

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

DBL™ Ergometrine Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Ergometrine Injection consists of ergometrine maleate BP 500 mcg/ml and maleic acid BP in water for injections BP.

## 3. PHARMACEUTICAL FORM

DBL™ Ergometrine Injection is a colourless or slightly yellowish solution for parenteral use.

It is a Solution for injection.

The pH range of the injection is 2.7 - 3.5.

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.

## 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

Ergometrine may be administered by 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 other life-threatening situation (see section 4.4).

*Prophylaxis of postpartum haemorrhage and postabortion haemorrhage*

The immediate postpartum dose of ergometrine maleate is 200 micrograms administered IM. 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).

In an emergency situation, 200 micrograms may be injected intravenously. 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 5mL with sodium chloride injection 0.9% before administration (see section 4.4).

#### *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).

### **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).

Ergometrine is contraindicated if there is any suspicion of retained placenta

Ergometrine is contraindicated in eclampsia or preeclampsia, 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).

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 preeclampsia, 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).

### *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 5mL 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). 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).

### *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).

### *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).

### *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.

## **Paediatric population**

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 0.2mg of oral ergometrine maleate or of 0.5mg 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 0.2mg of oral ergometrine maleate.

## **4.5 Interaction with other medicines and other forms of interaction**

### *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  $\alpha$ -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.

### **Effects on Laboratory Tests**

Prolactin serum concentrations may be decreased during the postpartum period.

## **4.6 Fertility, pregnancy and lactation**

### **Fertility**

No data available.

### **Pregnancy**

**Category C.** 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). Products containing ergometrine should therefore be avoided as far as possible during pregnancy.

### **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 breast-feeding.

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 machinery**

No data available.

## 4.8 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 drug produces serious adverse effects if the injections are not diluted and administered slowly (see section 4.4).

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]), 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 and section 4.5).

### *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 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. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **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).

In two reports of accidental administration of 0.2mg of oral ergometrine maleate or 0.5mg 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 0.2mg of oral ergometrine maleate (see section 4.4).

### **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 eg. 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **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.

## **5.2 Pharmacokinetic properties**

### **Absorption**

Ergometrine has a rapid onset of action following intravenous (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 intramuscular (IM) injection with uterine contractions initiated within 2-5 minutes. Uterine contractions persist for 3 hours or longer after IM administration.

### **Distribution**

Distribution of ergometrine has not been fully characterised.

### **Elimination**

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.

### **Reproductive and developmental toxicity**

No data available.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

- Maleic acid BP
- Water for injections BP.

### **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.

### **6.3 Shelf life**

18 months from date of manufacture stored at 2° to 8°C

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

The ampoules are to be stored at 2-8°C and protected from light. (Refrigerate, do not freeze)

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

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

<u>Strength</u>	<u>Volume</u>	<u>Pack</u>
500 micrograms/mL	1mL	5's

### **6.6 Special precautions for disposal**

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

## **7. MEDICINE SCHEDULE**

Prescription Medicine

## **8. SPONSOR**

Pfizer New Zealand Limited

P O Box 3998

Auckland, New Zealand

Toll Free Number: 0800 736 363

## **9. DATE OF FIRST APPROVAL**

22 September 1989

## **10. DATE OF REVISION OF THE TEXT**

12 June 2020

### Summary table of changes

<b>Section changed</b>	<b>Summary of new information</b>
4.4	Vasoconstriction has been added.