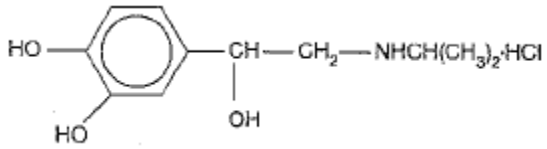
Isuprel™

NAME OF THE MEDICINE
Isoprenaline Hydrochloride

DESCRIPTION
Isoprenaline hydrochloride is 3,4-dihydroxy-alpha-[(isopropylamino) methyl] benzyl alcohol hydrochloride, a synthetic sympathomimetic amine that is structurally related to adrenaline but acts almost exclusively on beta-adrenergic receptors. It has the following structural formula:



CAS Number (51-30-9)

Each milliliter of the sterile 1:5000 solution contains 200 µg of isoprenaline hydrochloride and disodium edetate (EDTA), sodium citrate dihydrate, citric acid, sodium chloride, water for injection, and hydrochloric acid or sodium hydroxide used to adjust pH.

The sterile 1:5000 solution can be administered by the intravenous, intramuscular, subcutaneous or intracardiac routes.

PHARMACOLOGY
Isuprel™ acts primarily on the heart, and on the smooth muscle of bronchi, skeletal muscle vasculature and gastrointestinal tract.

Isuprel™ increases cardiac output due to its positive inotropic and chronotropic actions and by increasing venous return. With usual therapeutic doses, the increase in cardiac output is generally sufficient to maintain or increase systolic blood pressure. Intravenous infusion of Isuprel™ also lowers peripheral vascular resistance. The diastolic pressure, therefore, may be expected to fall in normal individuals. Thus the mean pressure may be reduced. The rate of discharge of cardiac pacemakers is increased with Isuprel™.

Isuprel™ relaxes most smooth muscle, the most pronounced effect being on bronchial and gastrointestinal smooth muscle. It produces marked relaxation in the smaller bronchi and may even dilate the trachea and main bronchi past the resting diameter.

Pharmacokinetics

The half-life of isoprenaline hydrochloride is brief, lasting only a few minutes following intravenous administration and up to 2 hours after subcutaneous administration. Isoprenaline is metabolised by catechol-ortho-methyl transferase, primarily in the liver. The major metabolite after intravenous administration is 3-O-methylisoprenaline, which is reported to have weak beta-adrenergic blocking activity, and its conjugates. The metabolites are excreted through the kidneys.

INDICATIONS

Isuprel™ is indicated:
For mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.

For serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation). (See Contraindications.)

For use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, are available. (See Contraindications.)

For bronchospasm occurring during anaesthesia.

As an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of hypovolaemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure and cardiogenic shock. (See Precautions.)

CONTRAINDICATIONS

Use of Isuprel™ is contraindicated in patients with tachyarrhythmias; tachycardia or heart block caused by digitalis intoxication; ventricular arrhythmias which require inotropic therapy; recent myocardial infarction; angina pectoris; hypersensitivity to isoprenaline.

PRECAUTIONS

Isuprel™ infusions may produce an increase in myocardial work and oxygen consumption. These effects may be detrimental to myocardial metabolism and functioning in patients in cardiogenic shock secondary to coronary artery occlusion and myocardial infarction.

In a few patients, presumably with organic disease of the A-V node and its branches, Isuprel™ has been reported, paradoxically, to precipitate Adams-Stokes seizures during normal sinus rhythm or transient heart block.

Adequate filling of the intravascular compartment by suitable volume expanders is of primary importance in most cases of shock, and should precede the administration of

isoprenaline. In patients with normal cardiac function, determination of central venous pressure is a reliable guide during volume replacement. If evidence of hypoperfusion persists after adequate volume replacement, Isuprel™ may be given.

In addition to the routine monitoring of systemic blood pressure, heart rate, urine flow, and electrocardiograph, the response to therapy should also be monitored by frequent determinations of the central venous pressure and blood gases. Patients in shock should be closely observed during Isuprel™ administration. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease the infusion rate or temporarily discontinue the infusion. Determinations of cardiac output and circulation time may also be helpful. Doses of Isuprel™ sufficient to increase the heart rate to more than 130 beats per minute may induce ventricular arrhythmia. If the cardiac rate increases sharply, patients with angina pectoris may experience anginal pain until the cardiac rate decreases.

