AUSTRALIAN PRODUCT INFORMATION – DBL™ ERGOMETRINE INJECTION (ERGOMETRINE MALEATE)

1. NAME OF THE MEDICINE

Ergometrine maleate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ergometrine is an amine ergot alkaloid. The molecular formula of ergometrine maleate, designated chemically as 9,10-didehydro-*N*-[(*S*)-2-hydroxy-1-methylethyl]-6-methylergoline-8-carboxamide hydrogen maleate is $C_{19}H_{23}N_3O_2,C_4H_4O_4$.

DBL™ Ergometrine Injection consists of ergometrine maleate BP and maleic acid BP in water for injections BP. The strength supplied is 500 micrograms/1 mL in a glass ampoule.

For the full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Ergometrine maleate occurs as a white to greyish-white or faintly yellow, odourless, microcrystalline powder which darkens with age and on exposure to light. The BP states that ergometrine maleate is soluble, and the USP that it is sparingly soluble in water; and slightly soluble in alcohol; practically insoluble in chloroform and ether.

DBL™ Ergometrine Injection is a colourless or slightly yellowish solution for parenteral use. The pH range of the injection is 2.7 to 3.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis

Ergometrine is administered after the delivery of the placenta for the purpose of contracting the uterus in order to prevent postpartum haemorrhage and postabortion haemorrhage due to uterine atony.

Treatment

Ergometrine is administered after the delivery of the placenta to promote involution of the uterus in order to treat postpartum haemorrhage and postabortion haemorrhage.

4.2 Dose and Method of Administration

Dosage

Prophylaxis of postpartum haemorrhage and postabortion haemorrhage

The immediate postpartum dose of ergometrine maleate is 200 micrograms administered intramuscularly. The injection should not be given until completion of the delivery is assured, and until the possibility of a second twin has been excluded (see **Section 4.4 Special warnings and precautions for use**).

In an emergency situation, 200 micrograms may be injected intravenously. Intravenous (IV) doses should be given slowly, over a period of at least 1 minute. Some clinicians recommend diluting the IV dose to a volume of 5 mL with sodium chloride injection 0.9% before administration (see **Section 4.4 Special warnings and precautions for use**).

Treatment of postpartum haemorrhage and postabortion haemorrhage

Ergometrine maleate 200 micrograms may be injected intramuscularly.

Some patients do not respond to ergometrine because of hypocalcaemia. Cautious IV administration of calcium may restore the oxytocic action (see **Section 4.4 Special warnings and precautions for use**).

Method of Administration

Ergometrine may be administered by intramuscular (IM) or IV injection. However, because the risk of severe adverse effects is increased with IV use of ergometrine, its use via this route is recommended only for emergencies such as excessive uterine bleeding or any **Section 4.4 Special warnings and precautions for use**).

4.3 Contraindications

Ergometrine is contraindicated in patients who have previously displayed hypersensitivity or idiosyncratic reactions to ergometrine, other ergot alkaloids or any of the ingredients in the DBL™ Ergometrine Injection preparation.

Ergometrine is contraindicated for the induction of labour and during the first and second stages of labour (see **Section 4.4 Special warnings and precautions for use**).

Ergometrine is contraindicated if there is any suspicion of retained placenta.

Ergometrine is contraindicated in eclampsia or pre-eclampsia, and in cases of threatened spontaneous abortion.

Ergometrine is contraindicated in severe or persistent sepsis.

Ergometrine is contraindicated in patients with peripheral vascular disease or heart disease and in patients with hypertension or a history of hypertension.

Ergometrine is contraindicated where impaired hepatic or renal function exists.

4.4 Special Warnings and Precautions for Use

Calcium deficiency

In patients with calcium deficiency, the uterus may not respond to ergometrine. Responsiveness can usually be restored by cautious administration of IV calcium salts. However IV calcium should be avoided in patients receiving digitalis.

Coronary artery disease

Patients may be more susceptible to angina or myocardial infarction caused by ergometrine induced vasospasm.

Heart rate

Heart rate may be decreased due primarily to an increase in vagal tone, and possibly to decreased central sympathetic activity and direct depression of the myocardium.

