine is known to cross the placenta and its clearance from fetus is slow. Concentrations of ergometrine achieved in fetus are not known. Ergometrine is also expected to be excreted in the breast milk and to reduce milk secretion.

Metabolism/Biotransformation
Ergometrine is mainly metabolized in the liver by hydroxylation and glucuronic acid conjugation and possibly N-demethylation. Like other ergot alkaloids it is a substrate for CYP3A4 enzymes.

Elimination
The plasma half life of ergometrine is reported to be in the range of 30 minutes to 120 minutes. When administered orally, the drug is mainly eliminated with the bile into the faeces as 12 hydroxyergometrine glucuronide. It is eliminated unchanged in the urine and can be detected up to 8 hours after injection.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol hemihydrate Ph. Eur, Sodium Acetate Trihydrate Ph. Eur, Glacial Acetic Acid Ph. Eur, Sodium Chloride Ph. Eur, Maleic Acid Ph. Eur

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months from date of manufacture stored at 2° to 8°C (Refrigerate, do not freeze) protect from light

6.4 Special precautions for storage

Store between 2-8°C (Refrigerate, do not freeze). Protect from light.

6.5 Nature and contents of container

Presentation

Each pack contains 5 ampoules of 1 mL.

The ampoules have two blue identification rings.

6.6 Special precautions for disposal <and other handling>

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

PSM Healthcare Limited t/a API Consumer Brands
14-16 Norman Spencer Drive
PO Box 76 401
Manukau
AUCKLAND 2241
Telephone: 0508 776746

9 DATE OF FIRST APPROVAL

31/12/1969

10 DATE OF REVISION OF THE TEXT

March 2019

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
-	Reformat as per new datasheet template effective 1/03/2017.
4.4	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.