Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Mutual Recognition Procedure

Sodium Nitrite 30 mg/mL Solution for Injection (sodium nitrite)

Sodium Thiosulfate 250 mg/mL Solution for Injection (sodium thiosulfate)

Nithiodote (Co-Packaged Sodium Nitrite 30 mg/mL Solution for Injection and Sodium Thiosulfate 250 mg/mL Solution for Injection)

(sodium nitrite and sodium thiosulphate)

Product Licence Numbers: PL 42589/0001-0003

European Procedure Numbers: UK/H/6481-6483/001/MR

Hope Pharmaceuticals Limited

Lay Summary

Sodium Nitrite 30 mg/mL Solution for Injection
Sodium Thiosulfate 250 mg/mL Solution for Injection
Nithiodote (Co-Packaged Sodium Nitrite 30 mg/mL Solution for Injection and Sodium Thiosulfate 250 mg/mL Solution for Injection)

(sodium thiosulfate, sodium nitrite)

This is a summary of the Public Assessment Report (PAR) for Sodium Nitrite 30 mg/mL Solution for Injection (PL 42589/0001; UK/H/6481/001/MR), Sodium Thiosulfate 250 mg/mL Solution for Injection (PL 42589/0002; UK/H/6482/001/MR) and Nithiodote (Co-Packaged Sodium Nitrite 30 mg/mL Solution for Injection and Sodium Thiosulfate 250 mg/mL Solution for Injection; PL 42589/0003; UK/H/6483/001/MR). It explains how Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote.

These products will be referred to as Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote in this lay summary, for ease of reading.

For practical information about using Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote, patients should read the package leaflets or contact their doctor or pharmacist.

What are Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote, and what are they used for?
Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote are medicines with 'well-established use'. This means that the medicinal use of the active substances of Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote, have been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote are used as antidotes for cyanide poisoning. Cyanide poisoning is a condition that develops when someone inhales, touches or swallows cyanide. Cyanide is a poisonous chemical that prevents the human body from absorbing oxygen. The lack of oxygen can damage organs and be life-threatening.

How do Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote work?
Sodium Nitrite Injection contains the active substance sodium nitrite, which prevents cyanide from binding to, and inhibiting, a protein (an enzyme) within the body important in respiration; respiration is a cellular process by which the body generates energy.

Sodium Thiosulfate Injectioncontains the active substance sodium thiosulfate, which converts cyanide to a less toxic chemical that can be removed from the body in the urine.

Nithiodote is a kit that contains both of the medicinal products listed above: Sodium Nitrite Injection and Sodium Thiosulfate Injection.

How are Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote used?
The pharmaceutical form of these medicines is a solution for injection and the route of administration is by injection into a vein.

These medicines can only be obtained with a prescription.

A doctor or nurse will give Sodium Nitrite Injection, Sodium Thiosulfate Injection or Nithiodote to the patient by injection into a vein. Sodium Nitrite Injection will be given to the patient followed immediately by Sodium Thiosulfate Injection.

For further information on how Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote are used, refer to the package leaflets and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

What benefits of Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote have been shown in studies?
As sodium nitrite and sodium thiosulfate are well-known substances, and their sequential use (giving sodium nitrite to the patient, followed immediately by sodium thiosulfate) as antidotes for cyanide poisoning, is well-established, data were provided in the form of literature references to show that sodium nitrite and sodium thiosulfate area safe and efficacious treatment as antidotes for cyanide poisoning.

What are the possible side effects from Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote?
Like all medicines, these medicines can cause side effects, although not everybody gets them.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflets or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why were Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote approved?
The sequential use of sodium nitrite and sodium thiosulfate as antidotes for cyanide poisoning is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote outweigh the risks and the grant of these marketing authorisations was recommended.

It was concluded that the data provided from literature references had shown that the sequential use of sodium nitrite and sodium thiosulfate is an effective antidotes in the treatment of cyanide poisoning. Furthermore, sequential use of sodium nitrite and sodium thiosulfate in the European Union has shown that this treatment has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote can be approved for use.

What measures are being taken to ensure the safe and effective use of Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote?
A Risk Management Plan has been developed to ensure that Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflets for these products, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote
Marketing Authorisations for Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote were granted in the UK on 19 June 2015.

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The full PAR for Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote follows this summary.

This summary was last updated in April 2019.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted Marketing Authorisations (MAs) to Hope Pharmaceuticals Limited for the medicinal products Sodium Nitrite 30 mg/mL Solution for Injection (PL 42589/0001), Sodium Thiosulfate 250 mg/mL Solution for Injection (PL 42589/0002) and Nithiodote (Co-Packaged Sodium Nitrite 30 mg/mL Solution for Injection and Sodium Thiosulfate 250 mg/mL Solution for Injection; PL 42589/0003). These are Prescription-Only Medicines (legal status POM).

These products will be referred to as Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote in this scientific discussion, for ease of reading.

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

Sodium Thiosulfate Injection is indicated for sequential use with 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.

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.

Sodium Nitrite Injection contains the active substance sodium nitrite. Sodium Thiosulfate Injection contains the active substance sodium thiosulfate. Nithiodote contains the active substances sodium nitrite and sodium thiosulfate.

Cyanide is an extremely toxic poison. In the absence of rapid and adequate treatment, 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. Sodium nitrite reacts with hemoglobin to form methemogobin, which removes cyanide ions from various tissues. Methemogobin couples with the cyanide ions to become cyanomethemogobin, which has relatively low toxicity. The function of sodium thiosulfate is to convert cyanide to thiocyanate, which is thought to be achieved by an enzyme known as rhodanese.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, as well-established use applications. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

No new non-clinical or clinical studies were conducted for these applications, which is acceptable given that these are bibliographic applications for products containing active substances of well-established use.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided

with these applications and are satisfactory.

National licences were granted in the UK on 19 June 2015.

Following the grant of the national licences, mutual recognition procedures were completed (Day 90) on 21 May 2018 for Sodium Nitrite Injection and Sodium Thiosulfate Injection, and 08 May 2018 for Nithiodote, with the UK as Reference Member State (RMS) and the following Concerned Member States (CMSs):

- Austria, Belgium, France, Ireland, Spain, the Netherlands, Sweden, and Poland for procedures UK/H/6481-6482/001/MR (for Sodium Nitrite Injection and Sodium Thiosulfate Injection),
- Ireland for procedure UK/H/6481/001/MR (for Nithiodote).

II QUALITY ASPECTS

II.1 Introduction

Sodium Nitrite Injection is formulated as a clear and colourless sterile solution, containing the active ingredient sodium nitrite. The excipient present is water for injections. 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.

Sodium Thiosulfate Injection is formulated as a clear and colourless sterile solution, containing the active ingredient sodium thiosulfate. The excipients present are boric acid, potassium chloride, water for injections and sodium hydroxide and/or boric acid for pH adjustment. 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.

