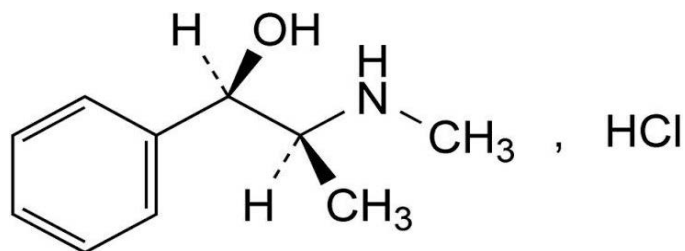


Product Information

Ephedrine Hydrochloride MYX™ Injection

NAME OF THE MEDICINE

Ephedrine hydrochloride



The molecular formula of ephedrine hydrochloride is $C_{10}H_{15}NO.HCl$. Its molecular weight is 201.7. The CAS registry number of ephedrine hydrochloride is 50-98-6.

DESCRIPTION

Ephedrine Hydrochloride MYX Injection is a sterile solution of ephedrine hydrochloride in water for injections. Each mL contains 25 mg of ephedrine hydrochloride (equivalent to 20.5 mg ephedrine) in Water for Injections.

Ephedrine Hydrochloride MYX Injection contains no preservative and is for single use in one patient on one occasion only. Discard any remaining residue.

PHARMACOLOGY

Ephedrine is a sympathomimetic which stimulates both alpha and beta adrenergic receptors, and also releases noradrenaline from its storage site. The main effects of therapeutic doses of ephedrine are relaxation of bronchial smooth muscle, cardiac stimulation and increased systolic and usually diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction. Ephedrine also decreases intestinal tone and motility, relaxes the bladder wall, contracts the sphincter muscle, relaxes the detrusor muscle, and decreases uterine activity. Ephedrine also has central nervous system stimulant effects. Tachyphylaxis to the effects of ephedrine may also occur after use for a short while possibly due to the depletion of noradrenaline stores.

Pharmacokinetics

Pharmacokinetic data for ephedrine following intravenous administration is limited. After intravenous administration, ephedrine is completely bioavailable and clinical effects occur within 3-5 minutes; these persist for 10-15 minutes before heart rate begins to decrease. Approximately 90% of an intravenous dose is excreted in the urine in 24 hours although, as an alkaloid, its excretion rate is reduced in alkaline urine. After intravenous administration, the majority of ephedrine is excreted unchanged in the urine, although this varies depending on urine pH. The major metabolite is the N-demethylated and biologically active norephedrine (up to 20%) with smaller amounts of other deaminated metabolites also reported. The elimination

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half-life of ephedrine is urinary pH dependent and has been reported to be from 3-7 hours, with faster excretion expected in acidic urine.

CLINICAL TRIALS

The supporting evidence for the use of ephedrine in the treatment of hypotension secondary to spinal anaesthesia is based on published literature.

Several published randomised controlled and prospective studies examined the efficacy of ephedrine for the treatment and prophylaxis of hypotension with spinal anaesthesia administered via the intravenous route. The studies included women undergoing caesarian section, lower extremity or lower abdominal surgery, or ASA-I/ASA-II patients. Patients were administered bolus dose in the range of 5 mg to 10 mg with the larger doses observed to provide greater efficacy. Most of the studies reported a dose titration using rescue IV ephedrine as a single bolus dose of around 2.5 mg to 10 mg, incremented as required when the systolic pressure or mean arterial pressure fell. On average, the studies reported patients required a total of 10 mg to 30 mg administered ephedrine dose. One of the dose response studies observed a greater incidence of reactive hypertension in patients given bolus doses of 30 mg ephedrine (45%) compared with those on the lower doses of 10 mg (5%) or 20 mg (25%)($p=0.009$). The efficacy varied between studies which may have been attributed to the administration of other drugs, prior fluid bolus, the level of the spinal block, the timing of the injection, the route and the dose of ephedrine used, and the study definition of hypotension. Overall, the body of literature evidence supports the use of ephedrine in the treatment of hypotension secondary to spinal anaesthesia administered via an IV bolus dose and with additional incremental rescue boluses as required to the effective dose.

INDICATIONS

Ephedrine Hydrochloride MYX Injection is indicated in the treatment of hypotension secondary to spinal anaesthesia.

CONTRAINDICATIONS

Ephedrine is contraindicated in closed angle glaucoma, since ephedrine may exacerbate the condition.

