AUSTRALIAN PRODUCT INFORMATION – DBL™ SODIUM NITROPRUSSIDE 50MG/2ML CONCENTRATED INJECTION VIAL (SODIUM NITROPRUSSIDE)

1. NAME OF THE MEDICINE

Sodium nitroprusside

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Sodium Nitroprusside concentrated injection is a sterile solution containing the equivalent of 50 milligram of sodium nitroprusside dihydrate [sodium nitrosylpentacyanoferrate (III)] per 2 mL.

3. PHARMACEUTICAL FORM

DBL™ Sodium Nitroprusside concentrated injection is a clear solution available in amber glass vials containing the equivalent of 50 mg sodium nitroprusside dihydrate in 2 mL solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Sodium Nitroprusside concentrated injection is indicated for:

1. Immediate reduction of blood pressure in patients with hypertensive crises. Concomitant oral antihypertensive medication should be started while the hypertensive emergency is being brought under control with sodium nitroprusside.

2. Producing controlled hypotension during anaesthesia in order to reduce bleeding in surgical procedures where surgeon and anaesthetist deem it appropriate.

3. Short term therapy of cardiac failure, to enhance cardiac output and lower myocardial oxygen requirements. Patients should be commenced on oral therapy as soon as possible.

4.2 Dose and method of administration

SODIUM NITROPRUSSIDE IS ONLY TO BE USED AS AN INFUSION WITH STERILE 5% GLUCOSE IN WATER. IT SHOULD NOT BE ADMINISTERED BY DIRECT INJECTION.

Product is for single use in one patient only. Discard any residue.

Dosage

Dilution to proper strength for infusion:

Depending on the desired concentration, DBL™ Sodium Nitroprusside concentrated injection containing 50 mg/2 mL sodium nitroprusside must be further diluted in 500-1000 mL of sterile 5% glucose injection. The diluted solution should be protected from light, using the supplied opaque sleeve, aluminium foil, or other opaque material. It is not necessary to cover the infusion drip chamber or the tubing.

Verification of the chemical integrity of the product:

Sodium nitroprusside solution can be inactivated by reactions with trace contaminants. The products of these reactions are often blue, green, or red, much brighter than the faint brownish colour of unreacted DBL™ Sodium Nitroprusside concentrated injection. Discoloured solutions, or solutions in which particulate matter is visible, should not be used. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C - 8°C for not more than 24 hours, protected from light

No other drugs should be administered in the same solution with sodium nitroprusside.

Avoidance of excessive hypotension:

While the average effective rate in adults and children is about 3 mcg/kg/min, some patients will become dangerously hypotensive when they receive DBL™ Sodium Nitroprusside concentrated injection at this rate. Infusion of sodium nitroprusside should therefore be started at a very low rate (0.3 mcg/kg/min), with upward titration every few minutes until the desired effect is achieved or the maximum recommended infusion rate (10 mcg/kg/min) has been reached. Because sodium nitroprusside's hypotensive effect is very rapid in onset and in dissipation, small variations in infusion rate can lead to wide, undesirable variations in blood pressure, **Sodium nitroprusside should not be infused through ordinary I.V. apparatus, regulated only by gravity and mechanical clamps. Only an infusion pump, preferably a volumetric pump, should be used.**

Because sodium nitroprusside can induce essentially unlimited blood-pressure reduction, **the blood pressure of a patient receiving this drug must be continuously monitored**, using either a continually reinflated sphygmomanometer or (preferably) an intra-arterial pressure sensor. Special caution should be used in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

When sodium nitroprusside is used in the treatment of acute congestive heart failure, titration of the infusion rate must be guided by the results of invasive haemodynamic monitoring with simultaneous monitoring of urine output. Sodium nitroprusside can be titrated by increasing the infusion rate until:

- measured cardiac output is no longer increasing,
- systemic blood pressure cannot be further reduced without compromising the perfusion of vital organs, or
- the maximum recommended infusion rate has been reached, whichever comes earliest. Specific haemodynamic goals must be tailored to the clinical situation, but improvements in cardiac output and left ventricular filling pressure must not be purchased at the price of undue hypotension and consequent hypoperfusion.