Nithiodote is a kit containing one 10 ml vial of the Sodium Nitrite Injection and one 50 ml vial of the Sodium Thiosulfate Injection, each described above.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

Sodium Nitrite

INN: Sodium nitrite
Chemical Name: Sodium nitrite
Structure:

Molecular formula: $NaNO_2$
Molecular weight: 69.0
Appearance: White to off-white solid that is hygroscopic
Solubility: Soluble in water (81.5 g/100 ml at 20ºC) and slightly soluble in alcohol.

Sodium nitrite is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

A specification is provided for the active substance that complies with the European Pharmacopoeia monograph. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

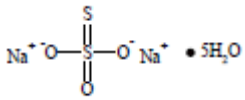
Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

Sodium thiosulfate

INN: Sodium thiosulfate
Chemical Name: Sodium thiosulfate pentahydrate
Structure:



Molecular formula: $Na_2O_3S_2.5H_2O$
Molecular weight: 248.19
Appearance: Transparent, colourless crystals, efflorescent in dry air.
Solubility: Freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride.

Sodium thiosulfate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

A specification is provided for the active substance that complies with the European Pharmacopoeia monograph. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Sodium Nitrite Injection

Pharmaceutical development

The formulation is well-established and satisfactory formulation studies have been conducted.

The only excipient used in the manufacture of the proposed formulation, water for injections, complies with the respective European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided for this excipient showing compliance with its proposed specification.

No excipients of animal or human origin are used in the finished product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and is satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from three production-scale batches that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years, with the storage conditions “Do not store above 25ºC. Keep the vial in the outer carton in order to protect from light.”, is acceptable.

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.

Suitable post approval stability commitments have been provided.

Sodium Thiosulfate Injection
Pharmaceutical development
The formulation is well-established and satisfactory formulation studies have been conducted.

All of the excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeial monographs. Satisfactory Certificates of Analysis have been provided for these excipients showing compliance with their proposed specifications.

No excipients of animal or human origin are used in the finished product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and is satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided from three production-scale batches that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 5 years with special storage conditions of “Do not store above 25ºC”. Based on the results, a shelf-life of 5 years with special storage conditions of “Do not store above 25ºC.”, is acceptable.

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.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Nithiodote
This product is a kit that contains one vial of Sodium Nitrite Injection and one vial of Sodium Thiosulfate Injection. The quality sections for this product reflect the combined information listed above for one vial of Sodium Nitrite Injection and one vial of Sodium Thiosulfate Injection.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of these Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
No new non-clinical data have been submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of sodium nitrite and sodium thiosulfate are well-established. The applicant's non-clinical overview has been written by an appropriately qualified person and provides an acceptable review of the available literature sources.

III.2 Pharmacology
Primary pharmacodynamics
The pharmacology of the individual active substances is adequately discussed in the applicant's non-clinical overview and is only briefly summarised below.

The mechanism of action of cyanide toxicity is believed to result from its inhibition of cytochrome oxidase, the terminal oxidase of the mitochondrial respiratory chain. Inhibition of cytochrome oxidase results in a blockade of aerobic metabolism and energy production leading to cellular hypoxia. Cyanide inhibition of cytochrome oxidase can be reversed either by the sequestration or the biotransformation of cyanide. The synergistic efficacy 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. Sodium nitrite reverses cyanide toxicity by sequestering cyanide. Sodium thiosulfate reverses cyanide toxicity by promoting the biotransformation of cyanide.

<u>Sodium nitrite</u>
Sodium nitrite reacts with hemoglobin to form methemoglobin, which is an oxidised form of hemoglobin that is incapable of binding to oxygen but has a high binding affinity for cyanide. When cyanide binds to methemoglobin it forms cyanomethemoglobin, which is nontoxic. The preferential binding of cyanide to methemoglobin effectively sequesters cyanide away from cytochrome oxidase, allowing resumption of aerobic metabolism and preventing cellular hypoxia. The chemical reaction is as follows:

sodium nitrite + hemoglobin	→	methemoglobin
methemoglobin + cyanide	→	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 methemoglobinaemia may be more efficacious against cyanide poisoning than comparable levels of methemoglobinaemia induced by other oxidants. Also, sodium nitrite appears to retain some efficacy even when the formation of methemoglobin is inhibited by methylene blue.

<u>Sodium thiosulfate</u>
Sodium thiosulfate reverses cyanide toxicity by promoting the biotransformation of cyanide. The primary metabolic pathway of cyanide detoxification is by enzymatic transulfuration of cyanide to thiocyanate, which is relatively nontoxic and readily excreted in the urine.

Sodium thiosulfate is thought to serve as a sulphur donor in the transulfuration reaction catalysed by the enzyme rhodanese, thus enhancing the detoxification of cyanide. The transulfuration reaction is summarized as follows:

rhodanese
sodium thiosulfate + cyanide → thiocyanate + sodium sulfate

Sodium nitrite and sodium thiosulfate
The evaluation of treatment efficacy has predominantly been completed in animal models due to the extreme toxicity of cyanide. Dogs were given subcutaneous (SC) injections of varying doses of sodium cyanide followed by different antidotes to determine the relative efficacy of each antidote.

The LD_{50} of a SC injection of sodium cyanide was determined to be approximately 6 mg/kg.

The dose of cyanide that was tolerated following a dose of sodium nitrite (22.5 mg/kg IV) was 4 to 5 times the LD_{50} of cyanide (27.1 mg/kg SC cyanide).

The dose of cyanide that was tolerated following a dose of sodium thiosulfate (2 g/kg IV) was 3 times the LD_{50} of cyanide (i.e., 18.4 mg/kg SC cyanide).

The cyanide dose that was tolerated following a dose of sodium nitrite (22.5 mg/kg) followed by a dose of sodium thiosulfate (2 g/kg) was 13-18 times the LD_{50} (96.7 mg/kg SC cyanide). Methemoglobin peaked at 65% of total body hemoglobin 30 minutes after administration of sodium nitrite and sodium thiosulfate and then was undetectable in about 11 hours.

Additional efficacy studies conducted in dog and other species (e.g., mice, sheep, monkey) have also documented the synergistic efficacy of intravenous sodium nitrite and sodium thiosulfate in the treatment of cyanide poisoning.

Secondary pharmacodynamics
Sodium nitrite-induced vasodilation has been suggested to contribute to the efficacy of sodium nitrite in reversing cyanide toxicity. Cardiovascular and respiratory changes are reported to occur before the formation of significant amounts of methemoglobin, after administration of sodium nitrite.

The cardiovascular effects of acute nitrite intoxication in animals include vasodilation, relaxation of smooth muscle, and lowering of blood pressure and a decrease in D-xylose absorption in the intestinal mucosa.

Safety Pharmacology
Safety pharmacology studies were not reported in the literature for sodium nitrite or sodium thiosulfate.

The cardiovascular effects of sodium nitrite and sodium thiosulfate have been evaluated in non-clinical studies. Sodium nitrite effects include vasodilation and lowering of blood pressure in dogs and monkeys. Sodium thiosulfate did not produce any measurable effects on blood pressure or heart rate in the dog.