If ventricular hyperexcitability (extrasystoles, polymorphic extrasystoles or sustained ventricular tachycardia) should occur, the dosage should be reduced and the electrocardiogram monitored.

Appropriate measures should be taken to ensure adequate ventilation. Careful attention should be paid to acid-base balance and to the correction of electrolyte disturbances.

In cases of shock associated with bacteraemia, suitable antimicrobial therapy is, of course, imperative.

There are case reports of occasional fatal cardiac dysrhythmia and myocardial necrosis at autopsy as a result of intravenous isoprenaline. ECG changes and serum CPK-MB level elevation consistent with transient myocardial ischaemia and abnormal echocardiographic findings suggestive of myocardial dysfunction have been documented with the use of intravenous isoprenaline hydrochloride infusion for the treatment of severe asthma exacerbations in children. Care should be taken to ensure that oxygen is always administered during isoprenaline infusions in patients with asthma. Heart rate, blood pressure, arrhythmias and evidence of myocardial ischaemia by ECG should be monitored. Arterial blood gases should also be monitored carefully and PaO_2 maintained above 60 torr. Where the ECG suggests myocardial ischaemia, cardiac enzymes including cardiac specific CPK-MB isoenzyme levels should be determined.

Use in pregnancy

Category A

Drugs which have been taken by a large number of pregnant women of childbearing age without any proven increase in the frequency of malformation or other direct or indirect harmful effects on the foetus having been observed.

There has been no clinical evidence of teratogenic effects attributable to Isuprel™ in more than 25 years' use of the drug. However, before administration of any drug to pregnant

women or lactating women, or women of childbearing potential, the expected benefit of the drug should be carefully weighed against the possible risk to the mother or child.

Use in lactation
It is unknown whether isoprenaline hydrochloride is excreted into breast milk. Caution should be exercised in administering to a nursing mother.

Paediatric Use
Dosage has not been established in children. (See Dosage and Administration.)

Use in the Elderly
The dosage of Isuprel™ should be carefully adjusted, particularly in the elderly and in patients with coronary insufficiency, ischaemic heart disease, hypertension, diabetes or hyperthyroidism, and in patients sensitive to sympathomimetic amines.

INTERACTIONS WITH OTHER MEDICINES
Isuprel™ should not be given simultaneously with adrenaline or digitalis because both drugs are direct cardiac stimulants and their combined effects may induce serious arrhythmias. The drugs may, however, be administered alternately, provided a proper interval has elapsed between doses.

Isuprel™ should be used with caution, if at all, when potent inhalational anaesthetics such as halothane and cyclopropane are employed, because of their potential to sensitise the myocardium to the effects of sympathomimetic amines.

Isoprenaline should not be used with chlorpromazine or monoamine oxidase inhibitors since the effects of isoprenaline may be magnified.

Caution should be maintained when using continuous intravenous isoprenaline hydrochloride infusions in conjunction with intravenous methyl xanthines (aminophylline, theophylline) and intravenous corticosteroids. The use of isoprenaline hydrochloride with aminophylline and corticosteroids may be additive in cardiotoxic properties and can lead to myocardial necrosis and death. Severe cardiac symptoms of sympathetic overactivation, i.e. hypertension, tachycardia, arrhythmias, seizures, myocardial ischaemia, and fatal myocardial necrosis, have been reported.

ADVERSE EFFECTS
Serious effects to Isuprel™ are infrequent. The following effects, however, have been reported:

CNS - Nervousness, headache, dizziness, restlessness, tension, fear of excitement and, rarely, tinnitus, light headedness and asthenia.

Cardiovascular - Tachycardia, palpitations, angina, Adams-Stokes attacks, hypertension, hypotension, ventricular arrhythmias, tachyarrhythmias and pulmonary oedema. In patients with acute myocardial infarction, isoprenaline may increase the ischaemic injury to the myocardium.

Other - Hot flashes, flushing of the skin, sweating, mild tremors, weakness and, rarely, nausea and vomiting.

These effects disappear quickly and usually do not require discontinuation of treatment with Isuprel™. No cumulative effects have been reported. Pulmonary oedema has been reported in a patient extremely intolerant of all sympathomimetic drugs.