The table below shows the infusion rates corresponding to the recommended initial and maximal doses (0.3 mcg/kg/min and 10 mcg/kg/min, respectively) for both adults and children of various weights. Some of the listed infusion rates are so slow or so rapid as to be impractical, and these practicalities must be considered when the concentration to be used is selected.

Note that when the concentration used in a given patient is changed, the tubing is still filled with a solution at the previous concentration.

Avoidance of cyanide toxicity:

As described in Section 5.2 Pharmacokinetic properties, when more than 500 mcg/kg of sodium nitroprusside is administered faster than 2 mcg/kg/min, cyanide is generated faster than the unaided patient can eliminate it. Administration of sodium thiosulfate has been shown to increase the rate of cyanide processing, reducing the hazard of cyanide toxicity. Although toxic reactions to sodium thiosulfate have not been reported, the co-infusion regimen has not been extensively studied, and it cannot be recommended without reservation. In one study, sodium thiosulfate appeared to potentiate the hypotensive effects of sodium nitroprusside.

Co-infusions of sodium thiosulfate have been administered at rates of 5-10 times that of sodium nitroprusside. Care must be taken to avoid the indiscriminate use of prolonged or high doses of sodium nitroprusside with sodium thiosulfate as this may result in thiocyanate toxicity and hypovolemia. Incautious administration of sodium nitroprusside must still be avoided, and all of the precautions concerning sodium nitroprusside administration must still be observed.

Infusion rates (mL/hour) to Achieve Initial (0.3 mcg/kg/min) and Maximal (10 mcg/kg/min) dosing of **DBL™ SODIUM NITROPRUSSIDE** concentrated injection				
Volume	500mL		1000mL	
DBL™ SODIUM NITROPRUSSIDE concentrated injection	50mg		50mg	
Concentration	100 mcg/mL		50 mcg/mL	
Pt weight (kg)	Init (mL/hour)	Max (mL/hour)	Init (mL/hour)	Max (mL/hour)
10	2	60	4	120
20	4	120	7	240
30	5	180	11	360
40	7	240	14	480
50	9	300	18	600
60	11	360	22	720
70	13	420	25	840
80	14	480	29	960
90	16	540	32	1080
100	18	600	36	1200

Consideration of methaemoglobinemia and thiocyanate toxicity:

Rare patients receiving more than 10 mg/kg of sodium nitroprusside will develop methaemoglobinaemia; other patients, especially those with impaired renal function, will predictably develop thiocyanate toxicity after prolonged, rapid infusions. In accordance with the descriptions in Section 4.8 Adverse effects (undesirable effects), patients with suggestive findings should be tested for these toxicities.

WARNING: Do not use flexible container in series connections.

Paediatric: Sodium nitroprusside can safely be used in children, provided that a satisfactory hypotensive response is obtained using doses calculated on a microgram/kg basis with adjustments as recommended for the adult.

Geriatric: Commence therapy with low doses since geriatric patients appear to be more sensitive to the hypotensive effects of the medicine. Induced hypotension in elderly patients, especially those with hypertension, carries a significant morbidity and mortality. Therefore, the medicine should be administered with caution in this age group.

Impaired liver function: Caution should be observed in patients with severe liver impairment as the medicine is largely metabolised by the hepatic enzyme rhodanase (trans-sulphurase), the enzyme responsible for the conversion of cyanide ions to thiocyanate. Patients with liver disease are therefore more susceptible to toxic effects associated with accumulation of cyanide.

Impaired renal function: Caution should be observed in patients with impaired renal function since thiocyanate, a major metabolite of the medicine, is excreted by the kidney. Toxicity from thiocyanate accumulation has occurred in patients with renal failure who have received prolonged nitroprusside infusion for hypertensive crises. Blood levels of thiocyanate should be determined if the medicine is used in patients suffering severe renal dysfunction.

4.3 Contraindications

Sodium nitroprusside should not be used in the treatment of compensatory hypertension, e.g. arteriovenous shunt or coarctation of the aorta.