The CNS effects of sodium nitrite have been studied in mice and rats. Nitrites have some form of sedative effect on the mice and irreversible effect on rat brain electrical changes following chronic exposure *in utero*.

Pharmacodynamic drug interactions
The combination of sodium nitrite and sodium thiosulfate produces synergistic efficacy in the treatment of cyanide poisoning. Efficacy studies conducted in mice, dog, sheep, and monkey consistently demonstrate, across species, the synergistic efficacy of intravenous sodium nitrite and sodium thiosulfate in the treatment of cyanide poisoning.

Conclusions on pharmacology
The primary, secondary and safety pharmacology of sodium nitrite and sodium thiosulfate have been reviewed adequately in the applicant's non-clinical overview. The combination has been in use for a significant period and so further discussion of non-clinical data is superseded by clinical experience.

III.3 Pharmacokinetics

Sodium nitrite

Sodium nitrite is administered intravenously for clinical use and therefore has 100% bioavailability. In mice, following oral gavage administration of 150 µg sodium nitrite, 85% of the dose disappeared from the stomach in 10 minutes, and 95% disappeared in 30 minutes. In male and female mice administered a single dose of 62.5 mg/kg sodium nitrite by gavage, plasma nitrite and blood methemoglobin concentrations peaked at 10 minutes in male mice and 5 (nitrite) and 60 minutes (methemoglobin) in female mice. In male and female rats administered a single dose of 40 mg/kg sodium nitrite by gavage, plasma nitrite and blood methemoglobin concentrations peaked at 30 minutes.

Intravenous (IV) injections and intratracheal (IT) instillation of 13N-labelled nitrite in mice and rabbits resulted in homogenous distribution of radioactivity in the heart, kidneys, liver, stomach, intestines, lungs and bladder (ranging from 4.2 to 10.5%) within 5 minutes. The 13N was equally distributed in plasma and red blood cells with 15-20% of the plasma 13N bound to proteins. Half-lives of nitrite plasma values in the distribution phase following administration of 20 mg/kg sodium nitrite IV were 48, 12 and 5 minutes for dogs, sheep and ponies, respectively

Urinary and faecal excretion of nitrite are very low since most of the nitrite that enters the bloodstream or passes down the GI tract is rapidly converted to nitrate, bound to the GI contents, or reduced by enteric bacteria. Nitrite is not secreted in significant amounts in saliva or bile. Nitrite can cross the placenta of rats; nitrite injected into pregnant animals appeared after a lag of approximately 20 minutes in fetal blood but at a lower concentration than in maternal blood.

There is a rapid decline in plasma levels of nitrite following IV administration, this is due to transport of nitrite into erythrocytes where it binds to hemoglobin and is transported into tissues where it may be oxidised to nitrate.

The majority of radiolabelled nitrite is excreted in urine and a minority is excreted in faeces. The most important pathway of elimination is oxidation of nitrite to nitrate. Elimination half-life of nitrite (metabolism plus urinary excretion) was 0.5 hour in dogs, sheep and ponies. Transport of large quantities of nitrite into milk is unlikely because of the rapid conversion of nitrite to nitrate. Nitrite doses inducing methemoglobinaemia in nursing rats did not produce methemoglobinaemia in suckling rats.

Formal drug interaction studies have not been conducted with sodium nitrite. As sodium nitrite will be administered as a single IV dose first and followed sequentially with IV sodium thiosulfate, only compatibility studies have been performed. No chemical incompatibility has been reported between sodium nitrite and sodium thiosulfate when they are administered sequentially through the same IV line. There are reports that sodium nitrite is chemically incompatible with hydroxocobalamin (Cyanokit SmPC) and should not be administered in the same IV line.

Sodium thiosulfate

Sodium thiosulfate is administered intravenously for clinical use and therefore has 100% bioavailability. Orally administered thiosulfate is subject to some attack in the gastrointestinal tract. At the pH in the stomach thiosulfate decomposes into sulphur, sulphite and a few minor products. Rats administered thiosulfate by oral gavage excreted 23% of the sulphur load as inorganic sulfate and 85% after intraperitoneal (IP) injection.

Following absorption of thiosulfate by the gut mucosa and passage into the portal vein thiosulfate is rapidly excreted or oxidised to sulfate. From 5-14% of an oral dose appears un-metabolised in the urine, depending on dose and species, but since a significant fraction of an IV dose is metabolised to

sulfate before excretion this 5-14% represents only a part of the fraction being absorbed into the circulation.

Thiosulfate is a normal constituent of the urine of higher animals. Excretion is rapid in dogs and varies dependent on dose. Pregnant dogs administered 1 gram sodium thiosulfate IV had depressed excretion of 40 to 44%.

Conclusions on pharmacokinetics
The pharmacokinetic properties of sodium nitrite and sodium thiosulfate have been reviewed adequately in the applicant's non-clinical overview.

III.4 Toxicology

The toxicology properties of sodium nitrite and sodium thiosulfate are discussed in detail in the applicant's non-clinical overview. The summaries of these findings are presented below.

Sodium nitrite
General Toxicity:
Single dose toxicity studies following intravenous (IV), subcutaneous (SC), or oral (PO) administration of sodium nitrite in mice, rats, rabbits and dogs have been reported in the scientific literature.

Repeat-dose studies of sodium nitrite in mice and rats have been reported in the scientific literature. These studies were formal Good Laboratory Practice (GLP) toxicity studies.

Mice were given up to 990 mg/kg sodium nitrite in males and up to 1,230 mg/kg sodium nitrite in females in drinking water for 14 weeks. All mice survived until the end of the study. Sperm motility was decreased in high dose males, and the estrous cycles of mid and high dose females were significantly longer than in the controls. There were increased incidences of squamous cell hyperplasia of the forestomach in high dose males and females, extramedullary haematopoiesis of the spleen in mid and high dose males and females, and degeneration of the testis in mid and high dose males.

Rats were given up to 310 mg/kg sodium nitrite in males and up to 345 mg/kg sodium nitrite in females in drinking water for 14 weeks. One female exposed to 2,254 mg/kg died before the end of the study. A 'no observed-adverse-effect level' (NOAEL) was not achieved in this study. Sperm motility in mid and high dose males was significantly decreased. Increased erythropoietic activity in the bone marrow of exposed males and females was observed. The incidences of squamous cell hyperplasia of the forestomach in high dose males and females were significantly increased.

Genotoxicity:
In vitro GLP genotoxicity studies were conducted in *Salmonella typhimurium*. Sodium nitrite was mutagenic in *Salmonella typhimurium* strain TA100, with and without Aroclor 1254-induced hamster and rat liver S9 enzymes; no mutagenicity was observed in strain TA98. Sodium nitrite has been reported to test positive in the bacterial reverse mutation assay (Ames assay) using *S. typhimurium* strains TA100 (± S9 metabolic activation), TA1530 (± S9 metabolic activation), and TA1535 in the absence of metabolic activation, and negative in *S. typhimurium* strains TA97, TA98, TA102, YG1024, DJ400, DJ460 (± S9 metabolic activation) and TA100 (only without metabolic activation).

