NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Isuprel™ 0.2 mg/mL Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the sterile 1:5000 solution contains 0.2 mg of Isoprenaline hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

A colourless, sterile, non pyrogenic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isuprel™ is indicated for:

1. Mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.

2. Serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia of fibrillation). (see section 4.3).

3. Use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, are available. (see section 4.3).

4. Bronchospasm occurring during anaesthesia.

5. As an adjunct to fluid and electrolyte replacement therapy and the use of other medicines and procedures in the treatment of hypovolaemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock. (see section 4.4).

4.2 Dose and method of administration

Isuprel™ can be administered by the intravenous, intramuscular, subcutaneous or intracardiac routes.

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 medicine 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 5mL (1mg) in 500mL of 5% Glucose Injection, BP	0.5 mcg to 5mcg per minute (0.25mL to 2.5mL) of diluted solution.

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

++ Rates over 30mcg 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 dose range***
Bolus intravenous injection	Dilute 1mL of solution 1:5000 (0.2mg) to 10mL with Sodium Chloride Injection BP, or 5% Glucose, Injection, BP	0.02mg to 0.06mg (1mL to 3mL of diluted solution 1:50,000)	0.01mg to 0.2mg (0.5mL to 10mL of diluted solution)
Intravenous infusion	Dilute 10mL of solution 1:5000 (2mg) in 500mL of 5% Glucose Injection, BP	5mcg/min (1.25mL of diluted solution 1:250,000 per minute)	
Intramuscular	Use Solution 1:5000 undiluted	0.2mg (1mL)	0.02mg to 1mg (0.1mL to 5mL)
Subcutaneous	Use Solution 1:5000 undiluted	0.2mg (1mL)	0.15mg to 0.2mg (0.75mL to 1mL)
Intracardiac	Use Solution 1:5000 undiluted	0.02mg (0.1mL)	

*Subsequent dosage and method of administration depend on the ventricular rate and the rapidity with which the cardiac pacemaker can take over when the medicine 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 1mL (0.2mg) to 10mL with sodium chloride injection, BP, or 5% glucose Injection, BP	0.01mg to 0.02mg (0.5mL to 1mL of dilute solution)	The initial dose may be repeated when necessary

Paediatric population

There are no well-controlled studies in children to establish appropriate dosing; however, the American Heart Association recommends an initial infusion rate of 0.1mcg/kg/min, with the usual range being 0.1mcg/kg/min to 1.0mcg/kg/min.

Adequacy and safety of intravenous isoprenaline in children are not established. Based on published literature, the initial dose of intravenous isoprenaline used in children is not established. Based on published literature, the initial dose of intravenous isoprenaline used in children (age 7 to 19 years of age) ranges between 0.05 to 0.17mcg/kg/min, which is increased gradually by 0.1 to 0.2mcg/kg/min at intervals of 15 to 20 minutes, titrated to clinical response; a maximum dose ranging between 1.3 to 2.7mcg/kg/min has been used. In children generally, post-operative cardiac patients with bradycardia require lower doses (0.029 ± 0.002mcg/kg/min) of intravenous isoprenaline than asthma patients (0.5 ± 0.21mcg/kg/min).

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Such solution should not be used.

Do not administer unless solution is clear and container is undamaged. Discard unused portion.

4.3 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 and previous history of hypersensitivity to isoprenaline.

4.4 Special warnings and precautions for use

Isoprenaline injection should generally be started at the lowest recommended dose. This may be gradually increased if necessary while carefully monitoring the patient.

Isoprenaline injection, by increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart. Most experts discourage its use as the initial agent in treating cardiogenic shock following myocardial infarction. However, when a low arterial pressure has been elevated by other means, isoprenaline injection may produce beneficial haemodynamic and metabolic effects.

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

Particular caution is necessary in administering isoprenaline injection to the elderly and patients with coronary insufficient, ischaemic heart disease, hypertension, aneurysms, diabetes or hyperthyroidism, and in patients sensitive to sympathomimetic amines.

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 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 ECG suggests myocardial ischaemia, cardiac enzymes including cardiac-specific CPK-MB isoenzyme levels should be determined.

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 vasoactive drugs. 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 the 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 a 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. Care is required when sympathomimetic agents are given to patients with diabetes mellitus or closed angle glaucoma.

Paediatric population

Dosage has not been established in children (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Adrenaline

Isuprel™ and adrenaline should not be administered simultaneously because both medicines are direct cardiac stimulants and their combined effects may induce serious arrhythmias. The medicines may, however, be administered alternately provided a proper interval has elapsed between doses.

Anaesthetics

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

Antidepressants, tricyclic or Maprotiline

Concurrent use may potentiate cardiovascular effects of isoprenaline and phenylephrine, possibly resulting in arrhythmias, tachycardia or severe hypertension or hyperpyrexia.

Beta-adrenergic blocking agents

Concurrent use with isoprenaline may result in mutual inhibition of therapeutic effects; beta-blockade may antagonise beta-2-adrenergic bronchodilating effects of isoprenaline; use of a cardioselective beta-2-adrenergic blocker, such as acebutolol, atenolol, or metoprolol, at low doses may reduce antagonism of the bronchodilating effect.

