Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sodium Nitrite Hope Pharmaceuticals 30 mg/mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains 300 mg of sodium nitrite (30 mg/mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

The solution for injection is a clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sodium nitrite is indicated for sequential use with sodium thiosulfate for the treatment of acute cyanide poisoning that is judged to be life-threatening.

When the diagnosis of cyanide poisoning is uncertain, the potentially life-threatening risks associated with sodium nitrite should be carefully weighed against the potential benefits, especially if the patient is not in extremis.

Sodium nitrite is to be administered together with appropriate decontamination and supportive measures (see section 4.4).

Consideration should be given to official guidelines for the treatment of cyanide intoxication.

4.2 Posology and method of administration

Posology
For intravenous use. For single use only.

Adults
10 mL (300 mg) of sodium nitrite (rate of 2.5 to 5 mL/minute) should be administered intravenously, immediately followed by 50 mL (12.5 g) of sodium thiosulfate (rate of 5 mL/minute).

Special populations

Older people
No specific dose adjustment is required in elderly patients (aged > 65 years).

Paediatric population
In infants to adolescents (0 to 18 years old), 0.2 mL/kg (6 mg/kg or 6-8 mL/m2 BSA) of sodium nitrite (rate of 2.5 to 5 mL/minute) not to exceed 10 mL should be administered intravenously, immediately followed by 1 mL/kg of body weight (250 mg/kg or approximately 30-40 mL/m2 of BSA) (rate of 2.5 to 5 mL/minute) not to exceed 50 mL total dose of sodium thiosulfate.

NOTE: If no treatment response is observed within 30 to 60 minutes or if signs of poisoning reappear, repeat treatment after 30 minutes of initial administration using one-half the original dose of both sodium nitrite and sodium thiosulfate.

In paediatric patients with known anaemia, it is recommended that the dosage of sodium nitrite should be reduced proportionately to the hemoglobin concentration (see section 4.4).

Renal and hepatic impairment
Although the safety and efficacy of sodium nitrite have not been studied in patients with renal and hepatic impairments, sodium nitrite is administered as emergency therapy in an acute, life-threatening situation only and no dose adjustment is required in these patients.

Method of administration
Comprehensive treatment of acute cyanide intoxication requires support of vital functions. Supportive care alonemay be sufficient treatment without administration of antidotes for many cases of cyanide intoxication, particularly in conscious patients without signs of severe toxicity. Administration ofcyanide antidotes should be considered adjunctive to appropriate supportive therapies such as airway, ventilatory, and circulatory support. Supportive therapies, including oxygen administration, should not be delayed to administer cyanide antidotes.

Sodium nitrite injection and sodium thiosulfate injection are administered by slow intravenous injection. Cyanide antidotes should be given as early as possible after a diagnosis of acute life-threatening cyanide poisoning has been established. Sodium thiosulfate may be administered soon after prior treatment with a fast-acting cyanide antidote such as sodium nitrite or hydroxocobalamin. Blood pressure must be monitored during infusion in both adults and children. The rate of infusion should be decreased if significant hypotension is noted.

All parenteral drug products should be inspected *visually* for particulate matter and discolouration prior to administration, whenever solution and container permit.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of seizures. Consideration must be given to decontamination measures based on the route of exposure.

Sodium nitrite does not substitute oxygen therapy and must not delay the set up of the above measures.

The presence and extent of cyanide poisoning are often initially unknown. There is no widely available, rapid, confirmatory cyanide blood test. Treatment decisions must be made on the basis of clinical history and/or signs and symptoms of cyanide intoxication.

Cyanide poisoning may result from exposure to smoke from closed space fires, inhalation, ingestion, or dermal exposure. Sources of cyanide poisoning include hydrogen cyanide and its salts, cyanogens, including cyanogenic plants, aliphatic nitriles, or prolonged exposure to sodium nitroprusside.