Hypertension

Hypertension may occur following administration of ergometrine especially when administered IV undiluted or too rapidly or when used in conjunction with regional anaesthesia or vasoconstrictors (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

Ergometrine can cause vasoconstriction and therefore should be used with caution in patients with Raynaud's phenomenon. Treatment should be stopped if sign of vasoconstriction develop.

Some patients, especially eclamptic or previously hypertensive patients, may be unusually sensitive to the hypertensive effects of ergometrine; generalised headaches, severe arrhythmias, seizures, and cerebrovascular accidents have been associated with ergometrine induced hypertension in these patients.

Blood pressure or central venous pressure may be elevated due to peripheral vasoconstriction, primarily of postcapillary vessels. This elevation has sometimes been associated with pre-eclampsia, history of hypertension, IV administration of ergometrine or concurrent use of local anaesthetics containing vasoconstrictors. Hypotension has also been reported.

General anaesthesia

Because nausea and vomiting may occur, ergometrine should be administered with care to patients under general anaesthesia (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

Intravenous use

IV administration of ergometrine produces serious adverse effects if the injections are not diluted and administered slowly. IV use of DBL™ Ergometrine Injection should be limited to patients with severe uterine bleeding or other life threatening emergency. IV doses should be given slowly, over a period of at least 1 minute. Some clinicians recommend diluting the IV dose to a volume of 5 mL with sodium chloride injection 0.9% before administration.

Labor and delivery

Ergometrine should not be administered prior to delivery of the placenta (see **Section 4.6 Fertility, pregnancy and lactation**). Before the IV use of ergometrine during severe uterine bleeding, inspection must be made for placental fragments.

High doses of ergometrine administered prior to delivery may cause uterine tetany and problems in the infant (hypoxia, intracranial haemorrhage).

If ergometrine is administered during the second or third stage of labour prior to delivery of the placenta, complications such as captivation of the placenta or missed diagnosis of a second infant due to excessive uterine contraction may occur. The placenta should be delivered, and the possibility of twin pregnancy should be ruled out, before ergometrine is administered.

Uterine overstimulation during labour can cause uterine tetany with uterine rupture, cervical or perineal lacerations, amniotic fluid embolism, or infantile trauma (see **Section 4.3 Contraindications**).

Porphyria

Ergometrine has been associated with clinical exacerbations of porphyria.

Prolactin

Prolactin serum concentrations may be decreased during the postpartum period (see **Section 4.6 Fertility, pregnancy and lactation**).

Prolonged therapy

Prolonged therapy with ergometrine may lead to gangrene and other signs of ergotism. Numbness or tingling of the extremities indicates the need to discontinue treatment.

Sympathomimetics

The vasoconstrictor effect of ergometrine is potentiated by sympathomimetics (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

Venoatrial shunts or mitral valve stenosis

Since ergometrine may cause serious adverse cardiovascular effects, ergometrine should be used cautiously or not at all in patients with venoatrial shunts or mitral valve stenosis.

Use in the elderly

No data available.

Paediatric use

Elimination of ergometrine may be prolonged in newborns. Neonates inadvertently administered ergometrine in overdose amounts have developed respiratory depression, cyanosis, seizures, decreased urine output, and severe peripheral vasoconstriction.

There have been reports of accidental administration of adult doses of ergometrine to neonates, sometimes instead of vitamin K. Symptoms have included peripheral vasoconstriction, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance.

In two reports of accidental administration of 0.2 mg of oral ergometrine maleate or of 0.5 mg of IM ergometrine maleate to neonates, peripheral cyanosis and gangrene, apnea, myoclonic movements, purpuric manifestations, and mild jaundice were noted. Treatment was mainly supportive; IV chlorpromazine controlled myoclonic movements. One death has been reported in an infant who received 0.2 mg of oral ergometrine maleate.

Effects on laboratory tests

Prolactin serum concentrations may be decreased during the postpartum period.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Antianginal agents

Ergot alkaloids may induce coronary vasospasm and may precipitate angina. The efficacy of glyceryl trinitrate or other antianginal agents may be reduced; increased doses of glyceryl trinitrate or antianginal agents may be necessary.

Beta blockers

Ergot causes vasoconstriction. The beta blockers do the same by blocking the normal beta-2-stimulated sympathetic vasodilatation. Ergot alkaloids have been reported to interact with beta-blockers resulting in excessive, additive peripheral vasoconstriction.

