

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pedmarqsi 80 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 100 mL contains 8 g of sodium thiosulfate as an anhydrous salt.

Each mL of solution for infusion contains 80 mg sodium thiosulfate.

Excipient(s) with known effect:

Each mL of solution for infusion contains 0.25 mg boric acid and 23 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

The solution for infusion is a clear, colourless solution essentially free of particulate matter, with a pH of 7.7 - 9.0 and an osmolality of 980 - 1 200 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

4.2 Posology and method of administration

Pedmarqsi is intended for hospital use only, under the supervision of an appropriately qualified physician.

Posology

The recommended dose of sodium thiosulfate for the prevention of cisplatin-induced ototoxicity is weight based and normalised to body surface area according to the table below:

Body Weight	Dose	Volume
> 10 kg	12.8 g/m ²	160 mL/m ²
5 to 10 kg	9.6 g/m ²	120 mL/m ²
< 5 kg	6.4 g/m ²	80 mL/m ²

Pre-treatment with antiemetics is recommended to reduce the incidence of nausea and vomiting (see section 4.4).

Special populations

Preterm and term newborn infants from birth to less than 1 month of age

Sodium thiosulfate is contraindicated in preterm and term newborn infants from birth to less than 1 month of age (see sections 4.3 and 4.4).

Renal impairment

No dose adjustment is recommended for patients with renal impairment (see section 5.2). Due to the sodium content of sodium thiosulfate, there is an increased risk of adverse reactions in patients with renal impairment (see section 4.4).

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment (see section 5.2).

Method of administration

For intravenous use.

Due to the hypertonic formulation, administration through a central vein is recommended.

For single use only.

Sodium thiosulfate is administered as a 15-minute infusion.

Time of administration in relation to cisplatin

The timing of sodium thiosulfate administration relative to cisplatin chemotherapy is critical.

If sodium thiosulfate is administered:

- Less than 6 hours after end of cisplatin infusion: may reduce cisplatin efficacy against the tumour
- More than 6 hours after end of cisplatin infusion: may not be effective in preventing ototoxicity

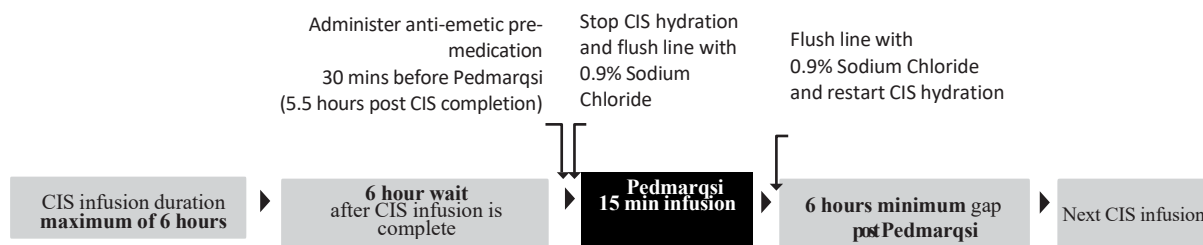
Only use sodium thiosulfate following cisplatin infusion duration of 6 hours or less. Do not use sodium thiosulfate if:

- Cisplatin infusion exceeds 6 hours, or
- A subsequent cisplatin infusion is planned within 6 hours

When cisplatin is administered on consecutive days, ensure a minimum 6-hour gap after sodium thiosulfate infusion before a subsequent cisplatin infusion is given.

After end of cisplatin infusion:

- Provide highly effective multi-agent intravenous antiemetic therapy 30 minutes prior to administration of sodium thiosulfate i.e. 5.5 hours after completion of cisplatin infusion
- This medicinal product is a ready to use solution for infusion
- Prepare the required mL of sodium thiosulfate, 80 mg/mL, in a syringe or add to an empty, sterile infusion bag
- Stop cisplatin hydration fluid and flush line with sodium chloride 0.9%
- Infuse sodium thiosulfate over 15 minutes (6 hours after completion of cisplatin infusion)
- Flush line with sodium chloride 0.9% and restart the cisplatin hydration immediately afterwards



CIS = cisplatin

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Neonates under the age of 1 month due to the risk of hypernatremia (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity reactions were reported in clinical studies following the administration of sodium thiosulfate (see section 4.8). Symptoms included rash, tachycardia, chills and dyspnoea.