Signs and symptoms of cyanide poisoning
Common signs and symptoms of cyanide poisoning include: nausea, vomiting, headache, altered mental status (e.g. confusion, disorientation), chest tightness, dyspnoea, tachypnoea or hyperpnoea (early), bradypnoea or apnoea (late), hypertension (early) or hypotension (late), cardiovascular collapse, seizures or coma, mydriasis, and plasma lactate concentration > 8 mmol/L.

In the setting of multiple casualties such as terrorism or chemical disaster, panic symptoms including tachypnoea and vomiting may mimic early cyanide poisoning signs. The presence of altered mental status (confusion and disorientation) and/or mydriasis is suggestive of true cyanide poisoning.

Smoke inhalation
Not all smoke inhalation victims necessarily will have cyanide poisoning, but may present with burns, trauma, and exposure to additional toxic substances aggravating the clinical picture. Before sodium nitrite is administered, it is recommended to check affected persons for the presence of the following:

- exposure to fire smoke in an enclosed area
- soot present around mouth, nose and/or oropharynx
- altered mental status

In this setting hypotension and/or a plasma lactate concentration ≥ 10 mmol/L (higher than the one mentioned under signs and symptoms due to the fact that carbon monoxide contributes to lactic acidaemia) are highly suggestive of cyanide poisoning. In the presence of the above signs, treatment with sodium nitrite must not be delayed to obtain a plasma lactate concentration.

Sodium nitrite has been associated with severe hypotension, methemoglobinemia, and death at doses less than twice recommended therapeutic doses. When the diagnosis of cyanide poisoning is uncertain and/orthe patient is not in extremis, special consideration should be given to administration of sodium nitrite if the patient is known or suspected to have diminished oxygen or cardiovascular reserve (e.g., smoke inhalation victims, pre-existing anaemia, substantial blood loss, cardiac or respiratory compromise) or to be at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency).

4.4.1 Hypotension
Hemodynamics should be monitored closely during and after administration of sodium nitrite, and infusion rates should be slowed if hypotension occurs. Sodium nitrite should be used with caution in the presence of other drugs that can reduce blood pressure.

4.4.2 Methemoglobinemia
In the presence of nitrites, hemoglobin is converted to methemoglobin, which has a higher binding affinity for cyanide than cytochrome oxidase. If methemoglobinemia becomes excessive (>40%) the effect of the antidote is negated as oxygen transport to the tissue is significantly impaired.

Sodium nitrite should be used with caution in persons with smoke inhalation injury or carbon monoxide poisoning because of the potential for worsening hypoxia due to methemoglobin formation.

Methemoglobin levels should be monitored and oxygen administered during treatment with sodium nitrite whenever possible. When sodium nitrite is administered to humans a wide range of methemoglobin concentrations occur. Methemoglobin concentrations as high as 58%have been reported after two 300-mg doses of sodium nitrite administered to an adult. Sodium nitrite should be used with caution in the presence of other drugs that may cause methemoglobinemia such as procaine and nitroprusside.

4.4.3 Anaemia
Sodium nitrite should be used with caution in adult patients with known anaemia. Adult patients with anaemia will form more methemoglobin (as a percentage of total hemoglobin) than persons with normal red blood cell (RBC) volumes. Optimally, these patients should receive a sodium nitrite dose that is reduced in proportion to their oxygen carrying capacity. The table below outlines a dosage regimen as a function of haemoglobin concentration. The dose may be increased to achieve the desired effect. A maximum dose of 300 mg (10 mL of a 3% solution) is recommended.

Adult Patients: Maximum initial dose of sodium nitrite according to haemoglobin level.		
Haemoglobin (g/L)	Maximum Initial Dose Sodium Nitrite (mg)	Maximum Initial Dose 3% Sodium Nitrite Solution (mL)
70	153	5.1
80	174	5.8
90	195	6.5
100	216	7.2
110	237	7.9
120	258	8.6
130	279	9.3
140	300	10

4.4.4 Paediatric Patients

Neonates and infants may be more susceptible than adults and older paediatric patients to severe methemoglobinemia when sodium nitrite is administered. Reduced dosing guidelines should be followed in paediatric patients based on weight and haemoglobin concentration. For children under 25 kg, where anaemia is suspected, it is recommended that the dose of sodium nitrite be reduced relative to the haemoglobin measurement. The table below outlines a dosage regimen as a function of haemoglobin concentration.

