PROFESIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

SYNTOMETRINE Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains: 5.I.U. synthetic oxytocin and 0,5 mg ergometrine maleate.

Excipient(s) with known effect:

Sugar content: Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

A clear, colourless solution with a faint bluish fluorescence

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 Posology and method of administration

Active management of third stage of labour

1 ml SYNTOMETRINE should be injected intramuscularly (**but not intravenously**), after delivery of the shoulder, or at the latest, immediately after delivery of the child. Expulsion of the placenta, which is normally separated by the first strong uterine contraction, should be assisted by controlled cord traction.

Prevention and treatment of postpartum haemorrhage

Following expulsion of the placenta, 1 ml intramuscularly, or intravenously if bleeding is heavy.

Intravenous injections should be given slowly.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;

Pregnancy and labour (induction of labour, first stage of labour, second stage of labour prior to the delivery of the anterior shoulder) due to the risk of uterine hypertonus and associated foetal complications (see section 4.6 Fertility, pregnancy and lactation)**;**

Primary or secondary uterine inertia;

Predisposition to uterine rupture as in patients of high parity or with a uterine scar from previous caesarean section;

Impaired renal or hepatic function;

Severe toxaemia of Human Reproduction;

Placenta praevia, mechanical obstruction to delivery, malposition of the

foetus, or obvious foetal distress;

Pre-eclampsia, eclampsia;

Porphyria;

Occlusive vascular disease, including Raynaud's phenomenon;

Sepsis;

Hypertension;

Cardiac disease.

4.4 Special warnings and precautions for use

Active management of the third stage of labour requires expert obstetric supervision.

SYNTOMETRINE should not be given in breech presentation until after delivery of the child, and in multiple births, not until the last child has been delivered.

In postpartum haemorrhage, if bleeding is not arrested by the injection of SYNTOMETRINE, the possibility of retained placental fragments should be excluded before a further injection is given.

Ergometrine derivatives are excreted in breast milk. It can also suppress lactation, so repeated use should be avoided (see 4.6 Fertility, Pregnancy and Lactation)

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 occlusive vascular diseases, such as Raynaud's phenomenon. Treatment should be stopped if signs of vasoconstriction develops.

Patients with coronary artery disease may be more susceptible to myocardial ischaemia and infarction caused by ergometrine-induced vasospasm.

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 medicines which prolong the QT interval or in patients with a history of long QT syndrome (see section 4.5).

Ergometrine is a substrate 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 ischaemia 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 medicines such as triptans (5HT1B/1D receptor agonists), sympathomimetics (including those in local anaesthetics), beta-blockers or other ergot alkaloids (see 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 (see section 4.5).

SYNTOMETRINE should only be given under full obstetric observation.
Intravenous injections should be given slowly to prevent bolus formation and hypertension.

4.5 Interactions with other medicines and other forms of interaction

Interactions related to both oxytocin and ergometrine administration.
Interactions resulting in concomitant use not recommended (see section 4.4)

Vasoconstrictors/Sympathomimetics

SYNTOMETRINE may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, including 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.

Inhalation anaesthetics

Inhalation anaesthetics (e.g. halothane, sevoflurane, desflurane, isoflurane) have a relaxing effect on uterus and produce a notable inhibition of uterine tone and thereby, may diminish the uterotonic effect of SYNTOMETRINE.

Interactions related to oxytocin administration

Interactions resulting in concomitant use not recommended (see section 4.4).

Medicines prolonging the QT interval

Oxytocin should be considered as potentially dysrhythmogenic, particularly in patients with other risk factors for torsades de pointes such as medicines 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).

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 raise the levels of ergot derivatives including SYNTOMETRINE, which may lead to ergotism. Combined use with SYNTOMETRINE should be avoided. Other weaker CYP3A4 inhibitors (e.g. cimetidine, delavirdine, grapefruit juice, quinupristin, dalfopristin) may interact similarly.

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.

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 SYNTOMETRINE.