It is also contraindicated in physically poor risk patients with known inadequate cerebral circulation or in moribund patients (ASA Risk 5), in patients with uncorrected anaemia or hypovolaemia, severe renal disease or disease states associated with vitamin B_{12} deficiency.

Patients with congenital (Leber's) optic atrophy or with tobacco amblyopia have unusually high cyanide/thiocyanate ratios. These rare conditions are probably associated with defective or absent rhodanase, and sodium nitroprusside should be avoided in these patients.

Sodium nitroprusside should not be used for the treatment of acute congestive heart failure associated with reduced peripheral vascular resistance such as high-output heart failure that may be seen in endotoxic sepsis.

4.4 Special warnings and precautions for use

SODIUM NITROPRUSSIDE IS ONLY TO BE USED AS AN INFUSION WITH STERILE 5% GLUCOSE IN WATER. IT SHOULD NOT BE ADMINISTERED BY DIRECT INJECTION.

The principal hazards of sodium nitroprusside administration are excessive hypotension and excessive accumulation of cyanide (see also Section 4.9 Overdose and Section 4.2 Dose and method of administration).

Excessive hypotension

Sodium nitroprusside can cause precipitous decreases in blood pressure (see Section 4.2 Dose and method of administration). In patients not properly monitored, these decreases can lead to irreversible ischemic injuries or death. Sodium nitroprusside should be used only when available equipment and personnel allow blood pressure to be continuously monitored.

Small transient excesses in the infusion rate of sodium nitroprusside can result in excessive hypotension, sometimes to levels so low as to compromise the perfusion of vital organs. These haemodynamic changes may lead to a variety of associated symptoms (see Section 4.8 Adverse effects (undesirable effects)). Nitroprusside induced hypotension will be self limited within 1 to 10 minutes after discontinuation of the nitroprusside infusion; during these few minutes, it may be helpful to put the patient into a head down (Trendelenburg) position to maximise venous return. If hypotension persists more than a few minutes after discontinuation of the infusion of sodium nitroprusside, sodium nitroprusside is not the cause, and the true cause must be sought.

Cyanide poisoning

Except when used briefly or at low (less than 2 micrograms/kg/min) infusion rates, sodium nitroprusside gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels. (When sodium thiosulfate is given, as described under Section 4.2 Dose and method of administration, the body's capacity for CN^- elimination is greatly increased.)

The usual dose rate is 0.5 to 10 microgram/kg/min, but infusion at the maximum dose rate should never last more than 10 minutes. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of sodium nitroprusside should be terminated immediately.

Methaemoglobin normally present in the body can buffer a certain amount of CN-, but the capacity of this system is exhausted by the CN- produced from about 500 microgram/kg of sodium nitroprusside. This amount of sodium nitroprusside is administered in less than an hour when the medicine is administered at 10 microgram/kg/min (the maximum recommended rate). Thereafter, the toxic effects of CN- may be rapid, serious, and even lethal.

The true rates of clinically important cyanide toxicity cannot be assessed from spontaneous reports or published data. Most patients reported to have experienced such toxicity have received relatively prolonged infusions, and the only patients whose deaths have been unequivocally attributed to nitroprusside induced cyanide toxicity have been patients who had received nitroprusside infusions at rates (30 to 120 microgram/kg/min) much greater than those now recommended. Elevated cyanide levels, metabolic acidosis, and marked clinical deterioration, however, have occasionally been reported in patients who received infusions at recommended rates for only a few hours and even, in one case, for only 35 minutes. In some of these cases, infusion of sodium thiosulfate caused dramatic clinical improvement, supporting the diagnosis of cyanide toxicity.

Cyanide toxicity may manifest itself as venous hyperoxaemia with bright red venous blood, as cells become unable to extract the oxygen delivered to them; metabolic (lactic) acidosis; air hunger; confusion; and death. Cyanide toxicity due to causes other than nitroprusside has been associated with angina pectoris and myocardial infarction; ataxia, seizures, and stroke; and other diffuse ischemic damage.

Hypertensive patients, and patients concomitantly receiving other antihypertensive medications, may be more sensitive to the effects of sodium nitroprusside than normal subjects.

Although acid-base balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance.

