

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0437/002/001**

Case No: 2031580

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**HOSPIRA UK Ltd**

**Queensway, Royal Leamington Spa, Warwickshire CV31 3RW, United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Sodium Nitroprusside 50mg Powder for Concentrate for Solution for Infusion**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **04/05/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Sodium Nitroprusside 50mg Powder for Concentrate for Solution for Infusion.

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial of powder for solution for infusion contains 50.0 mg of sodium nitroprusside.

For a full list of excipients, see section 6.1

#### 3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Vials containing a pink to red powder.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Sodium nitroprusside is indicated for the immediate reduction of blood pressure in patients in hypertensive crises.

The drug is effective in the management of hypertensive emergencies, irrespective of aetiology, and may be useful when other drugs have failed.

Sodium nitroprusside may also be used to produce controlled hypotension during anaesthesia in order to reduce bleeding in surgical procedures when surgeon and anaesthetist deem it appropriate.

Nitroprusside has also been used in the treatment of heart failure and other cardiac disorders where it is necessary to quickly reduce left ventricular outflow (afterload) and lower raised ventricular pressure (preload).

##### 4.2 Posology and method of administration

Sodium nitroprusside is to be administered only by intravenous infusion using a controlled infusion device, infusion pump, drip regulator, micro-drip regulator or similar device that will allow precise measurements of flow rate. Care should be taken to avoid extravasation.

Reconstitution can only be carried out using Glucose Intravenous Infusion. A concentrated solution of sodium nitroprusside may be prepared by dissolving 50 mg of the drug in 2-3 ml of Glucose Intravenous Infusion. The concentrated solution should be further diluted in 250, 500, or 1000 ml of Glucose Intravenous Infusion to provide solutions containing 200, 100 or 50 micrograms per ml respectively. Nitroprusside solutions should be protected from light by promptly wrapping the containers in aluminium foil or other opaque material.

Administration should be carried out at all times under close supervision. No other drug should be added to the infusion fluid for simultaneous administration with sodium nitroprusside and in hypotensive patients receiving concomitant antihypertensive medication, smaller doses of sodium nitroprusside might be required.

It is recommended that the blood pressure should not be allowed to drop rapidly and that systolic pressure should not be lowered below 60 mmHg. This can be achieved by increasing the dose slowly which should also prevent any physiological compensatory reactions resulting from the release of catecholamines and renins into the blood, which would lead to tachycardia.

The rate of administration should be adjusted to maintain the desired hypotensive effect, as determined by continuous blood pressure monitoring.

In order to avoid excessive levels of cyanide and thiocyanate and lessen the possibility of a precipitous drop in blood pressure, infusion rates greater than 10 micrograms per kilogram per minute should not be used. If, at this rate, an adequate reduction of blood pressure is not obtained within 10 minutes, the administration of Sodium Nitroprusside should be stopped.

The intravenous infusion should not be stopped suddenly as this might lead to an excessive rebound rise in blood pressure, but rather over a period of 15 to 30 minutes. In hypertensive emergencies sodium nitroprusside infusion may be continued until an alternative oral therapy can be safely introduced.

Intravenous infusion of sodium nitroprusside may be continued for several days but care must be taken to ensure that the blood cyanide concentration does not exceed 100 micrograms per 100 ml and that the serum cyanide concentration does not exceed 8 micrograms per 100 ml. If infusion is carried out for a period in excess of three days then the blood thiocyanate concentration should be checked and not exceed 100 micrograms per ml.

## **DOSAGE IN ADULTS**

### **A. In Hypertensive Crisis**

Dosage varies considerably between patients, hence the need for individual titration. In adults not receiving other hypotensive agents, the average dosage of sodium nitroprusside is 3 micrograms per kilogram per minute.

The initial dose is normally within the range of 0.5-1.5 micrograms per kilogram per minute, but can then be adjusted in a stepwise fashion, e.g. in increments of 0.5 micrograms per kilogram per minute every 5 minutes, to fall between 0.5 - 8 micrograms per kilogram per minute.

To maintain the blood pressure at 30 to 40% lower than the pretreatment diastolic blood pressure levels an average of 200 micrograms/minute (range of 20 to 400 micrograms/minute) is usually sufficient. In hypertensive patients receiving concomitant antihypertensive medication, smaller doses might be required.

### **B. In Heart Failure**

The initial dose should be between 10-15 micrograms per minute increased every 5-10 minutes in increments of 10 to 15 micrograms per minute as necessary to the normal range of 10-200 microgram per minute to obtain the desired response.