Bromocriptine

The use of ergot alkaloids may increase the incidence of rare cases of hypertension, strokes, seizures, and myocardial infarction associated with the postpartum use of bromocriptine.

Dopamine

Ergot alkaloids have been reported to interact with dopamine resulting in excessive peripheral vasoconstriction. Gangrene and peripheral ischaemia of hands and feet developed in a patient receiving both dopamine and ergometrine infusions. In addition, dopamine has been associated with pedal gangrene secondary to peripheral vasoconstriction and the combination of an ergot alkaloid may accentuate this effect. It would seem prudent to avoid concurrent use.

Doxycycline and Tetracycline

Although not documented with ergometrine, five patients taking ergotamine or dihydroergotamine developed ergotism when additionally treated with doxycycline or tetracycline. The importance of this interaction is uncertain. Be alert for any signs of ergotism in any patient given ergot derivatives and any of the tetracyclines. Impairment of liver function may possibly be a contributory factor.

Erythromycin

Although not documented with ergometrine, ergot toxicity can develop rapidly in patients on ergotamine or dihydroergotamine if they are given erythromycin.

General anaesthetics

Concurrent use of general anaesthetics may potentiate peripheral vasoconstriction.

Glyceryl trinitrate

Ergot alkaloids may induce coronary vasospasm and may precipitate angina. The efficacy of glyceryl trinitrate or other antianginal agents may be reduced; increased doses of glyceryl trinitrate or antianginal agents may be necessary. Glyceryl trinitrate may also reduce the first pass hepatic metabolism of dihydroergotamine.

Halothane

Halothane in concentrations greater than 1% may interfere with the oxytocic actions of ergometrine, resulting in severe uterine haemorrhage.

Methysergide

The concurrent use of ergot alkaloids and methysergide can increase the risk of severe and persistent spasm of major arteries in some patients. The combination should be used with great caution.

Nicotine

Enhanced vasoconstriction may result from the combined effects of nicotine absorption from heavy smoking and administration of ergometrine.

Sumatriptan

Although not documented with ergometrine, it has been suggested that the concurrent use of sumatriptan and ergotamine be avoided because of the theoretical risk of additive vasospastic reaction, in particular coronary vasoconstriction.

Tetracycline, see '**Doxycycline**' above.

Vasoconstrictors, including those present in some local anaesthetics, or Vasopressors

Concurrent use may result in enhanced vasoconstriction; dosage adjustments may be necessary.

The pressor effect of sympathomimetic pressor amines may be potentiated, resulting in potentially severe hypertension, headache, and rupture of cerebral blood vessels; gangrene developed in a patient receiving both dopamine and ergometrine infusions.

Also refer to **Section 6.2 Incompatibilities**.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available.

Use in pregnancy (Category C)

Category C: Drugs, which owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Ergometrine induces uterine contraction and may cause premature parturition or hypertonic labour. Tetanic contractions may result in decreased uterine blood flow and foetal distress (see

Section 4.4 Special warnings and precautions for use). Products containing ergometrine should therefore be avoided as far as possible during pregnancy.

Use in lactation

Ergometrine is secreted in breast milk. Ergot alkaloids have the potential to cause chronic ergot poisoning in the infant if used in higher than recommended doses or if used for a longer period of time than is generally recommended. Ergometrine is therefore contraindicated during breastfeeding.

Note: Ergot preparations are frequently given as a single dose postpartum to control haemorrhage. A single dose of ergometrine should not prevent the mother from breastfeeding.

The use of multiple doses in postpartum patients may lower prolactin levels and suppress lactation.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

When administered in correct doses to carefully selected patients who are closely monitored, there is little risk of serious adverse systemic effects in patients receiving ergometrine. However IV administration of the drugs produces serious adverse effects if the injections are not diluted and administered slowly (see **Section 4.4 Special warnings and precautions for use**).

Adverse effects do not appear to occur as frequently with ergometrine as with other ergot alkaloids. Ergometrine is usually indicated for a short duration and as a consequence, many of the side effects seen with the other ergot alkaloids do not occur.

Adverse reactions which have been observed following administration of ergometrine include:

Body as a whole

Gangrene (ergometrine shows less tendency to produce gangrene than ergotamine), headache, abdominal pain, allergic phenomena (including shock, hypertension, chest pain, palpitation, dyspnoea and bradycardia).