Children under 25 kg: Maximum initial dose of sodium nitrite according to haemoglobin level.		
Haemoglobin (g/L)	Maximum Initial Dose Sodium Nitrite (mg/kg)	Maximum Initial Dose 3% Sodium Nitrite Solution (mL/kg)
70	5.8	0.19
80	6.6	0.22
90	7.5	0.25
100	8.8	0.27
110	9.1	0.3
120	10	0.33
130	10.8	0.36
140	11.6	0.39

4.4.5 G6PD Deficiency
Because patients with G6PD deficiency are at increased risk of a hemolytic crisis with sodium nitrite administration, alternative therapeutic approaches should be considered in these patients. Patients with known or suspected G6PD deficiency should be monitored for an acute drop in hematocrit. Exchange transfusion may be needed for patients with G6PD deficiency who receive sodium nitrite.

Each 300 mg dose of sodium nitrite contains approximately 100 mg of sodium.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Possible interaction may occur with hydroxocobalamin. Sodium nitrite should not be co-administered with hydroxocobalamin in the same injection line.

Sodium nitrite should be used with caution in the presence of other drugs that may cause methemoglobinemia such as procaine and nitroprusside. It should also be used with caution in the presence of other drugs that can reduce blood pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy
Based on human experience sodium nitrite is suspected to cause congenital malformations when administered during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Sodium nitrite should not be used during pregnancy unless the clinical condition of the woman requires treatment with sodium nitrite.

Breastfeeding
It is unknown whether sodium nitrite is excreted in human milk. A risk to the suckling child cannot be excluded.
Breast-feeding should be discontinued during treatment with sodium nitrite.

Fertility
There are no fertility data from the use of sodium nitrite in animals.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

There have been no controlled clinical trials conducted to systematically assess the adverse events profile of sodium nitrite .

The medical literature has reported the following adverse events in association with sodiumnitrite administration. These adverse events were not reported in the context of controlled trials or with consistent monitoring and reporting methodologies for adverse events. Therefore, frequency of occurrence of these adverse events cannot be assessed.

System organ class	Frequency	Undesirable effect
Cardiac and vascular disorders	Not known	Syncope, hypotension*,tachycardia, , palpitations, dysrhythmia*
Blood and lymphatic system disorders	Not known	Methemoglobinemia*
Nervous system disorders	Not known	Headache, dizziness, blurred vision, seizures, confusion, coma*
Gastrointestinal disorders	Not known	Nausea, vomiting, abdominal pain
Respiratory, thoracic and mediastinal disorders	Not known	Tachypnea, dyspnea
Skin disorders	Not known	Urticaria
General disorders and administration site conditions	Not known	Anxiety, diaphoresis, lightheadedness, injection site tingling, cyanosis, acidosis,

*Description of selected adverse reactions
Severe hypotension, methemoglobinemia, cardiac dysrhythmias, coma and death have been reported in patients without life-threatening cyanide poisoning but who were treated with injection of sodium nitrite at doses less than twice those recommended for the treatment of cyanide poisoning.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Large doses of sodium nitrite result in severe hypotension and toxic levels of methemoglobin which may lead to cardiovascular collapse.

Sodium nitrite administration has been reported to cause or significantly contribute to mortality in adults at oral doses as low as 1 g and intravenous doses as low as 600 mg. A death attributed to sodium nitrite has been reported following administration of an adult dose (300 mg IV followed by a second dose of 150 mg) to a 17-month old child.