Glyceryl trinitrate and other antianginal drugs

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

CYP3A4 inducers

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Ergometrine has potent uterotonic activity. Therefore SYNTOMETRINE is contraindicated during pregnancy, first stage of labour and second stage labour prior to the delivery of the shoulder (see section 4.3).

SYNTOMETRINE should not be given in breech presentation until after delivery of the child, and in multiple births, not until the last child has been delivered.

Breastfeeding

Ergometrine derivatives are excreted 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

Taking SYNTOMETRINE can start labour. Women with contractions should not drive or use machines.

Patients should be warned of the possibility of dizziness and hypotension (see section 4.8 Undesirable effects).

4.8 Undesirable effects

a. Summary of the safety profile

The following side-effects 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, side effects are presented in order of decreasing seriousness.

b. Tabulated summary of adverse reactions

System organ class	**Adverse drug reaction**
Immune system disorders	Anaphylactic reaction Hypersensitivity reaction
Cardiac disorders	Myocardial infarction, Coronary arteriospasm, Cardiac dysrhythmias
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Vomiting, Nausea, Abdominal pain
Skin and subcutaneous tissue disorders	Angioedema
Reproductive system and breast disorders	Pelvic haematomas
Nervous system disorders	headache, dizziness

c. Description of selected adverse reactions

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

SYNTOMETRINE should be given under full obstetric observation.

Intravenous injections should be given slowly to prevent bolus formation and hypertension.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage may give rise to uterine hypertonicity, tetanic contraction, uterine rupture, extensive laceration of soft tissue, severe hypertension, water retention and intoxication with convulsions and coma, foetal bradycardia, foetal dysrhythmia, foetal asphyxia, foetal and also maternal death. Subarachnoid haemorrhage has occurred.

Overdosage of ergometrine maleate may give rise to gastro-intestinal disturbances, hyper- or hypotension, respiratory depression, hypothermia and coma.

The patient should be kept under close surveillance and fluid intake and output, and electrolytes should be monitored.

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. In severe arterial vasospasm vasodilators have been recommended; heparin and

dextran 40 have also been advocated to minimise the risk of thrombosis. Analgesics may be required for severe ischaemic pain.

Accidental administration to the newborn infant has been reported. In these accidental neonatal overdosage cases, symptoms such as respiratory depression, convulsions, cyanosis, oliguria, hypertonia, and dysrhythmia 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ergot alkaloids and oxytocin incl. analogues, in combination

ATC code: G02AC

Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis. The synthetic form is identical to the natural hormone. Oxytocin stimulates the smooth muscle of the uterus, towards the end of pregnancy, during labour, and immediately postpartum. 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. Effects of ergometrine on cardiovascular and central nervous system are myocardial infarction, coronary arteriospasm, cardiac dysrhythmias, headache and dizziness.

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 is found in breast milk.

Metabolism/Biotransformation

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 metabolising 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 to 20 min. 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 men 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 the foetus is slow. Concentrations of ergometrine achieved in the foetus are not known. Ergometrine is excreted in the breast milk and it reduces milk secretion.

Metabolism/Biotransformation

Ergometrine is mainly metabolised in the liver by hydroxylation and glucuronic acid conjugation and possibly N-demethylation. It is a substrate for CYP3A4 enzymes.

Elimination

The plasma half-life of ergometrine is in the range of 30-120 min. When administered orally, the medicine 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

None

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are included in the formulation: Sodium chloride, maleic acid, water for injection, nitrogen, chlorobutanol hemihydrate, sodium acetate and glacial acetic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator between 2 to 8 °C.

Do not freeze.

Protect from light.

Do not remove the outer container until required for use.

SYNTOMETRINE AMPOULES SHOULD BE KEPT OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

A 1 ml clear glass ampoule coded with two green-coloured rings on the neck of the ampoule. 5 ampoules of 1 ml in a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd.

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8. REGISTRATION NUMBER(S)

H/19/1966

BW: S2 B9310695

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 30 March 2001

10. DATE OF REVISION OF THE TEXT

Date amended: 15 December 2022