Ephedrine is contraindicated in patients with pheochromocytoma, since severe hypertension may result.

Ephedrine is contraindicated in patients with asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis) since the obstruction may increase as myocardial contractility improves.

Ephedrine is contraindicated in patients undergoing therapy with monoamine oxidase inhibitors (MAO inhibitors), or within 14 days of ceasing such therapy, since MAO inhibitors may prolong and intensify the cardiac and pressor effects of ephedrine.

Ephedrine is contraindicated in patients using linezolid.

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Ephedrine is contraindicated in patients undergoing general anaesthesia with cyclopropane or halothane or other halogenated hydrocarbons, since anaesthesia may increase cardiac irritability which may lead to arrhythmias.

Ephedrine is contraindicated in patients with tachyarrhythmias or ventricular fibrillation, since exacerbation of these conditions may occur.

Ephedrine is also contraindicated in patients with hypersensitivity to ephedrine and in patients with psychoneurosis.

PRECAUTIONS

The use of ephedrine as a pressor agent is not a substitute for replacement of blood, plasma, fluids and/or electrolytes. Blood volume depletion should be corrected as fully as possible before ephedrine therapy is instituted. In an emergency, ephedrine may be used as an adjunct to fluid volume replacement or as a temporary supportive measure to maintain coronary and cerebral artery perfusion until volume replacement therapy can be completed, but ephedrine must not be used as sole therapy in hypovolaemic patients.

Ephedrine may deplete noradrenaline stores in sympathetic nerve endings resulting in reduced cardiac and pressor effects of the drug. Consequently, it may be necessary to administer noradrenaline to replace tissue stores for restoration of the pressor effects of ephedrine.

Caution should be exercised if a dose greater than the maximum recommended bolus is administered as this may lead to undesirable hypertension.

Prolonged administration of pressor agents has been associated with oedema, haemorrhage, focal myocarditis, subpericardial haemorrhage, necrosis of the intestine and hepatic and renal necrosis. Since these effects have generally been observed in patients with severe shock and it is not clear if the drug or the shock state itself was responsible, they should therefore be taken into consideration before ephedrine is used.

Hypoxia, hypercapnia and acidosis may also reduce the effectiveness or increase the incidence of adverse effects of ephedrine, and should be identified and corrected prior to or concurrently with administration of the drug.

Ephedrine should be used with caution, if at all, in patients with hypertension or hyperthyroidism, since there is an increased risk of adverse effects in these patients.

Ephedrine should also be used with caution in patients with cardiovascular disease including angina, cardiac arrhythmia and coronary insufficiency, since the cardiovascular effects of ephedrine may exacerbate these conditions. Ephedrine may intensify the ischaemia in myocardial infarction by increasing myocardial oxygen demands.

Ephedrine should also be used with caution in geriatric males, especially those with prostatic hypertrophy, since ephedrine may cause acute urinary retention.

Ephedrine should also be used with caution in diabetic patients since drug induced hyperglycaemia may result in loss of diabetic control.

Athletes: warning, this product contains an active substance that may cause a positive reaction in anti-doping tests.

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Carcinogenicity

Carcinogenesis studies of ephedrine were conducted by administering 0, 125, or 250 ppm of ephedrine sulfate to groups of rats and mice for 103 weeks. Neoplasms that occurred in these studies were not considered to be related to administration of the drug. Two high dose female mice had ovarian granulose cell tumours, and luteomas were found in one low dose and one high dose female mouse. Because of the low incidence, these uncommon, benign tumours could not be clearly related to ephedrine sulfate administration.

Under the conditions of these studies, there was no evidence of carcinogenicity for rats or mice of either sex receiving 125 or 250 ppm ephedrine sulfate in the diet for 2 years.

Genotoxicity

Ephedrine sulfate was not mutagenic in four strains of *Salmonella typhimurium* (TA100, TA1535, TA97, or TA98) with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 activation. Ephedrine sulfate did not induce sister-chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells.

Patient monitoring

Cardiovascular parameters, including blood pressure and ECG, should be monitored during therapy with ephedrine. Urinary output should also be monitored.

Effects on fertility

The effects of ephedrine on male and female fertility have not been investigated in animal studies.

Use in pregnancy (Category A)

A Pregnancy Category A drug is defined by the Australian Drug Evaluation Committee as *'Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed'*.

Ephedrine may accelerate the foetal heart rate when used to control maternal hypotension during spinal anaesthesia for delivery. Ephedrine Hydrochloride MYX Injection should not be used if the maternal blood pressure is greater than 130/80 Hg.