Cyanosis may become apparent at a methemoglobin level of 10-20%. Other clinical signs and symptoms of sodium nitrite toxicity (anxiety, dyspnea, nausea, and tachycardia) can be apparent at methemoglobin levels as low as 15%. More serious signs and symptoms, including cardiac dysrhythmias, circulatory failure, and central nervous system depression are seen as methemoglobin levels increase, and levels above 70% are usually fatal. (See section 4.4)

Treatment of overdose involves supplemental oxygen and supportive measures such as exchange transfusion. Treatment of severe methemoglobinemia with intravenous methylene blue has been described in the medical literature; however, this may also cause release of cyanide bound to methemoglobin. Because hypotension appears to be mediated primarily by an increase in venous capacitance, measures to increase venous return may be most appropriate to treat hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidotes, ATC code: V03AB08 (sodiumnitrite)

Mechanism of action
Exposure to a high dose of cyanide can result in death within minutes due to the inhibition of cytochrome oxidase resulting in arrest of cellular respiration.

Specifically, cyanide binds rapidly with cytochrome a3, a component of the cytochrome c oxidase complex in mitochondria. Inhibition of cytochrome a3 prevents the cell from using oxygen and forces anaerobic metabolism, resulting in lactate production, cellular hypoxia and metabolic acidosis. In massive acute cyanide poisoning, the mechanism of toxicity may involve other enzyme systems as well.

The synergy resulting from treatment of cyanide poisoning with the combination of sodium nitrite and sodium thiosulfate is the result of differences in their primary mechanisms of action as antidotes for cyanide poisoning.

Pharmacodynamic effects

Sodium Nitrite
Sodium nitrite is thought to exert its therapeutic effect by reacting with hemoglobin to form methemoglobin, an oxidized form of hemoglobin incapable of oxygen transport but with high affinity for cyanide. Cyanide preferentially binds to methemoglobin over cytochrome a3, forming the nontoxic cyanomethemoglobin. Methemoglobin displaces cyanide from cytochrome oxidase, allowing resumption of aerobic metabolism. The chemical reaction is as follows:

$NaNO_2$ + Hemoglobin → Methemoglobin
HCN + Methemoglobin → Cyanomethemoglobin

Vasodilation has also been cited to account for at least part of the therapeutic effect of sodium nitrite. It has been suggested that sodium nitrite-induced methemoglobinemia may be more efficacious against cyanide poisoning than comparable levels of methemoglobinemia induced by other oxidants. Also, sodium nitrite appears to retain some efficacy even when the formation of methemoglobin is inhibited by methylene blue.

Sodium Thiosulfate
The primary route of endogenous cyanide detoxification is by enzymatic transulfuration to thiocyanate (SCN-), which is relatively nontoxic and readily excreted in the urine. Sodium thiosulfate is thought to serve as a sulfur donor in the reaction catalyzed by the enzyme rhodanese, thus enhancing the endogenous detoxification of cyanide in the following chemical reaction:

Rhodanese
$Na^2S^2O^3 + CN^- \rightarrow SCN^- + Na^2SO_3$

Clinical efficacy and safety
There have been no controlled clinical trials conducted to systematically assess the clinical efficacy and safety of sodiumnitrite .

5.2 Pharmacokinetic properties

Absorption
Intravenous administration of sodium nitrite is 100% bioavailable.

Distribution
After a 30 minutes intravenous infusion of 290-370 mg sodium nitrite, the reported half-life was approximately 40 minutes.

Biotransformation and elimination

Sodium nitrite is a strong oxidant, and reacts rapidly with hemoglobin to form methemoglobin. The pharmacokinetics of free sodium nitrite in humans have not been well studied. It has been reported that approximately 40% of sodium nitrite is excreted unchanged in the urine while the remaining 60% is metabolized to ammonia and related small molecules.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

Chemical incompatibility has been reported between sodium nitrite and hydroxocobalamin and these drugs should not be administered simultaneously through the same IV line. No chemical incompatibility has been reported between sodium thiosulfate and sodium nitrite, when administered sequentially through the same IV line.

6.3 Shelf life

5 years

From a microbiological point of view, Sodium Nitrite Solution for Injection should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25 °C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton of Sodium Nitrite Solution for Injection contains one 10 mL single use glass vial of sodium nitrite 30 mg/mL solution for injection (containing 300 mg of sodium nitrite). Each glass vial includes a chlorobutyl stopper and an aluminum cap with a plastic lid.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Hope Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER

PA22874/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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