In some patients the additive effects of a vasodilator and a potent inotropic agent may be used to advantage. If a vasodilator is used haemodynamic monitoring should be used to guide its administration.

If during treatment signs of hypotension, hypoperfusion or any other adverse effects are observed the infusion rate should be reduced or administration stopped.

The infusion may be continued until an alternative oral therapy can be safely introduced. The infusion therapy should not normally exceed 3 days.

### **C. In Controlled Hypotension During General Anaesthesia**

For the induction of hypotension during anaesthesia a maximum dose of 1.5 microgram per kilogram bodyweight per minute is recommended.

The intrinsic hypotensive effect of many anaesthetic agents must be remembered and all normal procedures for hypotensive techniques should be carried out.

#### D. Geriatric Patients

Commence therapy with low doses since geriatric patients appear to be more sensitive to the hypotensive effects of the drug. Therefore the drug should be administered with caution in this age group.

#### E. Children

Dosage recommendations have not been established.

### 4.3 Contraindications

1. Treatment of compensatory hypertension, e.g. arteriovenous shunt or coarctation of the aorta.
2. Inadequate cerebral circulation.
3. Cyanide and thiocyanate are metabolites of nitroprusside and may interfere with the metabolism of cyanocobalamin. Nitroprusside is therefore contraindicated in patients suffering from severe vitamin B<sub>12</sub> deficiency, hepatic failure and Leber's optic atrophy.

### 4.4 Special warnings and precautions for use

Thiocyanate may accumulate in the blood of patients receiving sodium nitroprusside therapy, especially those with impaired renal function or hyponatraemia. Since thiocyanate inhibits both uptake and binding of iodine, symptoms of hypothyroidism may occur.

Sodium nitroprusside should be administered only when adequate facilities are available to frequently monitor blood pressure, since the hypotensive effect is rapid. When I.V. infusion of sodium nitroprusside is decreased or discontinued, blood pressure usually begins to increase immediately and returns to pretreatment levels within 1-10 minutes.

Because sodium nitroprusside may interfere with vitamin B<sub>12</sub> distribution and metabolism, the drug should be used with caution in patients with low plasma vitamin B<sub>12</sub> concentrations.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effects of Sodium Nitroprusside are additive when used concomitantly with ganglionic blocking agents, general anaesthetics (e.g. halothane, enflurane), and with most other circulatory depressants.

### 4.6 Pregnancy and lactation

#### Use In Pregnancy

Adequate reproduction studies have not been performed with sodium nitroprusside, and its use in pregnancy or women of child bearing potential requires that the potential benefits be weighed against possible hazards to the mother and child or foetus.

**Use in Lactation**

It is not known if Sodium Nitroprusside is distributed into milk, therefore the drug should be used with caution in nursing mothers.

**4.7 Effects on ability to drive and use machines**

Not applicable.

**4.8 Undesirable effects**

Nausea, retching, diaphoresis, apprehension, headache, restlessness, muscle twitching, retrosternal discomfort, palpitations, drowsiness, dizziness, paraesthesia warmth and abdominal pain have been noted when the reduction in blood pressure is too rapid, but these symptoms quickly disappear when the rate of infusion is decreased or the infusion is temporarily discontinued and do not reappear with continued slower rate of administration.

Tachycardia and postural hypotension have also been reported. Irritation and reddening of the skin may occur at the injection site.

**4.9 Overdose****Treatment of Overdosage**

Overdosage will result in a fall in blood pressure below the desired level. Discontinuation of administration or a reduction in the rate of administration are usually sufficient measures for managing an overdose of sodium nitroprusside.

Infusion rates exceeding 10 micrograms per kg per minute may result in cyanide intoxication. This is best managed by the intravenous injection of sodium nitrite in conjunction with sodium thiosulphate.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

When Sodium Nitroprusside is administered by IV infusion to hypertensive or normotensive patients, a marked lowering of arterial blood pressure is produced. Venous pressure is also lowered and a moderate reduction in total peripheral resistance occurs. The effects of the drug on blood pressure are more pronounced in hypertensive than in normotensive patients.

The hypotensive action of Sodium Nitroprusside results from peripheral vasodilation caused by a direct action on vascular smooth muscle. Animal tests performed *in situ* have demonstrated no relaxation of other smooth muscle tissue, such as the uterus or duodenum, by Sodium Nitroprusside.