General:

Like other vasodilators, sodium nitroprusside can cause increases in intracranial pressure. In patients whose intracranial pressure is already elevated, sodium nitroprusside should be used only with extreme caution.

Use in anaesthesia:

When sodium nitroprusside (or any other vasodilator) is used for controlled hypotension during anaesthesia, the patient's capacity to compensate for anaemia and hypovolaemia may be diminished. If possible, pre-existing anaemia and hypovolaemia should be corrected prior to administration of sodium nitroprusside.

Hypotensive anaesthetic techniques may also cause abnormalities of the pulmonary ventilation/perfusion ratio. Patients intolerant of these abnormalities may require a higher fraction of inspired oxygen.

Extreme caution should be exercised in patients who are especially poor surgical risks (ASA Class 4 and 4E).

Monitoring of blood pressure:

Direct monitoring of blood pressure is mandatory.

Adequate facilities, equipment and personnel should be available for frequent and vigilant monitoring of blood pressure, since the hypotensive effect of sodium nitroprusside occurs rapidly.

It is recommended that the blood pressure should not be allowed to drop rapidly and the systolic pressure not be lowered below 60 mmHg. Too great a reduction in blood pressure may result in retching or vomiting, muscular twitching, diaphoresis and agitation.

When the infusion is slowed or stopped, blood pressure usually begins to rise immediately and returns to pre-treatment levels within one to ten minutes.

Sodium nitroprusside should be used with caution and initially in low doses in elderly patients, since they may be more sensitive to the hypotensive effect of the medicine.

Young, vigorous males may require somewhat larger than ordinary doses of sodium nitroprusside for hypotensive anaesthesia, however, the infusion rate of 10 micrograms/kg/minute should not be exceeded. Deepening of anaesthesia, if indicated, might permit satisfactory conditions to exist within the recommended dosage range.

Because of the rapid onset of action and potency of sodium nitroprusside, it should be administered with the use of an infusion pump, micro-drip regulator, or any similar device that would allow precise measurement of the flow rate.

Postural hypotension:

Patients should remain recumbent during the infusion to avoid severe postural hypotensive effects.

Coloured solution:

Sodium nitroprusside in aqueous solution yields the nitroprusside ion which reacts with even minute quantities of a wide variety of inorganic and organic substances to form usually highly coloured reaction products (blue, green or dark red). If this occurs, the infusion should be replaced.

Hypothyroidism:

Since thiocyanate inhibits both the uptake and binding of iodine, caution should be exercised in using sodium nitroprusside in patients with hypothyroidism and severe renal dysfunction. Thyroid hormone deficiency has been reported following prolonged infusions.

Hypothermia:

The medicine should be used with extreme caution if the patient is hypothermic.

Stress:

If in the clinical situation, stress, induced by pain or manipulation is reduced or eliminated during sodium nitroprusside infusion, the patient could experience a greater than expected reduction in blood pressure unless the rate of infusion is adjusted downward as required.

Tachyphylaxis:

Several authors have reported tachyphylaxis in young male patients during hypotensive anaesthesia. However, tachyphylaxis has not been reported to date with sodium nitroprusside in the treatment of hypertensive emergencies.

Use in hepatic impairment

Use caution when administering nitroprusside to patients with hepatic insufficiency.

Use in renal impairment

See section 4.2 Dose and method of administration, and section 4.3 Contraindications.

Use in the elderly

Refer to Section 4.2 Dose and method of administration.

Paediatric use

Refer to Section 4.2 Dose and method of administration.

Effects on laboratory tests

The cyanide level assay is technically difficult, and cyanide levels in body fluids other than packed red blood cells are difficult to interpret. Cyanide toxicity will lead to lactic acidosis and venous hyperoxaemia, but these findings may not be present until an hour or more after the cyanide capacity of the body's red cell mass has been exhausted.

4.5 Interactions with other medicines and other forms of interactions

Ganglion blocking agents and other antihypertensive agents, volatile liquid anaesthetics, inhaled anaesthetics, negative inotropes and most other circulatory depressants potentiate the hypotensive action of sodium nitroprusside.

