SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Syntometrine 500 micrograms/5 IU-Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml ampoule contains 500 micrograms ergometrine maleate and 5IU oxytocin.

Excipient with known effect:
Sodium chloride 7.000 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
The solution is clear, colourless, faintly bluish fluorescent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The active management of the third stage of labour (as a means to promote separation of the placenta and to reduce blood loss), or routinely, following the birth of the placenta, to prevent or treat postpartum haemorrhage.

4.2 Posology and method of administration

Syntometrine should be used under medical supervision only.

Adults:

Active management of third stage of labour: Intramuscular injection of 1ml after delivery of the anterior 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: Intramuscular injection of 1ml following expulsion of the placenta, or when bleeding occurs.

Special populations

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 (see sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Paediatric population: No data are available.

Elderly: Not applicable.

Method of administration
Intramuscular injection is the recommended route.
Intravenous administration of Syntometrine (0.5 to 1 mL by slow injection) is possible, but should be limited to use only in cases of severe haemorrhage due to uterine atony.

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 labour and second stage 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
- 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

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

In breech presentations and other abnormal presentations, Syntometrine should not be given until after delivery of the child, and in multiple births not until the last child has been delivered (see section 4.6 Fertility, pregnancy and lactation).

Ergometrine derivatives are excreted in breast milk but in unknown amounts. It can also suppress lactation, so repeated use should be avoided (see section 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 Raynaud's phenomenon.

Caution is required in patients with mild or moderate hypertension, cardiac disorder, or hepatic or renal impairment. Severe forms are contraindications (see section 4.3 Contraindications).

Patients with coronary artery disease may be more susceptible to angina or 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 drugs which prolong the QT interval or in patients with a history of long QT syndrome (see section 4.5 Interaction with other medicinal products and other forms of interaction).

In postpartum 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 excluded 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 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 drugs such as triptans (5HT1B/1D receptor agonists), sympathomimetics (including those in local anaesthetics),

beta-blockers or other ergot alkaloids (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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 Interaction with other medicinal products and other forms of interaction).

Syntometrine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to both oxytocin and ergometrine administration

Interactions resulting in concomitant use not recommended (see section 4.4 Special warnings and precautions for use)

Vasoconstrictors/Sympathomimetics

Syntometrine may enhance the vasopressor effects of vasoconstrictors 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 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, 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

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 (see section 4.4 Special warnings and precautions for use).

Breast-feeding

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

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

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	headache, dizziness
Cardiac disorders	myocardial infarction, coronary arteriospasm (see section 4.4 Special warnings and precautions for use) bradycardia, cardiac arrhythmias, chest pain
Vascular disorders	hypertension
Gastrointestinal disorders	vomiting, nausea, abdominal pain
Skin and subcutaneous tissue disorders	Rash, angioedema

Reporting of suspected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow card in the Google Play or Apple App Store.

4.9 Overdose

In the event of maternal intoxication the most likely symptoms would be those of ergometrine intoxication: nausea, vomiting, hypertension or hypotension, vasospastic reactions, respiratory depression, convulsions, coma.

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.

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 heart arrhythmia have been reported. Treatment has been symptomatic in most cases; respiratory and cardiovascular support have been required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: G02AC

Syntometrine combines the known sustained oxytocic action of ergometrine with the more rapid action of oxytocin on the uterus.

Following IM 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 around 3 hours compared with only 0.5 to 1 hour when oxytocin is given alone.

These properties make Syntometrine IM suitable for the active management of the third stage of labour and for the prevention or treatment of postpartum haemorrhage, particularly in situations where, for any reason, the IV administration of 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 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 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 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 the foetus is slow. Concentrations of ergometrine achieved in foetus are not known. Ergometrine is also expected to be excreted in the breast milk and to reduce milk secretion.

Metabolism/Biotransformation
Ergometrine is mainly metabolised 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 30-120 min. 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 h after injection.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6.1 List of excipients

Sodium chloride
Maleic acid
Water for injections
Chlorobutanol
Sodium acetate trihydrate
Acetic acid

6.2. Incompatibilities

None.

6.3 Shelf life

3 years.

6.4. Special Precautions for Storage

For prolonged periods store between 2° and 8°C. Protect from light. Syntometrine may be stored up to 25°C for 2 months when protected from light, but must then be discarded.

6.5 Nature and contents of container

Uncoloured borosilicate glass Type I snap ampoule. Packs of 5 ampoules.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Ltd
Avonbridge House
Bath Road
Chippenham
Wiltshire
SN15 2BB

8 MARKETING AUTHORISATION NUMBER(S)

PL 16853/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/05/03

10 DATE OF REVISION OF THE TEXT

21/11/2019