The applicant has completed one GLP genotoxicity study with sodium nitrite. Sodium nitrite was concluded to be negative for the induction of structural and numerical chromosome aberrations in both the nonactivated and the S9-activated test systems in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes. Sodium nitrite has also been reported to test negative in the mouse lymphoma assay in the absence of metabolic activation. Sodium nitrite has also been reported in the literature to test positive as a clastogen both *in vitro* and *in vivo*.

In vivo GLP genotoxicity studies were conducted in rat and mouse bone marrow, and mouse peripheral blood. Results of acute bone marrow micronucleus tests with sodium nitrite were negative. In addition,

a peripheral blood micronucleus assay conducted with mice from the 14-week study gave negative results. Sodium nitrite has also been reported in the literature to test positive as a clastogen *in vivo*.

Carcinogenicity:
These studies are not required for products given acutely (or for less than 6 months). The applicant has presented published literature data, however, of the long-term treatment (2 years) of rat and mice with sodium nitrite in drinking water. In these studies there was no evidence of carcinogenic activity of sodium nitrite in male mice. There was equivocal evidence of carcinogenic activity of sodium nitrite in female mice based on the positive trend in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach. In rats there was no evidence of carcinogenic activity of sodium nitrite in male or female rats.

In another study conducted in female pregnant rats, it was observed that incidences of malignant lymphoma were significantly increased in all exposed groups compared to the controls. Immunoblastic cell proliferation was also observed in some animals in each exposed group.

In a study in female mice, endometrial carcinogenesis was observed after the concurrent oral administration of ethylenethiourea and sodium nitrite to animals orally once a week for up to 6 months of the study. Male rats administered sodium nitrite at 3,000 ppm in drinking water for 4 weeks had significantly increased incidences of hyperplasia of the mucosa in the fore-stomach.

Reproductive and Developmental Toxicity:
Sodium nitrite produced no adverse effects on any fertility or reproductive parameter in mice. There was no evidence of teratogenicity in guinea pigs, mice, rats, or pigs.

Guinea pigs treated with 50 mg/kg sodium nitrite underwent normal parturition, animals treated 60 mg/kg/day (SC) resulted in abortion of the litters within 1-4 days of treatment, and all animals treated with 70 mg/kg (SC) died within 60 minutes of treatment. Further studies of a single dose of 60 mg/kg (SC) resulted in death of 96% fetuses examined at 3 or more hours after sodium nitrite administration and measurable blood levels of methemoglobin in the dams and their fetuses for up to 6 hours post treatment. Maternal methemoglobin levels were higher than the levels in the offspring at all times measured. A 60 mg/kg dose in the pregnant guinea pig that resulted in fetal death was 1.7 times higher than the highest clinical dose of sodium nitrite that would be used to treat cyanide poisoning (based on a body surface area comparison).

Sodium nitrite administered to rats in drinking water at 2 g/l or 3 g/l through gestation and lactation produced severe anemia, reduced growth and increased mortality in the offspring. Sodium nitrite administered to rats in drinking water from post-conception day 13 to delivery produced impaired learning behaviour (both auditory and visual) and reduced long-term retention of the passive avoidance response in the offspring.

In a further study sodium nitrite produced a delay in the development of acetylcholinesterase (AChE) and 5- hydroxytryptamine 5-HT positive fibre ingrowth into the hippocampal dentate gyrus and parietal neocortex during the first week of life of the offspring. These changes have been attributed to prenatal hypoxia following nitrite exposure.

<u>Sodium Thiosulfate</u>
General Toxicity:
In mice, the LD_{50} of sodium thiosulfate administered IV in rats was 1,190 mg/kg. In rats, the LD_{50} of sodium thiosulfate administered orally was > 5,000 mg/kg and administered IV was >2,500 mg/kg. In dogs, the LD_{50} of sodium thiosulfate administered IV was 3,000 mg/kg.

Rats administered 125 mg/kg intramuscular (IM) sodium thiosulfate, for 4 weeks or 3 months, developed deleterious changes in various organs. Changes in the capillary walls of the thyroid and adrenal cortex were visible at 4 weeks and after 3 months the vessels of the kidneys displayed clear

changes, including atrophy of the glomerula and dilation of the glomerula capillaries which were permeable to plasma. An increased permeability of liver capillary walls and an increase in Kupffer cells were noted.

Genotoxicity:
Sodium thiosulfate tested negative for mutagenic potential in the bacterial reverse mutation assay (Ames test) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 (± S9 metabolic activation).

Carcinogenicity:
Long-term studies in animals have not been performed to evaluate the potential carcinogenicity of sodium thiosulfate. As stated earlier, these studies are not required.

Reproductive and Developmental Toxicity:
There were no non-clinical studies examining the effects of sodium thiosulfate on fertility. There are no teratogenic effects in offspring of hamsters treated during pregnancy with sodium thiosulfate in doses similar to those given intravenously to treat cyanide poisoning in humans. Some studies suggest that treatment with sodium thiosulfate ameliorates the teratogenic effects of maternal cyanide poisoning in hamsters. Other studies suggest that sodium thiosulfate was not embryotoxic or teratogenic in mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400 and 580 mg/kg/day, respectively. No studies on the effects of sodium thiosulfate on prenatal or postnatal development were identified.

Conclusions on toxicology
The toxicology of sodium nitrite and sodium thiosulfate has been reviewed adequately in the applicant's non-clinical overview.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Sodium nitrite
An environmental risk assessment has been provided for sodium nitrite.

Sodium Nitrite Injection (30 mg/ml) is used as a cyanide antidote. The maximum daily dose is 450 mg.

Sodium nitrite is an inorganic salt, so a screen for persistence, bioaccumulation and toxicity (PBT) according to the European Union Technical Guidance Document on Risk Assessment (ECHA 2012) is not required.

The Predicted Environmental Concentration in surface water ($PEC_{surfacewater}$) was estimated considering the worst-case scenario of daily application of the maximum dose per inhabitant, i.e. 450 mg sodium nitrite. PECsurfacewater is 2.25 µg/l, which is higher than the trigger value of 0.01 µg/l and, therefore, a Phase II assessment was deemed necessary.

The Phase II assessment has been based upon literature, which is acceptable. The following has been summarised from the relevant literature:

- The predicted environmental exposition of the surface water aquatic organisms compared with the toxicity of the substance shows that the risk for aquatic organisms and microorganisms associated with sodium nitrite exposure is acceptable.

- The predicted environmental exposition in ground water compared with the toxicity of the substance shows that the risk associated with sodium nitrite exposure is acceptable.

- The Ready Biodegradability and water/sediment tests do not apply to inorganic substances. Therefore, it is not possible to conduct such tests with sodium nitrite.