The transition from sodium nitroprusside to oral antihypertensive therapy may predispose to severe, sudden hypertension.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Sodium nitroprusside has not been tested for effects on fertility.

Use in pregnancy – Pregnancy Category C

There are no adequate or well controlled studies of sodium nitroprusside in either laboratory animals or pregnant women. It is not known whether sodium nitroprusside can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Sodium nitroprusside should be given to a pregnant woman only if clearly needed. There have been no reports on its use in the hypertension of pre-eclampsia.

Sodium nitroprusside is used in high risk situations and there may be additional hazards associated with the drug. It crosses the placenta. Short term use for control of hypertensive crises may be safe provided the maternal pH and cyanide levels are monitored.

In three studies in pregnant ewes, nitroprusside was shown to cross the placental barrier. Foetal cyanide levels were shown to be dose related to maternal levels of nitroprusside. The metabolic transformation of sodium nitroprusside given to pregnant ewes led to fatal levels of cyanide in the foetuses. The infusion of 25 micrograms/kg/minute of sodium nitroprusside for one hour in pregnant ewes resulted in the death of all foetuses. Pregnant ewes infused with 1 microgram/kg/minute of sodium nitroprusside delivered normal lambs.

Use in lactation

It is not known whether sodium nitroprusside or its metabolites are excreted into breast milk, nor whether they have a harmful effect on the newborn. Therefore, the drug is not recommended for nursing mothers, unless the expected benefits outweigh any potential risk.

4.7 Effects on ability to drive and use machines

No specific studies have been conducted to assess the direct effect of sodium nitroprusside on the ability to drive and use machines. However, adverse effects of sodium nitroprusside include dizziness and drowsiness which could affect the ability to drive or use machines. See Section 4.8 Adverse effects (undesirable effects).

4.8 Adverse effects (undesirable effects)

The most important adverse reactions to sodium nitroprusside are the avoidable ones of excessive hypotension and cyanide toxicity, described above under Section 4.4 Special

warnings and precautions for use. The adverse effects described in this section develop less rapidly and, as it happens, less commonly.

Methemoglobinaemia: As described in Section 5.2 Pharmacokinetic properties, sodium nitroprusside infusions can cause sequestration of haemoglobin as methaemoglobin. The back conversion process is normally rapid, and clinically significant methaemoglobinaemia (>10%) is seen only rarely in patients receiving sodium nitroprusside. Even patients congenitally incapable of back converting methaemoglobin should demonstrate 10% methaemoglobinaemia only after they have received about 10 milligram/kg of sodium nitroprusside, and a patient receiving sodium nitroprusside at the maximum recommended rate (10 microgram/kg/min) would take over 16 hours to reach this total accumulated dose.

Methaemoglobin levels can be measured by most clinical laboratories. The diagnosis should be suspected in patients who have received >10 milligram/kg of sodium nitroprusside and who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methaemoglobinaemic blood is described as chocolate brown, without colour change on exposure to air.

When methaemoglobinaemia is diagnosed, the treatment of choice is 1 to 2 milligram/kg of methylene blue, administered intravenously over several minutes. In patients likely to have substantial amounts of cyanide bound to methaemoglobin as cyanmethaemoglobin, treatment of methaemoglobinaemia with methylene blue must be undertaken with extreme caution.

Thiocyanate toxicity: As described in Section 5.2 Pharmacokinetic properties, most of the cyanide produced during metabolism of sodium nitroprusside is eliminated in the form of thiocyanate. When cyanide elimination is accelerated by the co-infusion of thiosulfate, thiocyanate production is increased.

Thiocyanate is mildly neurotoxic (tinnitus, miosis, hyperreflexia) at serum levels of 1 millimol/L (60 milligram/L). Thiocyanate toxicity is life threatening when levels are 3 or 4 times higher (200 milligram/L).

The steady-state thiocyanate level after prolonged infusions of sodium nitroprusside is increased with increased infusion rate, and the half time of accumulation is 3 to 4 days. To keep the steady-state thiocyanate level below 1 millimol/L, a prolonged infusion of sodium nitroprusside should not be more rapid than 3 microgram/kg/min; in anuric patients, the corresponding limit is just 1 microgram/kg/min. When prolonged infusions are more rapid than these, thiocyanate levels should be measured daily.