Sodium thiosulfate may contain a trace amount of sodium sulfite. It may rarely cause several hypersensitivity reactions and bronchospasm. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Antihistamines (e.g. diphenhydramine and steroids) should be immediately available to administer in the event of an allergic reaction. If the reaction is such that the patient is to continue with sodium thiosulfate after the next cisplatin administration, premedication with antihistamines should be given and the patient observed carefully.

Electrolyte imbalance

A 12.8 g/m² dose delivers a sodium load of 162 mmol/m², a 9.6 g/m² dose delivers a sodium load of 121 mmol/m² and a 6.4 g/m² dose delivers a sodium load of 81 mmol/m². Electrolyte balance and blood pressure should be monitored carefully, and sodium thiosulfate should not be given if serum sodium is > 145 mmol/litre at baseline before sodium thiosulfate is administered within a treatment cycle.

Patients < 1 month of age have less well-developed sodium homeostasis; therefore, sodium thiosulfate is contraindicated in neonates (see section 4.3).

Serum magnesium, potassium and phosphate levels should also be monitored, and supplementation given if needed as the combination of fluid loading in association with cisplatin-based chemotherapy and the administration of sodium thiosulfate may cause transient electrolyte disturbance.

Nausea and vomiting

Transient increases in incidence and severity of nausea and vomiting may be observed with sodium thiosulfate infusion, due to the high sodium levels administered over a short time period (see section 4.8). In addition to any prophylactic antiemetics administered prior to cisplatin administration, additional multi-agent antiemetics should be given in the 30 minutes prior to sodium thiosulfate administration. Nausea and vomiting tend to stop soon after the sodium thiosulfate infusion has finished.

Renal impairment

Sodium thiosulfate is known to be substantially excreted by the kidney (see section 5.2), and the risk of adverse reactions of sodium thiosulfate may be greater in patients with impaired renal function. Because cisplatin chemotherapy is associated with renal toxicity, renal function should be monitored and caution applied with close monitoring of electrolytes if the glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m².

Excipients with known effect

This medicinal product contains 0.25 mg/mL boric acid as a buffer. Boric acid can affect fertility when chronically administered at doses greater than 0.2 mg/kg/day. This medicinal product is administered between 6-30 times intermittently over a 6-month period in conjunction with cisplatin chemotherapy. Along with boric acid from drinking water, this amounts to 0.17-0.22 mg/kg/day depending on the age and size of the child.

This medicinal product contains 23 mg sodium per mL, equivalent to 1.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This is also equivalent to 1.15-2.1% of the European Food Safety Authority (EFSA) safe daily intake of 1.1-2 g sodium for children aged 1 to 17 years and equivalent to 11.5% of the EFSA safe daily intake of 0.2 g in babies aged 7 to 11 months. This has to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Sodium thiosulfate should only be given at least 6 hours after the end of cisplatin infusion. Sodium thiosulfate should not be given when cisplatin is infused for longer than 6 hours or if a subsequent cisplatin infusion is planned within 6 hours (see section 4.2). The delayed administration prevents potential interference with cisplatin chemotherapy efficacy against the tumour.

No other interaction studies have been performed. Relevant pharmacokinetic interactions are unlikely as administration of thiosulfate is infrequent, only in conjunction with cisplatin and thiosulfate is rapidly eliminated within hours after administration. Sodium thiosulfate potentially induces CYP2B6 (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of sodium thiosulfate in pregnant women. Animal studies are insufficient with respect to reproductive toxicity with intravenous infusion of sodium thiosulfate (see section 5.3). As a precautionary measure, it is preferable to avoid the use of sodium thiosulfate during pregnancy.

Sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy. Cisplatin is not used during pregnancy unless the clinician considers the risk in an individual patient to be clinically justified. Patients receiving cisplatin are warned of the need to use appropriate contraception during treatment and for 6 months following cisplatin treatment, as cisplatin is embryotoxic and fetotoxic.

Breast-feeding

It is unknown whether sodium thiosulfate/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. As a precautionary measure, it is preferable to avoid the use of sodium thiosulfate during breast-feeding.

Sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy, during which breastfeeding is contraindicated in female patients.

Fertility

There are no clinical data available on the effects of sodium thiosulfate on fertility. There is insufficient information from animal studies to assess the effects of intravenous infusion of sodium thiosulfate on fertility.

Sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy. Cisplatin treatment is known to adversely affect fertility.

This medicinal product contains 0.25 mg/mL boric acid which can affect fertility when chronically administered at doses greater than 0.2 mg/kg/day (see section 4.4).

4.7 Effects on ability to drive and use machines

Sodium thiosulfate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reaction is hypersensitivity, observed at a frequency of ≥ 1 case per 10 patients (11%) (see section 4.4).

The most commonly reported adverse reactions with a frequency of ≥ 1 case per 10 patients are vomiting (44%), nausea (23%), hypernatraemia (19%), hypophosphataemia (18%) and hypokalaemia (21%).

Tabulated list of adverse reactions

Table 1 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level) and frequency. Frequencies have been evaluated according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Undesirable effect	Frequency
Immune system disorders	Hypersensitivity	Very common (11%)
Metabolism and nutrition disorders	Hypokalaemia	Very common (21%)
	Hypernatraemia	Very common (19%)
	Hypophosphataemia	Very common (18%)
	Metabolic acidosis	Common (3%)
	Hypocalcaemia	Common (7%)
Vascular disorders	Hypertension	Common (2%)
	Hypotension	Common (2%)
Gastrointestinal disorders	Vomiting	Very common (44%)
	Nausea	Very common (23%)

Description of selected adverse reactions

Nausea and vomiting

Administration of sodium thiosulfate is associated with a high incidence of nausea and vomiting. This nausea and vomiting tends to stop soon after the sodium thiosulfate infusion has finished (see section 4.4).

Hypernatraemia

A 12.8 g/m² dose delivers a sodium load of 162 mmol/m², a 9.6 g/m² dose delivers a sodium load of 121 mmol/m² and a 6.4 g/m² dose delivers a sodium load of 81 mmol/m². In clinical studies doses of sodium thiosulfate equivalent to these resulted in a small, transient increase in serum sodium levels, independent of age, body surface area, body weight, total daily sodium thiosulfate dose or cisplatin cycle. Sodium levels return to baseline by 18 hours or 24 hours after administration.

Electrolyte imbalance

Hypophosphataemia and hypokalaemia are very common following sodium thiosulfate treatment. Electrolyte balance and blood pressure should be monitored carefully (see section 4.4).

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 listed in [Appendix V](#).

4.9 Overdose

Excessive doses of sodium thiosulfate may be expected to produce severe nausea and vomiting as well as electrolyte imbalance, changes to blood pressure and acidosis. Treatment of an overdose should consist of general supportive measures including administration of fluids and observation of the clinical status of the patient. There is no specific antidote for overdose with sodium thiosulfate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

Mechanism of action

The mechanism of sodium thiosulfate protection against ototoxicity is not fully understood, but may include increasing levels of endogenous antioxidants, inhibition of intracellular oxidative stress, and direct interaction between cisplatin and the thiol group in sodium thiosulfate to produce inactive platinum species.

Concurrent incubation of sodium thiosulfate with cisplatin decreased the *in vitro* cytotoxicity of cisplatin to tumour cells; delaying the addition of sodium thiosulfate to these cultures prevented the protective effect.

Pharmacodynamic effects

There is no clinical pharmacodynamic information available beyond that given within the mechanism of action section.

Clinical efficacy and safety

The efficacy of sodium thiosulfate (STS) in preventing cisplatin (CIS)-induced ototoxicity was studied in two multicentre studies in which 112 paediatric patients with various solid tumour types were treated with STS following each administration of CIS. Safety has been established using 1 to 5 doses of sodium thiosulfate per chemotherapy cycle, with regimens varying from 1 dose of CIS+STS per cycle to 5 doses of CIS+STS per cycle.

Study 1 – pivotal study

Study 1 was a multicentre, randomised, controlled, open-label study to assess the efficacy and safety of STS in reducing ototoxicity in children receiving CIS chemotherapy for standard risk hepatoblastoma (SR-HB). Children between 1 month and 18 years of age with histologically confirmed newly diagnosed HB were eligible. Children were randomised 1:1 to receive STS after each CIS dose (CIS+STS arm) or to receive CIS alone.

CIS was administered as a 6-hour intravenous infusion. Four courses of CIS were given pre-surgery and 2 additional courses were given post-surgery.