Ephedrine has been shown to cross the placenta and undergo early metabolism and/or redistribution in the foetus. Ephedrine has been associated with an increased risk of mild metabolic acidosis with increased umbilical plasma concentrations of lactate, glucose, epinephrine, and norepinephrine and greater UV P_{CO2}.

Despite the transplacental passage of ephedrine and notable effects on the cord blood pH; it is uncertain whether this has the potential to affect clinical outcome on the neonate. Other studies have not demonstrated significant effects on neonatal outcomes.

Use in lactation

Ephedrine is distributed into breast milk, and therefore Ephedrine Hydrochloride MYX Injection is not recommended for use during lactation because of the risk of adverse effects in

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the infant. Therefore, the risk and the benefit of using ephedrine should be avoided or used with caution, and administered to a breast-feeding woman only if necessary.

Paediatric Use

Ephedrine Hydrochloride MYX Injection is not approved for use in this patient population.

INTERACTIONS WITH OTHER MEDICINES

Alpha blockers: Alpha blockers may decrease the vasopressor effect of ephedrine.

Atropine sulfate: Atropine sulfate may increase the vasopressor effect of ephedrine.

Beta blockers: Beta blockers may inhibit the cardiac and bronchodilator effects of ephedrine.

Cardiac glycosides: Concurrent use of cardiac glycosides and ephedrine may increase the risk of arrhythmias.

Ergotamine, ergometrine, methylethergometrine, oxytocin: Concurrent use of these drugs with ephedrine may result in a potentiation of the pressor effect of ephedrine. Concurrent use of ergotamine and ephedrine may also produce peripheral vascular ischaemia and gangrene.

Guanethidine: Ephedrine may decrease the antihypertensive effect of guanethidine.

Hydrocarbon inhalation anaesthetics, such as cyclopropane, halothane: These drugs may increase cardiac irritability, and concurrent use with ephedrine may lead to increased risk of arrhythmia (see **CONTRAINDICATIONS**).

Methyldopa: Concurrent use of methyldopa with ephedrine may result in a reduced pressor effect.

Monoamine Oxidase (MAO) inhibitors: Concurrent use of MAO inhibitors and ephedrine may result in potentiation of the cardiac and pressor effects of ephedrine (see **CONTRAINDICATIONS**).

Reserpine: Concurrent use of reserpine with ephedrine may result in a reduced pressor effect.

Sympathomimetic agents: Concurrent use of ephedrine and other sympathomimetics may result in increased cardiovascular and pressor effects and an increased risk of adverse effects.

Tricyclic antidepressants: Concurrent use of tricyclic antidepressant and ephedrine may result in potentiation of the cardiovascular and pressor effects of ephedrine.

Clonidine: Pretreatment with clonidine may increase the pressor effect of ephedrine.

Urinary Alkalinizers, such as acetazolamide, dichlorphenamide, sodium bicarbonate and sodium citrate: These drugs may increase the half life and decrease the elimination of ephedrine leading to enhanced therapeutic or toxic effects of ephedrine.

Theophylline: Concurrent use of ephedrine and theophylline may result in an increased incidence of adverse effects than when either drug is used alone. Adverse effects include those in the central nervous and the gastrointestinal systems.

Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate): Risk of vasoconstriction and/or of acute episodes of hypertension.

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Ergot alkaloids (dopaminergic action): Risk of vasoconstriction and/or episodes of hypertension.

Noradrenergic-serotonergic antidepressants (minalcipran, venlafaxine): Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

Sibutramine: Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

Antiepileptics: increased plasma concentration of phenytoin and possibly of phenobarbitone and primidone.

Doxapram: risk of hypertension.

Moclobemide: Risk of headache and palpitations, and increase in the effect of ephedrine of systolic blood pressure, and diastolic blood pressure.

Linezolid: Risk of vasoconstriction and/or episodes of hypertension.

ADVERSE EFFECTS

Body as a whole: pallor, fever, headache, dryness of nose, mouth and throat.

Ephedrine is reported to cause physical addiction after excessive long term use. Addiction is more likely to occur after oral use, since intramuscular, subcutaneous or intravenous administration of ephedrine would not normally occur over long periods.

Cardiovascular system: angina, palpitations, bradycardia, tachycardia, cardiac arrest, hypertension, hypotension, extrasystole and precordial pain. Arrhythmias, including ventricular fibrillation, may occur, especially in patients with organic heart disease or those receiving other drugs that sensitise the heart to arrhythmias.