Physiologic manoeuvres (e.g. those that alter the pH of the urine) are not known to increase the elimination of thiocyanate. Thiocyanate clearance rates during dialysis, on the other hand, can approach the blood flow rate of the dialyser.

Thiocyanate interferes with iodine uptake by the thyroid.

Other adverse effects reported are:

General: Too rapid reduction in blood pressure may cause adverse effects. Nausea, retching, diaphoresis, apprehension, headache, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness, drowsiness, paraesthesial warmth, and abdominal pain have been reported during use of the drug. These symptoms, however, rapidly disappeared with slowing

of the rate of infusion or temporary discontinuation of the infusion and did not reappear with continued slower rate of administration.

Cardiovascular: Tachycardia, postural hypotension, bradycardia, electro-cardiographic changes.

Dermatological: Irritation, rash and flushing, reddening of the skin at the injection site and venous streaking have been reported. Care should be taken to avoid extravasation.

Endocrine: Since thiocyanate inhibits both uptake and binding of iodine, symptoms of hypothyroidism may occur.

Haematologic: Decreased platelet aggregation.

Neurologic: Raised intracranial pressure.

Gastrointestinal: Ileus.

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 www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdosage of nitroprusside can be manifested as excessive hypotension or cyanide toxicity (see Section 4.4 Special warnings and precautions for use) or as thiocyanate toxicity (see Section 4.8 Adverse effects (undesirable effects)).

The acute intravenous mean lethal doses (LD_{50}) of nitroprusside in rabbits, dogs, mice, and rats are 2.8, 5.0, 8.4, and 11.2 mg/kg, respectively.

Treatment of cyanide toxicity:

Cyanide levels can be measured by many laboratories, and blood-gas studies that can detect venous hyperoxaemia or acidosis are widely available. **Acidosis may not appear until more than an hour after the appearance of dangerous cyanide levels, and laboratory tests should not be awaited. Reasonable suspicion of cyanide toxicity is adequate grounds for initiation of treatment.**

Treatment of cyanide toxicity consists of:

- discontinuing the administration of sodium nitroprusside;
- providing a buffer for cyanide by using sodium nitrite to convert as much haemoglobin into methaemoglobin as the patient can safely tolerate; and then
- infusing sodium thiosulfate in sufficient quantity to convert the cyanide into thiocyanate.

Haemodialysis is ineffective in removal of cyanide, but it will eliminate most thiocyanate.

Amyl nitrate via inhalation may be administered in environments where intravenous administration of sodium nitrite may be delayed. In a patient who already has a patent intravenous line, use of amyl nitrite confers no benefit that is not provided by infusion of sodium nitrite. Sodium nitrite is available in a 3% solution, and 4-6 mg/kg (about 0.2 mL/kg) should be injected over 2-4 minutes. This dose can be expected to convert about 10% of the patient's haemoglobin into methaemoglobin; this level of methaemoglobinaemia is not associated with any important hazard of its own. The nitrite infusion may cause transient vasodilatation and hypotension, and this hypotension must, if it occurs, be routinely managed.

Immediately after infusion of the sodium nitrite, sodium thiosulfate should be infused. This agent is available in 10% and 25% solutions, and the recommended dose is 150 to 200 milligram/kg; a typical adult dose is 50 mL of the 25% solution. Thiosulfate treatment of an acutely cyanide toxic patient will raise thiocyanate levels, but not to a dangerous degree.

The nitrite/thiosulfate regimen may be repeated, at half the original doses, after two hours.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia)..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The principal pharmacological action of sodium nitroprusside is relaxation of vascular smooth muscle and consequent dilation of peripheral arteries and veins. Other smooth muscle (e.g. uterus, duodenum) is not affected. Sodium nitroprusside is more active on veins than on arteries, but this selectivity is much less marked than that of nitroglycerin. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilation of the coronary arteries also occurs.