- The substance will distribute mainly if not exclusively to water if released to the water

compartment. This substance dissociates immediately into sodium and nitrite ions in water. The nitrite ion is a component of the nitrogen cycle. In the environment, bacteria of the genus Nitrobacter oxidise nitrites to nitrates and, therefore, is ubiquitous in water compartments and soils and even sewage treatment plants.

- The properties of sodium nitrite indicate that going through the sewage treatment the substance will not concentrate in the activated sludge. It should, therefore, not generate any risks in the terrestrial compartment in case of sludge spreading over the fields.

- The properties of sodium nitrite indicate no significant shifting of the drug substance to the sediment. No risk for the sediment compartment is indicated for the substance under consideration and further tests on sediment-dwelling organisms are not considered necessary.

Sodium thiosulfate
An environmental risk assessment has been provided for sodium thiosulfate.

Sodium Thiosulfate Injection (250 mg/ml) is used as a cyanide antidote. The maximum daily dose is 18.75 grams of sodium thiosulfate.

Sodium thiosulfate is an inorganic salt, so a screen for persistence, bioaccumulation and toxicity according to the European Union Technical Guidance Document on Risk Assessment (ECHA 2012) is not required.

The Predicted Environmental Concentration in Surface water ($PEC_{surfacewater}$) was estimated, considering the worst-case scenario of daily application of the maximum dose per inhabitant, i.e. 18750 mg sodium thiosulfate. $PEC_{surfacewater}$ is 93.75 µg/l, which is higher than the trigger value of 0.01 µg/l and, therefore, a Phase II assessment was deemed necessary.

The Phase II assessment has been based upon literature, this approach is acceptable. The following has been summarised from the relevant literature:

- The predicted environmental exposition of the surface water aquatic organisms compared with the toxicity of the substance shows that the risk for aquatic organisms and microorganisms associated with sodium thiosulfate exposure is acceptable.

- The predicted environmental exposition in ground water compared with the toxicity of the substance shows that the risk associated with sodium thiosulfate exposure is acceptable.

Conclusions on the ERA
Overall the ERA is considered to have been suitably explored by the applicant. Both components in these applications are considered to be inorganic salts and so concerns for PBT are negated. Although action limits for $PEC_{surfacewater}$ exceed the 0.01 µg/l action limit, the Experts have provided sufficient evidence from the literature to establish that sodium nitrite and sodium thiosulfate would not pose a risk to the environment.

III.6 Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicological properties of sodium nitrite and sodium thiosulfate are well-known. As these are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview discusses the information from cited literature for each of the active drug substances and is acceptable.

Sodium nitrite and sodium thiosulfate do not pose a risk to the environment.

From a non-clinical perspective the SmPCs are acceptable.

The grant of Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The applicant has not conducted a clinical development programme to support the development of co-packaged sodium nitrite injection and sodium thiosulfate injection for the treatment of cyanide poisoning. This is considered justified based upon the well-established use of sodium nitrite and sodium thiosulfate with an acceptable level of safety and efficacy for the treatment of life-threatening acute cyanide poisoning. The use of sodium nitrite injection and sodium thiosulfate injection is recommended by the National Poisons Information Service as an antidote for cyanide poisoning. The supportive literature also describes a number of cases from EU countries.

No randomised control trials have been conducted and are also not justified on ethical grounds. Therefore the literature references primarily comprise of case reports or case series from specialised centres. Most of the references are from the middle of the last century however the World Health Organisation (WHO), the Agency for Toxic Substances and Disease Registry (ATSDR), National Poisons Information Service (NPIS), British National Formulary (BNF) and European Medicines Agency (EMA) also recommend the use of sodium nitrite and sodium thiosulfate for the treatment of cyanide poisoning in their current guidelines. The products in these applications have also received approval from the Food and Drug Administration (FDA) within the last 3 years.

The applicant has provided a summary of each case reported in the literature and also the complete reference. These support the use of these products in both adults and children. As expected, earlier treatment results in complete or better recovery, although the adverse effects of methemogobinaemia must be borne in mind. For this reason, the dosing in children is also based on body weight rather than the complete adult dose.

Due to the extreme toxicity of cyanide, experimental evaluation of treatment efficacy has predominantly been completed in animal models including mice, dog, sheep and monkey. These results in animals are consistent with the efficacy of sodium nitrite and sodium thiosulfate reported in human cases of cyanide poisoning.

IV. 2 Pharmacokinetics

No new data have been submitted with these applications and none are required.

IV. 3 Pharmacodynamics

No new data have been submitted with these applications and none are required.

IV. 4 Clinical Efficacy

No new data have been submitted with these applications and none are required.

IV.5 Clinical Safety

No new data have been submitted with these applications and none are required.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sodium Nitrite Injection, Sodium Thiosulfate Injection and Nithiodote.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are

listed below:

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Low blood pressure (hypotension)	A side effect is reduced blood pressure. The frequency is not known yet. Symptoms can improve if the rate of infusion is decreased or dose adjusted.	You will be given the medicine by injection into a vein by a doctor or nurse. Your doctor will choose the dose that is right for you. Your blood pressure will be monitored during use and the dose of the medication and/or rate of infusion will be adjusted if significant hypotension occurs.
Have a history of elevated levels of methemoglobin (This is a modified form of hemoglobin that reduces the amount of oxygen in the bloodstream and can cause weakness or breathlessness)(methemoglobinemia)	A side effect is a blood disorder resulting in oxygen deprivation in tissues (methemoglobinemia). The frequency which it occurs is not known yet. Symptoms can improve if the rate of infusion is decreased or dose adjusted.	Provide airway, ventilatory, and circulatory support when administered. You will be given the medicine by injection into a vein by a doctor or nurse. You will be monitored during use and the dose of the medication and/or the rate of infusion adjusted if necessary.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Reduction in number of red blood cells in the bloodstream (anaemia) in patients with G6PD deficiency	Anaemia can make the skin appear pale and can cause weakness or breathlessness. Sodium nitrite should be used with caution in patients with known anaemia. Patients with anaemia will form more methemoglobin (as a percentage of total haemoglobin) than persons with normal red blood cell (RBC) volumes. Because patients with G6PD deficiency are at increased risk of a haemolytic 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 red blood cells (hematocrit).
Foetal death	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.
Prolonged bleeding time	Sodium thiosulphate can increase the time it takes for blood to clot.
Overdose	Large doses of sodium nitrite result in severe hypotension and toxic levels of methemoglobin which may lead to cardiovascular collapse.
Chemical incompatibility with Cyanokit (hydroxocobalamin)	Chemical incompatibility has been reported between sodium nitrite and sodium thiosulfate and hydroxocobalamin and these drugs should not be administered simultaneously through the same IV line.

Missing information

Sodium Nitrite:
- Use during lactation
- Effect on fertility

Sodium Thiosulfate:
- Use in pregnancy and lactation

Summary of risk minimisation measures by safety concern
Routine risk minimisation measures are listed in the SmPCs and package leaflets. These medicines have no additional risk minimisation measures.

