Summary Product Characteristics

1. Name of the proprietary product:

Name of the nonproprietary International Product: Ergometrine Injection BP

Route of Administration: For IM / IV use

2. Qualitative and Quantitative composition:
Batch size : 190 lit

Sr. No	Material	Specification	Rationale	Composition	Overage %	Qty per ml	Qty/Batch Size
1.	Ergometrine Maleate	BP	Active ingredients	0.5 mg/ 1ml	---	0.5 mg	# 96.9 gms
2	DL-Methionine	BP	Used as buffering agent	0.50 % w/v		5.0mg	0.950 kg
3	Maleic Acid	BP	Used as buffering agent	0.478 mg/ml		0.478 mg	90.820 gms
4.	Water for Injections	BP	Vehicle	QS	---	Qs to 1 ml	190.0 lit

Where,
BP: British Pharmacopoeia

These quantities are calculated on the basis of standard potency and LOD. Quantity may changes if standard potency and LOD changes

3. Pharmaceutical Form: Liquid injection

A colourless or faintly yellow solution

4. Clinical Particulars:

4.1 Therapeutic Indications:
Ergometrine Injection is used in the active management of the third stage of labour and in the treatment of post-partum haemorrhage. Ergometrine Injection may be given by intramuscular or intravenous injection.

4.2 Posology and method of administration

Ergometrine Injection should be used under medical supervision only

Adults:

Active Management of the Third Stage of Labour

Ergometrine Injection is administered (often in combination with synthetic oxytocin 5 units) intramuscularly as a dose of 500 micrograms following the delivery of the anterior shoulder of the infant or at the latest immediately after delivery of the baby.

Prevention and Treatment of Postpartum Haemorrhage

Doses of 200 micrograms to 500 micrograms of Ergometrine are given intramuscularly, following expulsion of the placenta or when bleeding occurs. In emergencies, Ergometrine Injection may be given intravenously at a dose of 250 micrograms to 500 micrograms.

Use in special populations

Patients with renal impairment or hepatic impairment

No studies have been performed in patients with renal or hepatic impairment. However, considering the metabolic pathway of ergometrine, 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 Ergometrine Injection at a dose of 250 micrograms to 500 micrograms (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 substance 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 e.g. Raynaud's disease / phenomenon

• Sepsis

4.4 Special warnings and precautions for use

Ergometrine may give rise to widespread vasoconstriction and rarely acute pulmonary oedema.

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

In breech presentations and other abnormal presentations, Ergometrine Injection, 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).

Caution is required in patients with mild or moderate hypertension, or with mild or moderate degrees of cardiac, liver or kidney disease. 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.

If in the treatment of postpartum haemorrhage, bleeding is not arrested by the injection, 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 Ergometrine Injection 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 Ergometrine Injection is used concurrently with other vasoconstrictors or other ergot alkaloids. Concurrent use of vasoconstrictors and Ergometrine Injection 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 Interaction with other medicinal products and other forms of interaction).

Caution is required when using Ergometrine Injection 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).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Ergometrine Injection with the following medicinal products is not recommended:

Vasoconstrictors/Sympathomimetics

Ergometrine Injection 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 Ergometrine Injection can potentiate the uterine action of prostaglandins and analogues and vice versa.

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 Ergometrine 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.

Consideration should be given to the concomitant use of Ergometrine Injection with the following medicinal products:

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 ergometrine.

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, Ergometrine Injection is contraindicated during pregnancy, during induction of labour, and during first and second stage labour prior to the delivery of the anterior shoulder (see section 4.3 Contraindications).

In breech presentation and other abnormal presentations, Ergometrine Injection 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

Receiving Ergometrine Injection can start labour. Women with contractions should not drive or use machines. Patients should be warned of the possibility of dizziness and hypotension

4.8 Undesirable effects

Immune system disorders

Anaphylactic/Anaphylactoid reactions with associated symptoms of dyspnoea, hypotension, collapse or shock

Nervous system disorders

Headache, dizziness

Ear & labyrinth disorders

Tinnitus

Cardiac disorders

Cardiac arrhythmias, palpitations, bradycardia, chest pain, coronary arteriospasm with very rare reports of myocardial infarction

Vascular disorders

Hypertension, vasoconstriction

Respiratory disorders

Dyspnoea, pulmonary oedema

Gastrointestinal disorders

Nausea, vomiting, abdominal pain

Skin & subcutaneous tissue disorders

Skin rashes

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of acute poisoning include nausea, vomiting, diarrhoea, extreme thirst, coldness, tingling and itching of the skin, tachycardia, vasospastic reactions, respiratory depression**,** confusion, convulsions and coma. Angina, hypertension or hypotension may also occur.

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 of ergometrine-containing medicinal products 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

ATC code: G02AB03

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. Uterine stimulation occurs within 7 minutes of intramuscular injection and almost immediately following intravenous injection. The sustained uterine contractions produced by ergometrine are effective in controlling uterine haemorrhage.

Ergometrine has weak antagonist actions at dopaminergic receptors in certain blood vessels. Compared with other ergot alkaloids, effects of ergometrine on cardiovascular and central nervous system are less pronounced. It has a partial agonist action in blood vessels (less than ergotamine) and has little or no antagonist action at α adrenergic receptors.

5.2 Pharmacokinetic properties

Absorption

Ergometrine is rapidly absorbed after administration by mouth or by intramuscular injection. Uterotonic effect can be observed within 10 minutes following oral administration and within 7 minutes of intramuscular injection.

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. Pharmaceutical particulars

6.1 List of excipients

DL-Methionine

Maleic Acid

Water for Injections

6.2 Incompatibilities

Ergometrine Injection is incompatible with various drugs according to resulting pH, temperature and concentration of drugs. Mixing with other drugs in the same syringe should therefore be avoided. Ergometrine may, however, be diluted to a volume of 5mls with 0.9% Sodium Chloride Injection prior to IV administration.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool place below 25°C. Protect from light.

6.5 Nature and contents of container

1 ml amber glass ampoule is packed in a PVC tray (10 x 1ml) along with Pack insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder:

Malven Medics Int'Co Ltd

4 Ligali Street Ogudu, Lagos Nigeria

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text