Cardiovascular system

Coronary artery vasospasm, peripheral vasospasm, hypotension, hypertension (possibly sudden and/or severe [see **Section 4.4 Special warnings and precautions for use**]), thrombophlebitis, myocardial infarction (single case report), ventricular arrhythmias; and transient chest pain, palpitation, and bradycardia alone or as part of allergic phenomena (see *Body as a whole*).

Hypertension may occur following administration of ergometrine especially when administered IV undiluted or too rapidly or when used in conjunction with regional anaesthesia or vasoconstrictors (see **Section 4.4 Special warnings and precautions for use** and **Section 4.5 Interactions with other medicines and other forms of interactions**).

Digestive system

Diarrhoea, nausea, oesophageal spasm, vomiting.

Mesenteric ischaemia and large bowel infarction have been reported (single case report).

Metabolic and nutritional

Water intoxication.

Musculoskeletal system

Leg cramps, unmasking of myasthenia gravis (single case report).

Nervous system

Dizziness, hallucinations, vertigo.

Respiratory system

Dyspnoea alone or as part of allergic phenomena (see *Body as a whole*); nasal congestion, pulmonary oedema, pleural thickening.

Skin and appendages

Sweating.

Special senses

Unpleasant taste, tinnitus.

Urogenital system

Haematuria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

The principal manifestations of serious overdose are convulsions and gangrene.

Other symptoms of overdose include the following:

bradycardia, confusion, diarrhoea, dizziness, dyspnoea, drowsiness, fast and/or weak pulse, miosis, hypercoagulability, loss of consciousness, nausea and vomiting, numbness and coldness of the extremities, pain in the chest, peripheral vasoconstriction, respiratory depression, rise or fall in blood pressure, severe cramping of the uterus, tachycardia, tingling, unusual thirst.

There have been reports of accidental administration of adult doses of ergometrine maleate to neonates, sometimes instead of vitamin K. Symptoms have included peripheral

vasoconstriction, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance (see **Section 4.4 Special warnings and precautions for use - Paediatric use**).

In two reports of accidental administration of 0.2 mg of oral ergometrine maleate or 0.5 mg of IM ergometrine maleate to neonates, peripheral cyanosis and gangrene, apnea, myoclonic movements, purpuric manifestations, and mild jaundice were noted. Treatment was mainly supportive; IV chlorpromazine controlled myoclonic movements. One death was reported in an infant who received 0.2 mg of oral ergometrine maleate (see **Section 4.4 Special warnings and precautions for use - Paediatric use**).

Treatment

There is no specific antidote for the management of ergometrine overdose. Supportive and symptomatic treatment should be initiated.

Ergometrine should be discontinued immediately.

Convulsions should be treated with appropriate anticonvulsants eg phenytoin or diazepam.

Hypercoagulability should be controlled by the administration of heparin.

Severe hypertension may require treatment with sodium nitroprusside or hydralazine.

Peripheral ischaemia may be treated with sodium nitroprusside or phentolamine. Gangrene may require surgical amputation.

A vasodilator e.g. glyceryl trinitrate may be required for myocardial ischaemia and/or hypertension. The vasodilator should be administered with dosage adjusted according to heart rate and blood pressure.

ECG monitoring may be required to assess cardiac function and perfusion. Frequent monitoring of vital signs as well as blood gases and electrolytes is recommended.

Monitoring of serum ergometrine levels is not predictive of the outcome of overdose.

It is not known if use of forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion will hasten the elimination of ergometrine, especially in overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). In New Zealand, call 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ergometrine stimulates contractions of uterine and vascular smooth muscle.

Following administration of usual therapeutic doses of ergometrine, intense contractions of the uterus are produced and are usually followed by periods of relaxation. Larger doses of the drugs, however, produce sustained, forceful contractions followed by only short or no periods of relaxation.

Ergometrine increases the amplitude and frequency of uterine contractions and uterine tone which in turn impedes uterine blood flow. Contraction of the uterine wall around bleeding vessels at the placental site produces haemostasis. Ergometrine also increases contractions of the cervix.