Vascular disorder: Cerebral haemorrhage.

Gastrointestinal system: nausea, vomiting, reduced appetite, mild epigastric distress, hypersalivation.

Nervous system: nervousness, anxiety, restlessness, insomnia, mood or mental changes, fear, irritability, trembling, sweating. Large doses may cause dizziness, lightheadedness, weakness, vertigo, confusion, delirium, euphoria. Long term therapy in large doses may lead to psychosis characterized by paranoia, hallucinations, depression and bizarre mentation.

Renal and urinary system: difficult or painful urination, acute urinary retention (especially with prostatic hypertrophy).

Respiratory system: shortness of breath, respiratory difficulty, dyspnoea, pulmonary oedema.

Skin and appendages: sweating.

Blood and lymphatic system disorders: primary haemostasis modifications.

Immune system disorders: hypersensitivity.

Psychiatric disorders: confusion, anxiety, depression, psychotic states, fear.

Eye disorders: episodes of angle-closure glaucoma.

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Investigations: hypokalaemia, changes in blood glucose levels

DOSAGE AND ADMINISTRATION

Ephedrine Hydrochloride MYX Injection is not approved for use in children (see PRECAUTIONS).

Ephedrine Hydrochloride MYX Injection must be diluted prior to administration.

The injection should be given slowly. Care should be taken to avoid extravasation, since this may result in tissue necrosis and sloughing. Ephedrine hydrochloride should be administered in the lowest effective dose.

Dilute 1 mL of Ephedrine Hydrochloride MYX Injection to 10 mL with saline 0.9% to produce a 2.5 mg/mL solution. This solution should be given as a slow intravenous injection of 2.5 to 5 mg (maximum 10 mg), repeated as needed every 3-4 min to a maximum of 30 mg.

A lack of efficacy after 30 mg should lead to reconsideration of the choice of the therapeutic agent.

During therapy with a pressor agent, blood pressure should be elevated to slightly less than the patient's normal blood pressure. In previously normotensive patients, systolic blood pressure should be maintained at 80 to 100 mmHg. In previously hypertensive patients, systolic blood pressure should be maintained at 30 to 40 mmHg below their usual blood pressure. In some patients with very severe hypotension, maintenance of even lower blood pressure may be desirable if blood or fluid volume replacement has not been completed.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2–8 °C for not more than 24 hours.

Compatibilities

Ephedrine is reported to be compatible with 0.9% sodium chloride and lactated Ringer's injection.

Incompatibilities

Ephedrine is reported to be physically incompatible with the phenobarbitone sodium, pentobarbitone sodium, quinalbarbitone sodium and thiopentone sodium, and with hydrocortisone sodium succinate in some infusion solutions.

OVERDOSAGE

Due to the rapid onset, but short duration of the drug, it is rarely necessary to actively manage adverse effects, as they tend to be of short duration and self limiting.

Clinical features

Symptoms associated with overdosage of ephedrine include headache, severe nausea or vomiting, chills or fever, dizziness or lightheadedness, anxiety, nervousness, restlessness, mood changes, convulsions, severe weakness, blurred vision or enlarged pupils, ongoing fast

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heartbeat, severe or ongoing chest pain, severe hypertension or hypotension, and severe breathing difficulties.

Paranoid psychosis, delusions and hallucinations may also follow ephedrine overdose.

Treatment

Treatment of overdose involves the following measures:

- reduce dosage or discontinue administration of ephedrine
- general supportive therapy, including monitoring and maintaining vital signs, blood gases, electrolytes and ECG.

The following additional measures may need to be considered:

- beta blockers to control tachycardia and arrhythmia
- nitroprusside to reduce severe hypertension
- diazepam to control convulsions. General anaesthesia and neuromuscular blocking agents may need to be considered to treat refractory seizures
- dexamethasone to treat pyrexia.

In case of overdose, immediately contact the Poisons Information Centre for advice on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Ephedrine Hydrochloride MYX Injection is a clear and colourless solution, containing 25 mg/mL ephedrine hydrochloride.

Ephedrine Hydrochloride MYX Injection is supplied as packs of 5 x 1 mL yellow glass ampoules.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Mayne Pharma International Pty Ltd

ABN 88 007 870 984

1538 Main North Road

Salisbury South, SA 5106

POISON SCHEDULE OF THE MEDICINE

Schedule 4

Product Information

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

21 July 2016

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