The drug has no direct effect on vasomotor centres, sympathetic nerves, or adrenergic receptors. The hypotensive effect of Sodium Nitroprusside is augmented by concomitant use of other hypotensive agents and is not blocked by adrenergic blocking agents or vagotomy. Pressor agents such as epinephrine which stimulate the myocardium directly are the only drugs that cause an increase in blood pressure during Sodium Nitroprusside therapy. Resistance to the drug's hypotensive effects and tachyphylaxis are very rare.

The effects of Sodium Nitroprusside on cardiac performance appear to depend on preexisting performance. Changes in cardiac performance are attributed mainly to a reduction in left ventricular afterload resulting from vasodilation but may also be related to reduction in venous return to the heart resulting from peripheral vascular pooling of blood, decreased arteriolar resistance, and increased diastolic compliance. The drug has no direct effect on the myocardium, but it may exert a direct coronary vasodilator effect. When Sodium Nitroprusside is administered to hypertensive patients, a slight increase in heart rate usually occurs and cardiac output is usually decreased slightly.

Decreases in cardiac index and stroke index are common; however, these decreases do not occur consistently and increases have occurred in some patients.

When Sodium Nitroprusside is administered to patients with refractory heart failure and/or acute myocardial infarction, substantial improvement in left ventricular performance results with cardiac output, cardiac index, and stroke volume being increased and left ventricular filling pressure being decreased. In patients with congestive heart failure, a slight but clinically important slowing of the heart rate results, as well as reduction or cessation of arrhythmias.

A reduction in myocardial oxygen consumption during Sodium Nitroprusside use has been noted which could prove beneficial when infarcted areas of the heart are already short of oxygen. In patients with congestive heart failure, improvement in cardiac performance is accompanied by prompt diuresis, with urine volume and sodium excretion both being increased.

Moderate doses of Sodium Nitroprusside in hypertensive patients produce renal vasodilation without an appreciable increase in renal blood flow or a decrease in glomerular filtration. Mean renal arterial pressure and renal vascular resistance are slightly decreased. The acute reduction in mean arterial pressure is accompanied by an increase in renin activity of renal venous plasma.

## **5.2 Pharmacokinetic properties**

### ABSORPTION:

IV infusion of Sodium Nitroprusside produces an almost immediate reduction in blood pressure. Blood pressure begins to rise immediately when the infusion is slowed or stopped and returns to pretreatment levels within 1-10 minutes.

### DISTRIBUTION:

Distribution of Nitroprusside in the body as well as passage across the placenta into milk, or across the blood-brain barrier has not been studied.

### ELIMINATION:

Sodium Nitroprusside is rapidly metabolised, probably by interaction with sulphhydryl groups in the erythrocytes and tissues.

Cyanogen (cyanide radical) is produced which is converted to thiocyanate in the liver by the enzyme rhodanase. A thiocyanate oxidase present in the erythrocytes may oxidise small quantities of thiocyanate back to cyanogen. Toxic symptoms begin to appear at plasma thiocyanate concentrations of 50-100 µg/ml; fatalities have been reported at concentrations of 200 µg/ml.

Sodium Nitroprusside is excreted entirely as metabolites, principally thiocyanate. In animals, Sodium Nitroprusside metabolites are excreted mainly in urine, exhaled air, and probably in faeces. The elimination half-life of thiocyanate is 2.7-7 days when renal function is normal but is longer in patients with impaired renal function or hyponatraemia.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

None.

## 6.2 Incompatibilities

Nitroprusside forms highly coloured reaction products with a wide variety of therapeutic agents, and admixture should be avoided.

## 6.3 Shelf Life

**Prior to first use:** As packaged for sale – 3 years

**In use:** 24 hours when stored at 2-8°C.

## 6.4 Special precautions for storage

**Prior to first use:** Do not store above 30°C. Keep container in the outer carton. Keep the container tightly closed.

**In use:** Chemical and physical in-use stability has been demonstrated for 24 hours at a temperature not above 25°C and protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

## 6.5 Nature and contents of container

5 ml amber Type I glass vial with rubber closure in a pack of 5 vials.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use. Discard any unused contents.

Dilute following reconstitution.

No preparation other than Glucose Intravenous Infusion should be used for reconstitution/dilution.

Following reconstitution/dilution protect from light by covering with aluminium foil or other opaque material as quickly as possible.

The prepared infusion solution has a very faint brownish tint; if it is highly coloured it should be discarded.

## 7 MARKETING AUTHORISATION HOLDER

HOSPIRA Uk Ltd  
Queensway  
Royal Leamington Spa  
Warwickshire CV31 3RW  
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA 0437/002/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 05 May 1987

Date of last renewal: 04 May 2007

**10 DATE OF REVISION OF THE TEXT**

October 2008