Ergometrine produces vasoconstriction, mainly of capacitance vessels; increased central venous pressure, elevated blood pressure, and, rarely, peripheral ischaemia and gangrene may result. Like other ergot alkaloids, ergometrine produces arterial vasoconstriction by stimulation of alpha-adrenergic and serotonin receptors and inhibition of endothelial-derived relaxation factor release. The drug has only slight alpha-adrenergic blocking activity and its vasoconstrictor effects are less than those of ergotamine.

The main clinical use of ergometrine is in the production of rhythmic contractions of the uterus

Clinical trials

No data available.

5.2 Pharmacokinetic Properties

Absorption

Ergometrine has a rapid onset of action following IV injection. Uterine contractions are usually initiated almost immediately or within 1 minute and persist for 45 minutes after IV injection.

Ergometrine is also reported to be rapidly and completely absorbed after IM injection with uterine contractions initiated within 2 to 5 minutes. Uterine contractions persist for 3 hours or longer after IM administration.

Distribution

Distribution of ergometrine has not been fully characterised.

Metabolism/Excretion

Little is known about the elimination of ergometrine. Elimination of ergometrine appears to be principally by metabolism in the liver. It has been suggested that ergometrine is principally eliminated by nonrenal mechanisms (ie metabolism in the liver, excretion in faeces). Elimination of ergometrine may be prolonged in neonates.

5.3 Preclinical Safety Data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maleic acid

Water for injections

6.2 Incompatibilities

Ergometrine has been reported to be incompatible with solutions containing the following: adrenaline hydrochloride, amylobarbitone sodium, ampicillin sodium, cephalothin sodium, chloramphenicol sodium succinate, chlortetracycline hydrochloride, heparin sodium, metaraminol tartrate, methicillin sodium, nitrofurantoin sodium, novobiocin sodium, pentobarbitone sodium, sulphadiazine sodium, sulphafurazole diethanolamine, thiopentone sodium, vitamin B complex with C, warfarin sodium.

Also refer to **Section 4.5 Interactions with other medicines and other forms of interactions.**

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

The ampoules are to be stored at 2 to 8°C and protected from light.

6.5 Nature and Contents of Container

DBL™ Ergometrine Injection is supplied in glass ampoules and is available in the following strengths and pack sizes:

Strength	Volume	Pack
500 micrograms/mL	1mL	5's

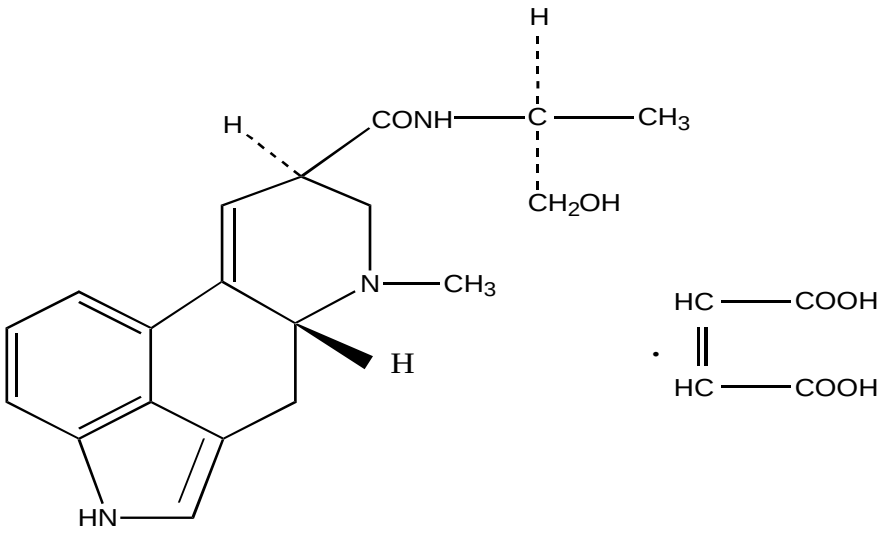
6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure

The structural formula of ergometrine maleate is shown below:



Its molecular weight is 441.5.

CAS number

The CAS registry numbers of ergometrine and ergometrine maleate are 60-79-7 and 129-51-1 respectively.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription only Medicine)

8. SPONSOR

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Toll Free Number: 1800 675 229
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9. DATE OF FIRST APPROVAL

06 March 1997

10. DATE OF REVISION

03 June 2020

Summary Table of Changes

Section changed	Summary of new information
4.4	Vasoconstriction has been added.