

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nithiodote Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each kit contains one vial (300 mg) of sodium nitrite (30mg/mL) and one vial (12.5 g) of sodium thiosulfate (250 mg/mL). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solutions for Injection

The solutions for injection are clear, colourless solutions in single dose vials

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nithiodote is indicated 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 Nithiodote should be carefully weighed against the potential benefits, especially if the patient is not in extremis.

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 populations

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 5 mL/minute) not to exceed 50 mL total dose of sodium thiosulfate.

NOTE: If signs of poisoning reappear, repeat treatment using one-half the original dose of both sodium nitrite and sodium thiosulfate.

In adult and 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).

Method of administration

Comprehensive treatment of acute cyanide intoxication requires support of vital functions. Supportive care alone may be sufficient treatment without administration of antidotes for many cases of cyanide intoxication, particularly in conscious patients without signs of severe toxicity. Administration of sodium nitrite, followed by sodium thiosulfate, 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 sodium nitrite and sodium thiosulfate.

Sodium nitrite injection and sodium thiosulfate injection are administered by slow intravenous injection. They should be given as early as possible after a diagnosis of acute life-threatening cyanide poisoning has been established. Sodium nitrite should

be administered first, followed immediately by sodium thiosulfate. 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 discoloration 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 acidemia) 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

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/or the 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 bloodloss, cardiac or respiratory compromise) or to be at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency).

4.3.1 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.

4.3.2 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.

4.3.3 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

4.3.4 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

4.3.5 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.

Sodium Thiosulfate

Sodium thiosulfate drug product may contain trace impurities of sodium sulfite. The presence of a trace amount of sulfites in this product should not deter administration of the drug for treatment of emergency situations, even if the patient is sulfite-sensitive.

Each 12.5 g dose of sodium thiosulfate contains approximately 3.6 g of sodium, 115 mg of potassium, and 140 mg of boric acid.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Possible interaction may occur with hydroxocobalamin. Nithiodote 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

Sodium Nitrite

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).

Nithiodote should not be used during pregnancy unless the clinical condition of the woman requires treatment with sodium nitrite.

Sodium Thiosulfate

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sodium thiosulfate in pregnant women. Animals studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Nithiodote during pregnancy.

Breastfeeding

It is unknown whether sodium nitrite and sodium thiosulfate are excreted in human milk.

A risk to the suckling child cannot be excluded.

Breast-feeding should be discontinued during treatment with Nithiodote.

Fertility

There are no fertility data from the use of Nithiodote 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 Nithiodote. The medical literature has reported the following adverse events in association with sodium nitrite 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.

Sodium Nitrite

System organ class	Frequency	Undesirable effect
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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, light headedness, injection site tingling, cyanosis, acidosis, fatigue, weakness, generalized numbness and tingling

*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.

Sodium Thiosulfate

System organ class	Frequency	Undesirable effect
Cardiac and vascular disorders	Not known	Hypotension
Nervous system disorders	Not known	Headache, disorientation
Gastrointestinal disorders	Not known	Nausea*, vomiting*
Blood and lymphatic system disorders	Not known	Prolonged bleeding time*
General disorders and administration site conditions	Not known	Salty taste in mouth, warm sensation over body

*Description of selected adverse reactions

Nausea and vomiting

In humans, rapid administration of concentrated solutions or solutions not freshly prepared, and administration of large doses of sodium thiosulfate have been associated with a higher incidence of nausea and vomiting. However, administration of 0.045g sodium thiosulfate per kilogram up to a maximum of 15 g in a 10-15% solution over 10-15 minutes was associated with nausea and vomiting in 7 of 26 patients without concomitant cyanide intoxication.

Prolonged bleeding time

In a series of 11 human subjects, a single intravenous infusion of 50 mL of 50% sodium thiosulfate was associated with increases in clotting time 1-3days after administration. However, no significant changes were observed in other hematological parameters.

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

Sodium Nitrite

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.

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 maybe most appropriate to treat hypotension.

Sodium Thiosulfate

There is limited information about the effects of large doses of sodium thiosulfate in humans. Oral administration of 3 g sodium thiosulfate per day for 1-2 weeks in humans resulted in reductions in room air arterial oxygen saturation to as low as 75%, which was due to a rightward shift in the oxygen hemoglobin dissociation curve. The subjects returned to baseline oxygen saturations 1 week after discontinuation of sodium thiosulfate. A single intravenous administration of 20 mL of 10% sodium thiosulfate reportedly did not change oxygen saturations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidotes,

ATC code: V03AB08 (sodium nitrite) and V03AB06 (sodium thiosulfate)

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.

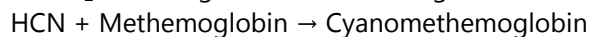
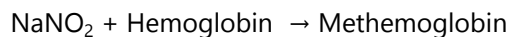
Specifically, cyanide binds rapidly with cytochrome a₃, a component of the cytochrome c oxidase complex in mitochondria. Inhibition of cytochrome a₃ prevents the cell from using oxygen and forces anaerobic metabolism, resulting in lactate production, cellular hypoxia and metabolic acidosis. In massive 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

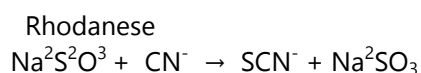
Sodium nitrite is thought to exert its therapeutic effect by reacting with hemoglobin to form methemoglobin, an oxidized form of hemoglobin incapable of oxygen transport but with high affinity for cyanide. Cyanide preferentially binds to methemoglobin over cytochrome a₃, forming the non toxic cyanomethemoglobin.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



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 non toxic 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:



Clinical efficacy and safety

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

5.2 Pharmacokinetic properties

Absorption

Sodium thiosulfate taken orally is not systemically absorbed. Intravenous injection of sodium thiosulfate is 100% bioavailability.

Distribution

Sodium thiosulfate is rapidly distributed throughout extra cellular fluid after IV administration. The volume of distribution of sodium thiosulfate is 150mL/kg.

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.

Most of the thiosulfate is oxidized to sulfate or is incorporated into endogenous sulphur compounds; a small proportion is excreted through the kidneys.

Approximately 20-50% of exogenously administered thiosulfate is eliminated unchanged via the kidneys. After an intravenous injection of 1 g sodium thiosulfate in patients, the reported serum thiosulfate half-life was approximately 20 minutes. However, after an intravenous injection of a substantially higher dose of sodium thiosulfate (150 mg/kg, that is, 9 g for 60 kg body weight) in normal healthy men, the reported elimination half-life was 182 minutes.

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 and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Nitrite Solution for Injection

Water for Injections

Sodium Thiosulfate Solution for Injection

Boric Acid for pH adjustment

Potassium Chloride for tonicity adjustment

Water for Injections

Sodium Hydroxide and/or Boric Acid for pH adjustment

6.2 Incompatibilities

Chemical incompatibility has been reported between Nithiodote 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

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Each Nithiodote kit consists of one 10 mL glass vial of sodium nitrite 30 mg/mL solution for injection (containing 300 mg of sodium nitrite) and one 50 mL glass vial of sodium thiosulfate 250mg/mL solution for injection (containing 12.5 g of sodium thiosulfate).

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Hope Pharmaceuticals Ltd
Kyletelogue House
9 Cherrywood Park
Tallanstown
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Ireland

8 MARKETING AUTHORISATION NUMBER

PA22874/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th July 2018

Date of last Renewal: 4th October 2022

10 DATE OF REVISION OF THE TEXT

October 2023