SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Sodium Thiosulfate 250 mg/mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 12.5 g of sodium thiosulfate (250 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 sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Sodium thiosulfate is indicated for sequential use with 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.

4.2 Posology and method of administration
Posology
For intravenous use. For single use only.
Adults
10 mL of sodium nitrite (rate of 2.5 to 5 mL/minute) should be administered intravenously, immediately followed by 50 mL 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**

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 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 discolouration prior to administration, whenever solution and container permit.

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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**

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.

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

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

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Undesirable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac and vascular disorders</td>
<td>Not known</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Not known</td>
<td>Headache, disorientation</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Not known</td>
<td>Nausea*, vomiting*</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known</td>
<td>Prolonged bleeding time*</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Not known</td>
<td>Salty taste in mouth, warm sensation over body</td>
</tr>
</tbody>
</table>
*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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: Yellow Card Scheme - Website: www.mhra.gov.uk/yellowcard.

### 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:

\[
\text{NaNO}_2 + \text{Hemoglobin} \rightarrow \text{Methemoglobin}
\]

\[
\text{HCN} + \text{Methemoglobin} \rightarrow \text{Cyanomethemoglobin}
\]

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:

\[
\text{Rhodanese} \\
\text{Na}_2\text{S}_2\text{O}_3 + \text{CN}^- \rightarrow \text{SCN}^- + \text{Na}_2\text{SO}_3.
\]

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 and development.

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

6.4 Special precautions for storage
Do not store above 25°C.
6.5 Nature and contents of container
Each carton of Sodium Thiosulfate Solution for Injection contains one 50 mL glass vial of sodium thiosulfate 250 mg/mL solution for injection (containing 12.5 g of sodium thiosulfate).

6.6 Special precautions for disposal
No special requirements for disposal.

7 MARKETING AUTHORITY

Hope Pharmaceuticals, Ltd.
120 Baker Street
London W1U 6TU
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 42589/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
19/06/2015

10 DATE OF REVISION OF THE TEXT
07/12/2015