CNS Stimulants

Concurrent use with isoprenaline may result in additive CNS stimulation to excessive levels, which may cause unwanted effects such as nervousness, irritability, insomnia, or possibly convulsions or cardiac arrhythmias; close observation is recommended.

Digitalis Glycosides

Concurrent use with isoprenaline and phenylephrine may increase the risk of cardiac arrhythmias; caution and electrocardiographic monitoring are very important if concurrent use is necessary.

Levodopa

Concurrent use with isoprenaline and phenylephrine may increase the possibility of cardiac arrhythmias; dosage reduction of the sympathomimetic is recommended.

Nitrates

Concurrent use with isoprenaline and phenylephrine may reduce the antianginal effects of these medications.

Sympathomimetics

Concurrent use may increase the cardiovascular effects of either the other sympathomimetics or isoprenaline and phenylephrine and the potential for side effects.

Thyroid hormones

Concurrent use may increase the effects of either these medications or isoprenaline and phenylephrine; thyroid hormones enhance risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease; dosage adjustment is recommended, although problem is reduced in euthyroid patients.

MAOI's, Chlorpromazine

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

Xanthines/Corticosteroids

Caution should be maintained when using continuous intravenous isoprenaline infusions in conjunction with intravenous methyl xanthines (aminophylline, theophylline) and intravenous corticosteroids. The use of isoprenaline 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.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

Category A.

Medicines 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 medicine. Isoprenaline may delay the second stage of labour by inhibiting contraction of the uterus. However, before administration of any medicine to pregnant or lactating women, or women of childbearing potential, the expected benefit of the medicine should be carefully weighed against the possible risk to the mother or child.

Lactation

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

4.7 Effects on ability to drive and use machinery

No data available.

4.8 Undesirable 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, nausea, vomiting, tinnitus, light headedness and asthenia.

Cardiovascular

Tachycardia, palpitations, angina, Adams-Stokes attacks, hypertension, hypotension, ventricular arrhythmias, tachyarrhythmias and pulmonary oedema. In a few patients, presumably with organic disease of the AV node and its branches, isoprenaline hydrochloride injection has been reported to precipitate Adams-Stokes seizures during normal sinus rhythm or transient heart block.

Other

Hot flashes, flushing of the skin, sweating, mild tremors, weakness.

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 to all sympathomimetic drugs.

The following effects to isoprenaline hydrochloride have been reported in healthy adult controls undergoing upright tilt testing:

Symptoms	**Patients (n=15)**	**Control Gr (n=13)**	**Control GII (n=9)**
* P=0.03 (difference between patients vs. controls)			
Warmth	87%	93	78
Diaphoresis	87	77	56
Dizziness	80	77	56
Pallor	40	69	78
Visual Blurring*	33	77	56
Nausea	40	39	22
Shakiness	20	8	22
Weakness	27	15	0
Headache	33	8	0
Dyspnoea	29	15	0

Toxicity

The oral LD_{50} of isoprenaline in mice is 3,850mg/kg ± 1,190mg/kg of pure drug in solution.

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

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

In case of accidental overdosage as evidenced mainly by the tachycardia or other arrhythmias, palpitations, angina, hypotension, or hypertension, reduce rate of administration or discontinue Isuprel™ until patients 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.

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

Isoprenaline hydrochloride (also called isoproterenol 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.

Isoprenaline is a potent non selective beta-adrenergic agonist with low affinity for alpha-adrenergic receptors.

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

Isoprenaline increases cardiac output due to its positive inotropic and chronotropic actions and 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 isoprenaline 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 isoprenaline.

Isoprenaline 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.

In man, isoprenaline causes less hyperglycaemia than does adrenaline. Isoprenaline and adrenaline are equally effective in stimulating the release of free fatty acids and energy production.

5.2 Pharmacokinetic properties

Isoprenaline is readily absorbed when given parenterally.

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-o-methyl transferase primarily in the liver. The major metabolite after intravenous administration is 3-*0*-methylisoprenaline, which is reported to have weak β-adrenergic blocking activity, and its conjugates. Isoprenaline is a relatively poor substrate for MAO and is not taken up by sympathetic neurons to the same extent as adrenaline and noradrenaline. The duration of action of isoprenaline may therefore be longer than that of adrenaline, but it is still brief. The metabolites are excreted through the kidneys.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- Citric acid
- Disodium edetate
- Hydrochloric acid
- Nitrogen
- Sodium chloride
- Sodium citrate dihydrate
- Sodium hydroxide
- Water for injection

6.2 Incompatibilities

No data available.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 25°C. Protect from Light.

6.5 Nature and contents of container

Injection, 200 microgram/1 mL ampoules: 25’s; 1 mg/5 mL ampoules: 10’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, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

31 Dec 1969

10. DATE OF REVISION OF THE TEXT

12 February 2019

Summary table of changes

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance
6.1	Update to INN