In the CIS+STS arm, the STS intravenous infusion was administered over 15 minutes, beginning 6 hours after completion of each CIS infusion. Doses of STS were dependent on the child's weight as follows: children > 10 kg received an equivalent of 12.8 g/m² STS, children ≥ 5 to ≤ 10 kg received an equivalent of 9.6 g/m² STS, and children < 5 kg received an equivalent of 6.4 g/m² STS.

A total of 129 children were registered and 114 children were randomised in the study (61 patients in the CIS+STS arm and 53 patients in the CIS Alone arm). Of the 114 patients randomised, 5 patients withdrew prior to treatment: 2 patients due to withdrawal of parental consent, 2 patients due to reclassification as high risk HB, and 1 due to ineligibility.

Hearing loss was defined as a Brock Grade ≥ 1 measured using audiologic evaluations after the end of study treatment or at an age of at least 3.5 years when a reliable result could be obtained, whichever was later. The proportion of children in the CIS+STS arm with hearing loss at age ≥ 3.5 years (20 children [35.1%]) was approximately one-half compared with the CIS Alone arm (35 children [67.3%]) (Table 2). Event free survival and OS were also evaluated.

Table 2: Summary of patient population and hearing loss in study 1

	CIS alone	CIS + STS
Patient population		
N (intent to treat population)	52	57
Age (years), median (min, max)	1.1 (0.3, 5.9)	1.1 (0.1, 8.2)
Weight (kg) (mean, SD)	10.25 (3.26)	10.23 (3.76)
N (treated population)	56	53
Number of CIS cycles (mean, SD)	5.8 (1.0)	5.9 (0.6)
Cumulative CIS dose (mg/m ²) (mean, SD)	362.851 (98.871)	363.860 (96.607)
Cumulative STS dose (g/m ²) (mean, SD)	--	85.149 (24.390)
Patients who experienced hearing loss		
N (intent to treat population)	52	57
Yes, n (%)	35 (67.3)	20 (35.1)
No, n (%)	17 (32.7)	37 (64.9)
Relative Risk (95% CI)		0.521 (0.349, 0.778)
p-value		<0.001

The risk of having hearing loss was statistically significantly lower in the CIS+STS arm compared with the CIS Alone arm, corresponding to a clinically meaningful 48% lower risk after STS treatment.

At a median of 4.27 years of follow up, the hazard ratio between the treatment arms in Event-free survival (EFS) was ([CIS+STS vs CIS Alone]: 0.96; 95% CI: 0.42, 2.23) and in overall survival (OS) (hazard ratio: 0.48; 95% CI: 0.09, 2.61).

Study 2 – supportive study

Study 2 was a multicentre, randomised, controlled, open-label study to assess the efficacy and safety of STS in preventing hearing loss in children receiving CIS chemotherapy for the treatment of newly diagnosed germ cell tumour (25.6%), hepatoblastoma (5.6%), medulloblastoma (20.8%), neuroblastoma (20.8%), osteosarcoma (23.2%), atypical teratoid/rhabdoid tumour (1.6%), choroid plexus carcinoma (0.8%), and anaplastic astrocytoma (0.8%); or any other malignancy treated with CIS; 7.5% had prior cranial radiation. Children between 1 year and 18 years of age and scheduled to receive a chemotherapy regimen that included a cumulative CIS dose of ≥ 200 mg/m², with individual CIS doses to be infused over ≤ 6 hours, were eligible. Children were randomised 1:1 to receive either STS 6 hours after each CIS dose (CIS+STS) or chemotherapy that included CIS, without subsequent STS (CIS Alone).

CIS was administered according to the sites' disease-specific cancer treatment protocols in use at the time. When multiple daily doses of CIS were scheduled, the protocol stipulated at least a 10-hour delay between any STS infusion and the beginning of the next day's CIS infusion.

In the CIS+STS arm, 10.2 g/m² STS was administered by intravenous infusion over 15 minutes, beginning 6 hours after the completion of each CIS infusion. A dose reduction was included for

children whose therapeutic protocol administered CIS on a per kg basis due to young age or low body weight, which was 341 mg/kg STS.

