

# 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 of Ergometrine Maleate and 5 International Units (equivalent to 8.5 micrograms) of Oxytocin.

Excipient with known effect:

Contains 2.76 mg/ml (0.120 mmol/ml) of sodium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for Injection.

Clear glass ampoules containing a clear colourless, solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Syntometrine is indicated in 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 in those patients who have not recently received a pressor agent.

### 4.2 Posology and method of administration

#### Posology

Syntometrine should only be administered by a healthcare professional.

#### Adults

*Active management of third stage of labour:* Intramuscular injection of 1 ml to be administered to the mother following delivery of the baby's anterior shoulder or immediately after delivery of the baby. Expulsion of the placenta -usually 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:* Intramuscular injection of 1 ml to be administered to the mother 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 patients

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

#### 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 delivery of the anterior shoulder) due to the risk of uterine hypertonus and associated fetal complications (see section 4.6 Fertility, pregnancy and breast-feeding).
- Severe hypertension (including pre-eclamptic toxemia, eclampsia).
- Occlusive vascular disease.
- Severe cardiac disorders.
- Severe hepatic or renal impairment
- Sepsis.

### 4.4 Special warnings and precautions for use

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 4.6 Fertility, pregnancy and breast-feeding).

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

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).

Caution should be exercised in the presence of mild or moderate hypertension, cardiac disorder, hepatic or renal impairment. Severe forms of the conditions are contraindications (see sections 4.3 Contraindications).

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

Caution should be exercised in the presence of malnutrition or following previous administration of a pressor agent.

Patients with coronary artery disease may be more susceptible to myocardial ischemia and infarction caused by ergometrine-induced vasospasm (see section 4.8 Adverse drug reactions).

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). Syntometrine may rarely give rise to acute pulmonary oedema.

If in the treatment of postpartum haemorrhage, bleeding is not arrested by the injection of Syntometrine, the possibility of a retained placental fragment, 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 anesthesia may lead to severe postpartum hypertension. Methylergometrine may enhance the vasoconstrictor/vasopressor effects of other drugs such

as triptans (5HT<sub>1B/1D</sub> receptor agonists), sympathomimetics (including those in local anesthetics), 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 warning 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 warning 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**

#### **Oxytocin**

Treatment of rats with oxytocin early in pregnancy, at doses considered sufficiently in excess of the maximum recommended human dose, caused embryonic loss in one study. No standard animal reproduction and embryo-fetal development studies with oxytocin are available.

The genotoxic potential of oxytocin has not been determined in vivo. Oxytocin did not induce chromosomal aberration and sister chromatic exchange in human peripheral lymphocytes in vitro.

No carcinogenicity studies with oxytocin are available.

There are no standard animal studies on the potential effect of oxytocin on fertility.

#### **Ergometrine**

Treatment of rats with ergometrine in early pregnancy reduced implantation rates, most likely related to suppression of prolactin release. No standard animal reproduction and embryo-fetal development studies with ergometrine are available. The use of ergometrine is contraindicated during pregnancy because of its uterotonic effects.

The genotoxic potential of ergometrine has not been determined.

No studies are available which evaluated the carcinogenic potential of ergometrine.

There are no standard animal studies on the potential effect of ergometrine on fertility.

#### **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 birth 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**

Not applicable

### **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.

<b>System Organ Class</b>	<b>Adverse drug reaction</b>
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 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 HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

#### **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 (both published and unpublished) 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 has 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 rapid uterine action of oxytocin with the sustained uterotonic effect of ergometrine. 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 SyntometrineIM 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<sup>®</sup> 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-HT<sub>2</sub> 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 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 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 that already included in other sections of the SPC.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store in a refrigerator (2-8°C).  
Keep the ampoules in the outer carton in order to protect from light.

### **6.5 Nature and contents of container**

Uncoloured borosilicate glass type I snap ampoule. Packs of 5 and 10.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

Do not use ampoules which have become discoloured.

For single use only. Any remaining solution should be discarded.

## **7 MARKETING AUTHORISATION HOLDER**

Essential Pharma Limited  
Vision Exchange Building  
Triq It-Territorjals Zone 1  
Central Business District  
Birkirkara  
CBD 1070  
Malta

## **8 MARKETING AUTHORISATION NUMBER**

PA22587/004/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 1<sup>st</sup> April 1979

Date of last renewal: 1<sup>st</sup> April 2009

**10 DATE OF REVISION OF THE TEXT**

May 2026