IV.7 Discussion on the clinical aspects

The discussion of the literature references support the use of these products for the treatment of cyanide poisoning and the dosing recommendation proposed in the SmPCs. No efficacy or safety studies have been conducted and the inferences are based on case reports from the literature. However, the biological mechanism of action is well known and, therefore, this can be accepted.

There are safety concerns with the use of the antidotes themselves, however, it is likely that patients will be treated either in specialised centres or at least under the supervision of an experienced physician, who would be knowledgeable about the management of these poisons. Therefore, for life-threatening cyanide poisoning the safety profile can be considered acceptable. Appropriate instructions in the product literature are mentioned and the RMP is in place to mitigate any risks.

V USER CONSULTATION

The package leaflet for Nithiodote has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

For Sodium Nitrite Injection and Sodium Thiosulfate Injection, a user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Nithiodote. The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cyanide poisoning is a life-threatening condition, and for good clinical outcome immediate treatment in the form of antidote, as well as supportive therapy, is necessary. The sequential intravenous injection of sodium nitrite and sodium sulfate are well-established as one of the treatment options in the EU, as well as many other countries, for over 20 years.

The quality of these products is considered acceptable.

There is a safety concern of the adverse effect of methemogobinemia due to sodium nitrite, however, with appropriate dosing, and the availability of methylene blue, this risk is considered manageable.

It will be almost impossible to conduct clinical studies to satisfy the usual regulatory requirements and, therefore, these are not expected. However, robust risk minimisation measures are in place.

Therefore the benefit/risk profile of the products under consideration is favourable. The Summaries of Product Characteristics (SmPC), package leaflets and labelling are satisfactory and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and package leaflets for these products are available on the MHRA website.

Representative copies of the labels are provided below in Annexes 1, 2 and 3 on pages 21-26.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Outcome**	**Assessment report attached Y/N**
Type 1B	To update sections 2, 3, 4.1, 4.2, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.3, 6.4, 6.5 and 6.6 of the UK SmPC to align with the SmPC approved at the end of procedure for UK/H/6481/001/MR. The labelling and PIL were also updated accordingly.	SmPC PIL Labelling	15/01/2019	15/03/2019	Approved	Yes (Annex 1)
Type 1B	To update sections 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3, 6.1, 6.3, 6.4, 6.5 and 6.6 of the UK SmPC to align with the SmPC approved at the end of procedure for UK/H/6482/001/MR. The labelling and PIL were also updated accordingly	SmPC PIL Labelling	15/01/219	15/03/2019		Yes (Annex 2)
Type 1B	To update sections 2, 3, 4.1, 4.2, 4.5, 4.8, 5.1, 6.1 and 6.5 of the UK SmPC to align with the SmPC changes approved at the end of procedure for UK/H/6483/001/MR. The labelling and PIL were also updated accordingly	SmPC PIL Labelling	15/01/2019	20/03/2019	Approved	Yes (Annex 3)

Annex 1

Reference: PL 42589/0001, Application 0031
Product: Sodium Nitrite 30 mg/mL Solution for Injection

Type of Procedure: National
Submission Category: Type IB variation

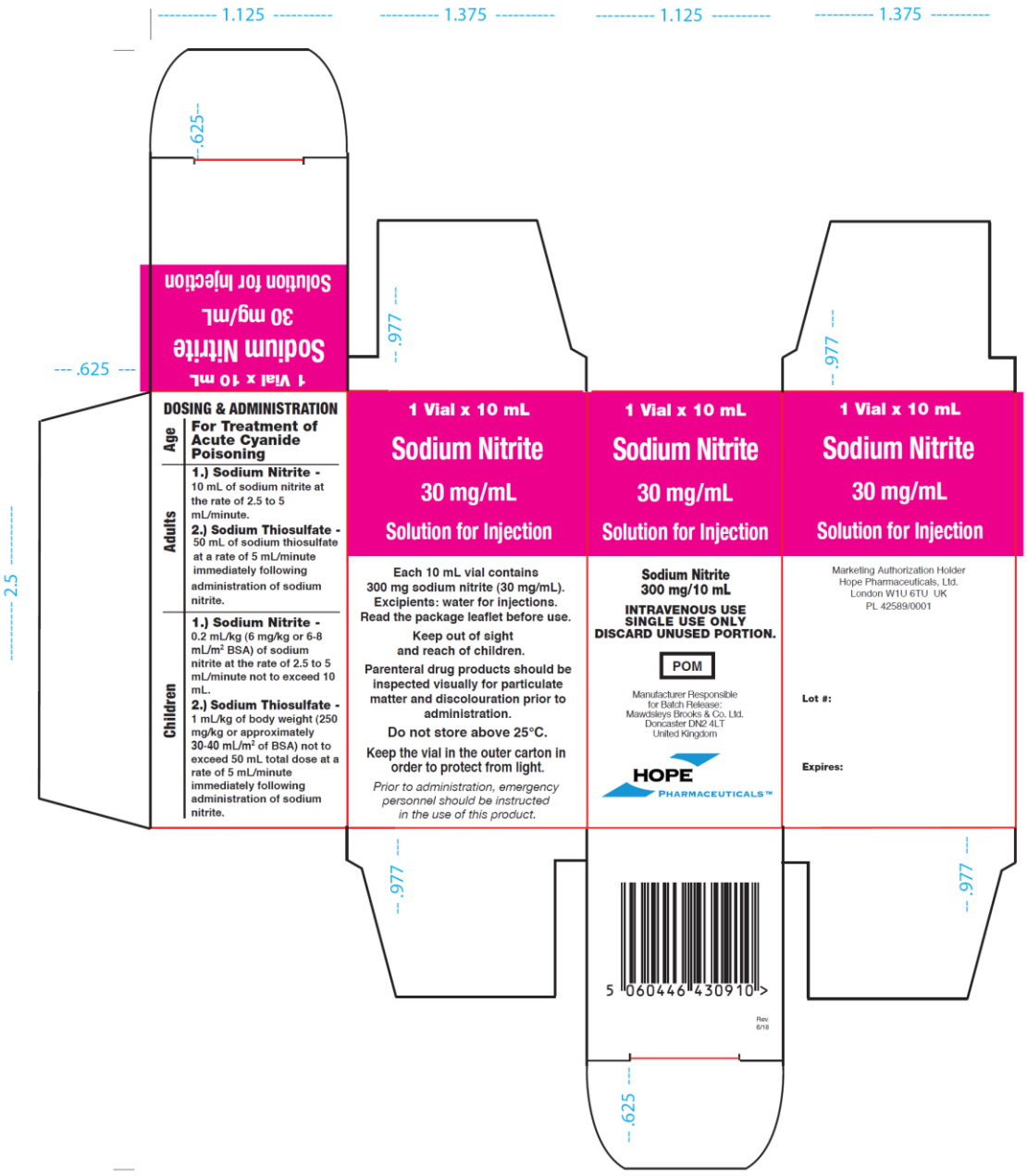
Reason:
To update sections 2, 3, 4.1, 4.2, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.3, 6.4, 6.5 and 6.6 of the UK SmPC to align with the SmPC approved at the end of procedure for UK/H/6481/001/MR. The labelling and PIL were also updated accordingly.