The primary endpoint was the proportional incidence of hearing loss between the CIS+STS arm and the CIS alone arm, as defined by comparison of American Speech-language-Hearing Association (ASHA) criteria assessed at baseline and 4-weeks after the final course of cisplatin. EFS, i.e. presence or absence of tumour progression or recurrence or development of subsequent malignant neoplasm, and OS were also evaluated.

A total of 131 children were registered and 125 children were randomised in the study (61 patients in the CIS+STS arm and 64 patients in the CIS Alone arm). Of the 125 patients randomised, 2 patients withdrew prior to treatment: 1 patient due to withdrawal of parental consent, and 1 due to investigator decision.

In the 104 patients who had both baseline and 4-week follow-up hearing assessments, the proportion of children in the CIS+STS arm with hearing loss (14 patients [28.6%]) was approximately one-half of the proportion in the CIS Alone arm (31 patients [56.4%]) (Table 3).

Table 3: Summary of patient population and hearing loss in study 2

	CIS alone	CIS + STS
Patient population		
N (intent to treat population)	64	61
Age (years), median (min, max)	8.3 (1, 18)	10.7 (1, 18)
N (intent to treat population)	64	59
Weight (kg) (mean, SD)	37.3 (24.9)	39.1 (28.3)
N (safety population)	64	59
Number of CIS cycles (mean, SD)	3.8 (1.5)	3.1 (1.4)
Cumulative CIS dose (mg/m ²) (mean, SD)	391.47 (98.40)	337.57 (118.33)
Cumulative STS dose (g/m ²) (mean, SD)	--	108.23 (80.24)
Patients who experienced hearing loss		
N (efficacy population)	55	49
Yes, n (%)	31 (56.4)	14 (28.6)
No, n (%)	24 (43.6)	35 (71.4)
Relative Risk (95% CI)		0.516 (0.318, 0.839)
p-value		0.0040

The risk of having hearing loss was statistically significantly lower in the CIS+STS arm compared with the CIS Alone arm, corresponding to a clinically meaningful 48% lower risk after STS treatment.

At a median of 5.33 years of follow up, the hazard ratio in EFS between arms was ([CIS+STS vs CIS Alone]: 1.27; 95% CI: 0.73, 2.18). A disparity in OS was observed (hazard ratio: 1.79; 95% CI: 0.86, 3.72). In patients categorised post-hoc with localised disease, the hazard ratio between arms in EFS was (hazard ratio: 1.02; 95% CI: 0.49, 2.15) and in OS (hazard ratio: 1.23; 95% CI: 0.41, 3.66).

5.2 Pharmacokinetic properties

Absorption

Sodium thiosulfate is poorly absorbed after oral administration and has to be administered intravenously. At the end of a sodium thiosulfate intravenous infusion, plasma levels of sodium thiosulfate are maximal and decline rapidly thereafter with a terminal elimination half-life of approximately 50 minutes. A return to pre-dose levels occurs within 3 to 6 hours after infusion. More than 95% of sodium thiosulfate excretion in urine occurs within the first 4 hours after administration.

Hence, there is no plasma accumulation when sodium thiosulfate is administered on 2 consecutive days.

In children and adults, the maximum sodium thiosulfate plasma levels after a 15-minute infusion of a dose equivalent to 12.8 g/m² was approximately 13 mM. Thiosulfate plasma levels change in a dose proportional manner. Age did not appear to influence the maximum plasma levels of sodium thiosulfate or the decline afterwards. A population PK model incorporating growth and maturation variables for the paediatric population showed that the predicted sodium thiosulfate plasma levels at the end of infusion were consistent across the recommended dose levels for the indicated age and body weight ranges.

Distribution

Sodium thiosulfate does not bind to human plasma proteins. Sodium thiosulfate is an inorganic salt and thiosulfate anions do not readily cross membranes. Hence, the volume of distribution appears largely confined to extracellular spaces and estimated at 0.23 L/kg in adults. In animals, sodium thiosulfate has been found to distribute to the cochlea. Distribution across the blood brain barrier or placenta appears absent or limited. Thiosulfate is an endogenous compound ubiquitously present in all cells and organs. Endogenous serum thiosulfate levels were $5.5 \pm 1.8 \mu\text{M}$ in adult volunteers.