In association with the decrease in blood pressure, sodium nitroprusside administered intravenously to hypertensive and normotensive patients produces slight increases in heart rate and a variable effect on cardiac output. In hypertensive patients, moderate doses induce renal vasodilatation roughly proportional to the decrease in systemic blood pressure, so there is no appreciable change in renal blood flow or glomerular filtration rate.

In normotensive subjects, acute reduction of mean arterial pressure to 60 to 75 mm Hg by infusion of sodium nitroprusside caused a significant increase in renin activity. In the same study, ten renovascular hypertensive patients given sodium nitroprusside had significant increases in renin release from the involved kidney at mean arterial pressures of 90 to 137 mm Hg.

The hypotensive effect of sodium nitroprusside is seen within a minute or two after the start of an adequate infusion, and it dissipates almost as rapidly after an infusion is discontinued. The effect is augmented by ganglionic blocking agents and inhaled anaesthetics.

Clinical trials

Many trials have verified the clinical significance of the metabolic pathways described above. In patients receiving unopposed infusions of sodium nitroprusside, cyanide and thiocyanate levels have increased with increasing rate of sodium nitroprusside infusion. Mild to moderate metabolic acidosis has usually accompanied higher cyanide levels, but peak base deficits have lagged behind the peak cyanide levels by an hour or more.

Progressive tachyphylaxis to the hypotensive effects of sodium nitroprusside has been reported in several trials and numerous case reports. This tachyphylaxis has frequently been attributed to concomitant cyanide toxicity, but the only evidence adduced for this assertion has been the observation that in patients treated with sodium nitroprusside and found to be resistant to its hypotensive effects, cyanide levels are often found to be elevated. In the only reported comparisons of cyanide levels in resistant and non-resistant patients, cyanide levels did not correlate with tachyphylaxis. The mechanism of tachyphylaxis to sodium nitroprusside remains unknown.

5.2 Pharmacokinetic properties

Infused sodium nitroprusside is rapidly distributed to a volume that is approximately coextensive with the extracellular space. The drug is cleared from this volume by intraerythrocytic reaction with haemoglobin (Hgb), and sodium nitroprusside's resulting circulatory half life is about 2 minutes.

The products of the nitroprusside/haemoglobin reaction are cyanmethaemoglobin (cyanmet Hgb) and cyanide ion (CN^-). Safe use of sodium nitroprusside injection must be guided by knowledge of the further metabolism of these products. The essential features of nitroprusside metabolism are:

- one molecule of sodium nitroprusside is metabolised by combination with haemoglobin to produce one molecule of cyanmethaemoglobin and four CN^- ions;
- methaemoglobin, obtained from haemoglobin, can sequester cyanide as cyanmethaemoglobin;
- thiosulfate reacts with cyanide to produce thiocyanate;
- thiocyanate is eliminated in the urine;
- cyanide not otherwise removed binds to cytochromes; and
- cyanide is much more toxic than cyanmethaemoglobin or thiocyanate.

Cyanide ion is normally found in serum; it is derived from dietary substrates and from tobacco smoke. Cyanide binds avidly (but reversibly) to ferric ion (Fe^{+++}), most body stores of which are found in erythrocyte methaemoglobin (metHgb) and in mitochondrial cytochromes. When CN^- is infused or generated within the bloodstream, essentially all of it is bound to methaemoglobin until intraerythrocytic methaemoglobin has been saturated.

When the Fe^{+++} of cytochromes is bound to cyanide, the cytochromes are unable to participate in oxidative metabolism. In this situation, cells may be able to provide for their energy needs by utilising anaerobic pathways, but they thereby generate an increasing body burden of lactic acid. Other cells may be unable to utilise these alternate pathways, and they may die hypoxic deaths.

CN^- levels in packed erythrocytes are typically less than 1 micromol/L (less than 25 microgram/L); levels are roughly doubled in heavy smokers.

At healthy steady state, most people have less than 1% of their haemoglobin in the form of methaemoglobin. Nitroprusside metabolism can lead to methaemoglobin formation (a) through dissociation of cyanmethaemoglobin formed in the original reaction of sodium nitroprusside with Hgb and (b) by direct oxidation of Hgb by the released nitroso group. Relatively large quantities of sodium nitroprusside, however, are required to produce significant methaemoglobinaemia.