DOSAGE AND ADMINISTRATION

Isuprel™ should generally be started at the lowest recommended dose and the rate of administration gradually increased if necessary while carefully monitoring the patient.
The usual route of administration is by intravenous infusion or bolus intravenous injection. In dire emergencies, the drug may be administered by intracardiac injection. If time is not of the utmost importance, initial therapy by intramuscular or subcutaneous injection is preferred. Elderly patients may be more sensitive to the effects of sympathomimetics and lower doses may be required.

Adults

Recommended dosage for adults with shock and hypoperfusion states

Route of Administration	Preparation of Dilution [+]	Infusion Rate [++]
Intravenous infusion	Dilute 5 mL (1 mg) in 500 mL of 5% Glucose Injection, BP	0.5µg per minute (0.25 mL to 2.5 mL of diluted solution)

[+]Concentrations up to 10 times greater have been used when limitation of volume is essential.

[++]Rates over 30 microgram per minute have been used in advanced stages of shock. The rate of infusion should be adjusted on the basis of heart rate, central venous pressure, systemic blood pressure and urine flow. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease or temporarily discontinue the infusion.

Recommended dosage for adults with heart block, Adams-Stokes attacks and cardiac arrest

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Administration
Bolus intravenous injection	Dilute 1 mL of solution 1:5000 (0.2 mg) to 10 mL with Sodium Chloride Injection BP, or 5% Glucose Injection, BP	0.02 mg to 0.06 mg (1 mL to 3 mL of diluted solution 1:50,000)	**Dose Range*** 0.01 mg to 0.2 mg (0.5 mL to 10 mL of diluted solution)
Intravenous infusion	Dilute 10 mL of solution 1:5000 (2 mg) in 500 mL of 5% Glucose Injection, BP	5µg/min (1.25 mL diluted solution 1:250,000 per minute)	-
Intramuscular	Use solution 1:5000 undiluted	0.2 mg (1 mL)	0.02 mg to 1 mg (0.1 mL to 5 mL)
Subcutaneous	Use solution 1:5000 undiluted	0.2 mg (1 mL)	0.15 mg to 0.2 mg (0.75 mL to 1 mL)
Intracardiac	Use solution 1:5000 undiluted	0.02 mg (0.1 mL)	-

* Subsequent dosage and method of administration depend on the ventricular rate and rapidity with which the cardiac pacemaker can take over when the drug is gradually withdrawn.

Recommended dosage for adults with bronchospasm occurring during anaesthesia

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Dose Range
Bolus intravenous injection	Dilute 1 mL (0.2 mg) to 10 mL with Sodium Chloride Injection BP, or 5% Glucose Injection, BP	0.01 mg to 0.02 mg (0.5 mL to 1 mL of dilute solution)	The initial dose may be repeated when necessary

Children

There are no well controlled studies in children to establish appropriate dosing. However, the American Heart Association recommends an initial infusion rate of 0.1µg/kg/min to 1.0 µg/kg/min.

Parenteral drug products should be inspected visually (in diffused light) for particulate matter and discolouration prior to administration. Such solutions should not be used.

OVERDOSAGE

The acute toxicity of Isuprel™ in animals is much less than that of adrenaline. Excessive doses in animals or humans can cause a striking drop in blood pressure, and repeated large doses in animals may result in cardiac enlargement and focal myocarditis.

In cases of accidental overdosage, as evidenced mainly by tachycardia or other arrhythmias, palpitations, angina, hypotension or hypertension, reduce rate of

administration or discontinue Isuprel™ until the patient's condition stabilises. Blood pressure, pulse, respiration and ECG should be monitored.

Very cautious use of a non-selective beta receptor antagonist should be considered if symptoms are very severe, but close monitoring of airway function would be essential.
It is not known whether Isuprel™ is dialysable.

The oral LD50 of Isuprel™ in mice is 3,850 mg/kg ± 1,190 mg/kg of pure drug in solution.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C. Protect from Light.
Injection 200 microgram/1 mL ampoules: 25's; 1000 microgram/5 mL ampoules: 10's.

NAME AND ADDRESS OF SPONSOR

Australian Sponsor:
Pfizer Australia Pty Ltd
ABN 50 008 422 348
38 – 42 Wharf Road
West Ryde NSW 2114

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine**)**

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

ISUPREL 1:5000 isoprenaline hydrochloride

1mg/5mL injection ampoule	15/03/1994
200 microgram/1mL injection ampoule	10/09/1991

DATE OF MOST RECENT AMENDMENT

27 September 2017