Supporting Evidence
The Company has submitted updated SmPC fragments (sections 2, 3, 4.1, 4.2, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.3, 6.4, 6.5 and 6.6), PIL and labelling.

Evaluation
The updated documents are satisfactory.

Conclusion
The amendment to the SmPC fragments, PIL and labelling can be approved.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website. Representative current labelling is presented below:



Decision - Approved on 15 March 2019.

Annex 2

Reference: PL 42589/0002, Application 0025
Product: Sodium Thiosulfate 250 mg/mL Solution for Injection

Type of Procedure: National
Submission Category: Type IB variation

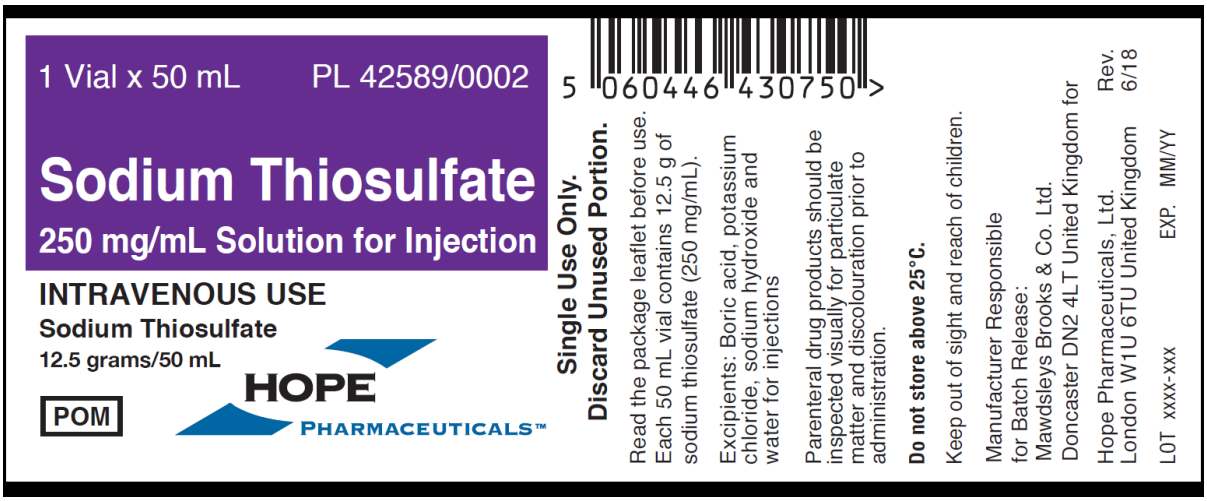
Reason:
To update sections 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3, 6.1, 6.3, 6.4, 6.5 and 6.6 of the UK SmPC to align with the SmPC approved at the end of procedure for UK/H/6482/001/MR. The labelling and PIL were also updated accordingly.

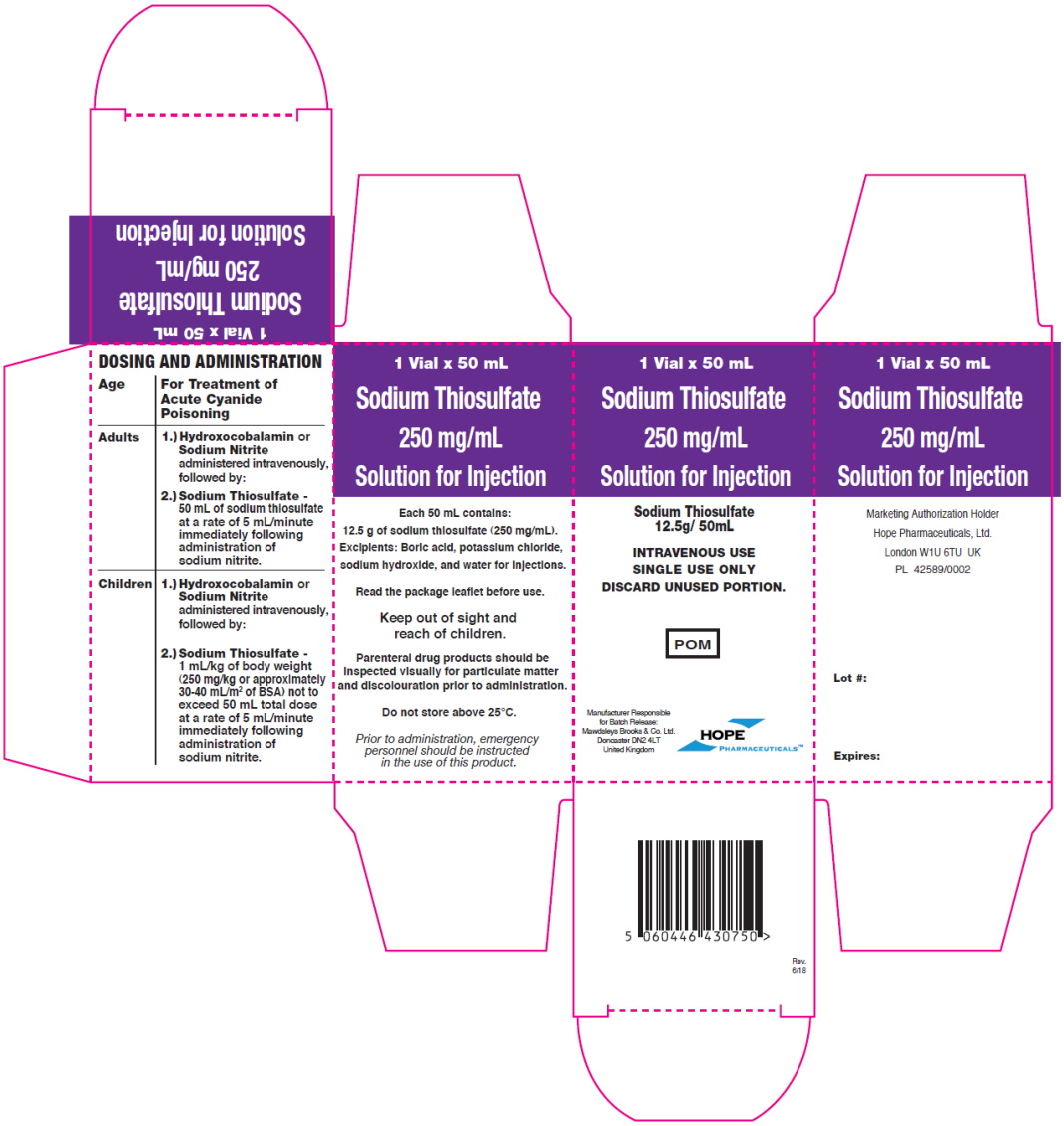
Supporting Evidence
The Company has submitted updated SmPC fragments (sections 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3, 6.1, 6.3, 6.4, 6.5 and 6.6), PIL and labelling.