At physiologic methaemoglobin levels, the CN- binding capacity of packed red cells is a little less than 200 micromol/L (5 milligram/L). Cytochrome toxicity is seen at levels only slightly higher, and death has been reported at levels from 300 to 3000 micromol/L (8 to 80 milligram/L). Put another way, a patient with a normal red cell mass (35 mL/kg) and normal methaemoglobin levels can buffer about 175 microgram/kg of CN^-, corresponding to a little less than 500 microgram/kg of infused sodium nitroprusside.

Some cyanide is eliminated from the body as expired hydrogen cyanide, but most is enzymatically converted to thiocyanate (SCN^-) by thiosulfate-cyanide sulfur transferase (rhodanase, EC 2.8.1.1), a mitochondrial enzyme. The enzyme is normally present in great excess, so the reaction is rate limited by the availability of sulfur donors, especially thiosulfate, cystine, and cysteine.

Thiosulfate is a normal constituent of serum, produced from cysteine by way of beta-mercaptopyruvate. Physiological levels of thiosulfate are typically about 0.1 millimol/L (11 milligram/L), but they are approximately twice this level in children and in adults who are not eating. Infused thiosulfate is cleared from the body (primarily by the kidneys) with a half life of about 20 minutes.

When thiosulfate is being supplied only by normal physiologic mechanisms, conversion of CN^- to SCN^- generally proceeds at about 1 microgram/kg/min. This rate of CN^- clearance corresponds to steady state processing of a sodium nitroprusside infusion of slightly more than 2 microgram/kg/min. CN^- begins to accumulate when sodium nitroprusside infusions exceed this rate.

Thiocyanate (SCN^-) is also a normal physiological constituent of serum, with normal levels typically in the range of 50 to 250 micromol/L (3 to 15 milligram/L). Clearance of SCN^- is primarily renal, with a half life of about 3 days. In renal failure, the half life can be doubled or tripled.

5.3 Preclinical safety data

Genotoxicity

The mutagenic potential of sodium nitroprusside has not been assessed.

Carcinogenicity

Sodium nitroprusside has not undergone adequate carcinogenicity testing in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

See Section 4.2 Dose and method of administration.

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

Store below 25°C. Protect from light. Retain in carton until time of use.

6.5 Nature and contents of container

It is presented in a 2 mL amber coloured, rubber stoppered vial.

Strength	Volume	Pack Size	AUST R
50 milligram/2 mL	2 mL vial	1	177111

6.6 Special precautions for disposal

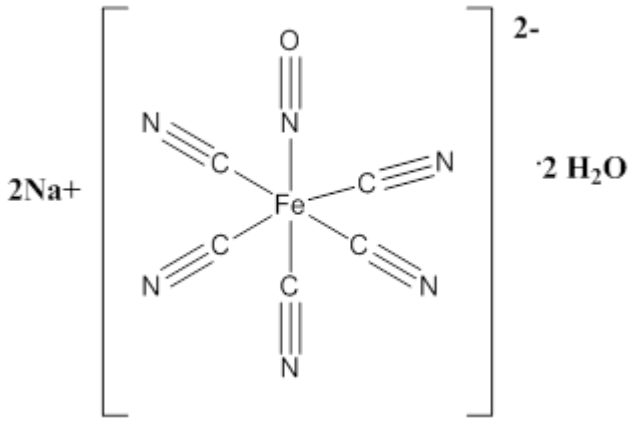
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemically, sodium nitroprusside is $Na_2Fe(CN)_5NO$ - $2H_2O$. It is a reddish-brown powder which is soluble in water. In aqueous solution, it is photosensitive and must be protected from light.

Chemical structure

The chemical formula of sodium nitroprusside is $Na_2Fe(CN)_5NO$ - $2H_2O$, its molecular weight is 298.0.



CAS number

13755-38-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

09 May 2012

10. DATE OF REVISION

06 September 2019

Summary Table of Changes

Section changed	Summary of new information
All	All sections reformatted in line with the new form.
2; 4; & 6	Editorial