SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Natriumthiosulfaat Hope 250 mg/ml, oplossing voor injectie

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mL vial contains 12.5 g of sodium thiosulfate (250 mg/mL).

Excipient of known effect:
3.6 g of sodium in 50 ml of solution for injection.
115 mg of potassium in 50 ml of solution for injection.
140 mg of boric acid in 50 mL of solution for injection.

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 thiosulfate is indicated for sequential use with hydroxocobalamin or sodium nitrite 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 thiosulfate should be carefully weighed against the potential benefits, especially if the patient is not in extremis.

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

4.2 Posology and method of administration

Posology

For intravenous use. For single use only.

Adults

Initial dose: 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).

Alternatively, an initial dose of 5 g hydroxocobalamin administered as an intravenous infusion over 15 minutes 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/m^2 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/m^2 of BSA) (rate of 2.5 to 5 mL/minute) not to exceed 50 mL total dose of sodium thiosulfate.

Alternatively, in infants to adolescents (0 to 18 years old), the initial dose of hydroxocobalamin is 70 mg/kg body weight not exceeding 5 g followed by 1 mL/kg of body weight (250 mg/kg or approximately 30-40 mL/m^2 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 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 Sodium Nitrite SmPC section 4.4).

Renal and hepatic impairment

Although the safety and efficacy of sodium thiosulfate have not been studied in patients with renal and hepatic impairments, sodium thiosulfate 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 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 cyanide 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 thiosulfate 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 thiosulfate 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 thiosulfate must not be delayed to obtain a plasma lactate concentration.

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 which is equivalent to 180% of the WHO recommended maximal daily intake of 2 g sodium for an adult.

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

4.5 Interaction with other medicinal products and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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 sodium thiosulfate during pregnancy.

Breastfeeding

It is unknown whether sodium thiosulfate is excreted in human milk. A risk to the suckling child cannot be excluded.

Breast-feeding should be discontinued during treatment with sodium thiosulfate.

Fertility

There are no fertility data from the use of sodium thiosulfate 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 thiosulfate.

The medical literature has reported the following adverse events in association with sodium thiosulfate 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	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 0.045 g 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 1-3 days 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.

4.9 Overdose

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: 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 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:

$$Na_2S_2O_3 + CN^- \xrightarrow{\text{Rhodanese}} SCN^- + Na_2SO_3$$

Clinical efficacy and safety

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

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 extracellular fluid after IV administration. The volume of distribution of sodium thiosulfate is 150 mL/kg.

Biotransformation and elimination

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric Acid
Potassium Chloride
Water for Injections
Sodium Hydroxide and/or boric acid for pH Adjustment

6.2 Incompatibilities

Chemical incompatibility has been reported between sodium thiosulfate 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 Thiosulfate 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.

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 Thiosulfate Solution for Injection contains one 50 mL single use glass vial of sodium thiosulfate 250 mg/mL solution for injection (containing 12.5 g of sodium thiosulfate). 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.
9 Cherrywood
Tallanstown
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

Natriumthiosulfaat Hope 250 mg/ml, oplossing voor injectie – RVG 122254

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

Datum van eerste verlening van de vergunning: 10 juli 2018
Datum van laatste verlenging: 4 oktober 2022

10 DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 2 juni 2023