Evaluation
The updated documents are satisfactory.

Conclusion
The amendment to the SmPC fragments, PIL and labelling can be approved.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website. Representative current labelling is presented below:





Decision - Approved on 15 March 2019.

Annex 3

Reference: PL 42589/0003, Application 0044
Product: Nithiodote (Co-Packaged Sodium Nitrite 30 mg/mL Solution for Injection and Sodium Thiosulfate 250 mg/mL Solution for Injection)

Type of Procedure: National
Submission Category: Type IB variation

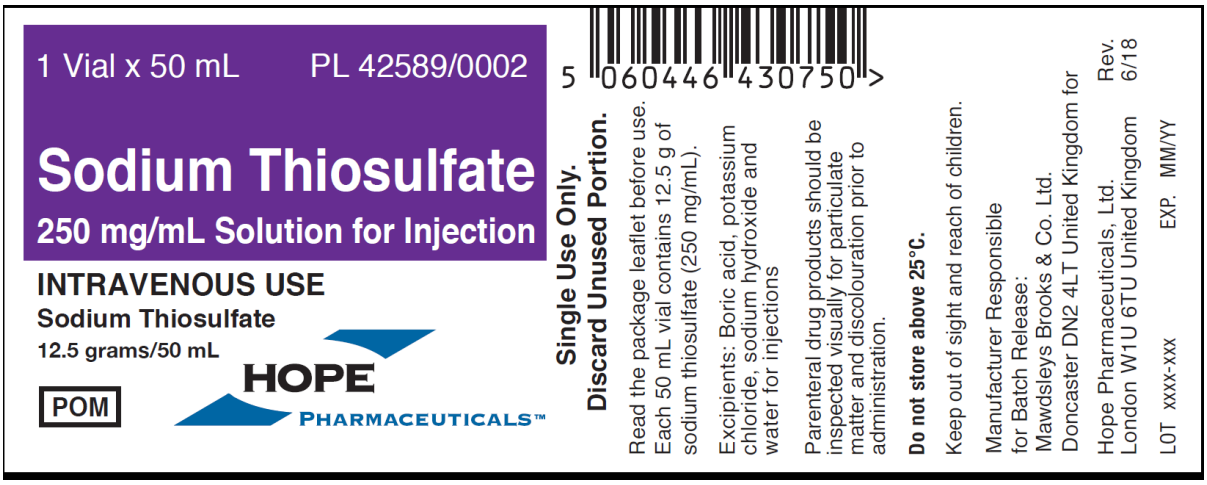
Reason:
To update sections 2, 3, 4.1, 4.2, 4.5, 4.8, 5.1, 6.1 and 6.5 of the UK SmPC to align with the SmPC changes approved at the end of procedure for UK/H/6483/001/MR. The labelling and PIL were also updated accordingly.

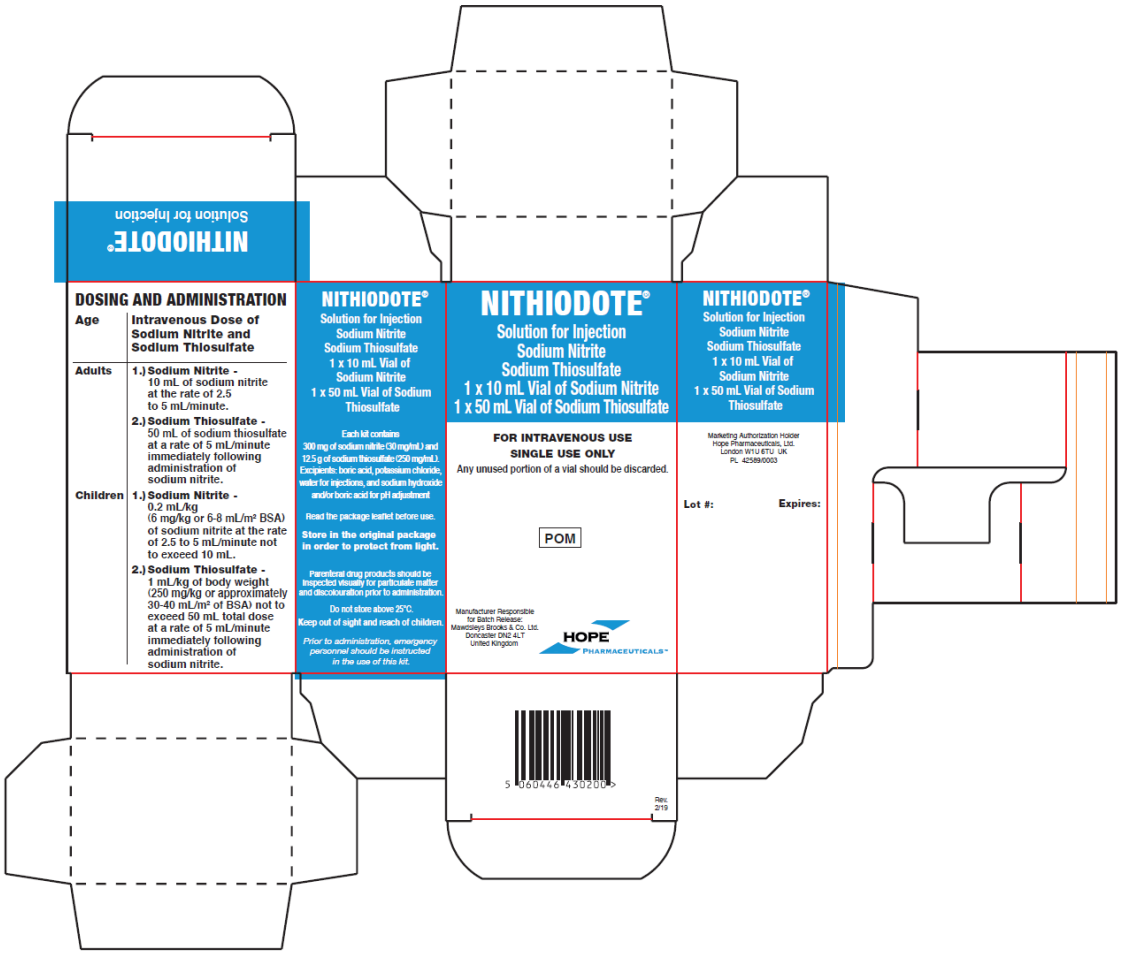
Supporting Evidence
The Company has submitted updated SmPC fragments (sections 2, 3, 4.1, 4.2, 4.5, 4.8, 5.1, 6.1 and 6.5), PIL and labelling.

Evaluation
The updated documents are satisfactory.

Conclusion
The amendment to the SmPC fragments, PIL and labelling can be approved.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website. Representative current labelling is presented below:





Decision - Approved on 20 March 2019.