Biotransformation

Metabolites of sodium thiosulfate have not been determined as part of clinical studies. Thiosulfate is an endogenous intermediate product of sulfur-containing amino acid metabolism. Thiosulfate metabolism does not involve CYP enzymes; it is metabolised through thiosulfate sulfur transferase and thiosulfate reductase activity to sulfite, which is rapidly oxidised to sulfate.

Elimination

Sodium thiosulfate (thiosulfate) is excreted through glomerular filtration. After administration, thiosulfate levels in urine are high, and approximately half of the sodium thiosulfate dose is retrieved unchanged in urine, nearly all excreted within the first 4 hours after administration. Thiosulfate renal clearance compared well with inulin clearance as a measure for the GFR.

Excretion of endogenously produced thiosulfate in bile was very low and did not increase after sodium thiosulfate administration. No mass balance studies have been performed, but it is expected that non-renal clearance will mainly result in renal excretion of sulfates. A small part of the sulfane sulfur of sodium thiosulfate may become part of endogenous cellular sulfur metabolism.

Renal impairment

In haemodialysis patients, total clearance of sodium thiosulfate was $2.04 \pm 0.72 \text{ mL/min/kg}$ (off dialysis) compared to $4.11 \pm 0.77 \text{ mL/min/kg}$ in healthy volunteers. This clearance was essentially similar to the non-renal clearance observed in the healthy volunteers ($1.86 \pm 0.45 \text{ mL/min/kg}$). In the absence of any glomerular filtration in haemodialysis patients, this only resulted in approximately a 25% increase in the maximum thiosulfate plasma levels and nearly a 2-fold increase in total exposure. The plasma concentration of thiosulfate is deemed to be the most important parameter associated with the efficacy of the product. Moreover, the most frequent adverse reactions are considered to be related to the sodium load with sodium thiosulfate administration and concurrent electrolyte imbalances (see section 4.4). Non-clinical studies indicated that dose limiting acute effects were related to the sodium intake. Sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy. Cisplatin is contraindicated in patients with pre-existing renal impairment and, therefore, in the absence of cisplatin administration sodium thiosulfate would not be administered.

Hepatic impairment

No information is available for use of sodium thiosulfate in patients with hepatic impairment. However, thiosulfate sulfur transferase/reductase activity is ubiquitous, including tissue like red blood cells, liver, kidney, intestine, muscle and brain. Therefore, the changes in thiosulfate pharmacokinetics in hepatically impaired patients are likely limited and without clinical significance.

Interactions studies

Sodium thiosulfate does not bind to human plasma proteins. The chemical properties of sodium thiosulfate, along with the observations that sodium thiosulfate does not distribute readily across membrane barriers and is excreted through glomerular filtration, make an interaction with membrane drug transporters unlikely.

In vitro studies

Cytochrome P450 enzymes

Sodium thiosulfate is an inducer of CYP2B6 but not of CYP1A2 or CYP3A4. Sodium thiosulfate is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at clinically relevant concentrations.

5.3 Preclinical safety data

Genotoxicity

Sodium thiosulfate was not genotoxic in an *in vitro* bacterial reverse mutation assay (Ames test) with or without metabolic activation and was not clastogenic in an *in vitro* mammalian cell assay (sister chromatid exchange) using human peripheral lymphocytes.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the potential carcinogenicity of sodium thiosulfate.

Impairment of fertility

There is insufficient information from animal studies to assess the effects of intravenous infusion of sodium thiosulfate on fertility.

Developmental toxicity

There is insufficient information from animal studies to assess developmental risks with intravenous infusion of sodium thiosulfate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

Chemical and physical in-use stability has been demonstrated for 24 hours at controlled room temperature for product stored in polyvinyl chloride, ethylene vinyl acetate and polyolephine intravenous bags.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Type I, 100 mL, clear glass vials sealed with a chlorinated butyl rubber stopper and an aluminium flip-off overseal. Each vial contains 100 mL of solution for infusion.

Vials are supplied in cartons of 1 vial pack.

6.6 Special precautions for disposal and other handling

This medicinal product is a sterile and ready to use solution for infusion.

Each vial is intended for single use only, and any unused solution should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Fennec Pharmaceuticals (EU) Limited
Regus House, Harcourt Centre
Block 4 Harcourt Rd, Saint Kevin's
Dublin
D02 HW77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1734/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

MIAS Pharma Limited
Suite 2, Stafford House
Strand Road
Portmarnock
Co. Dublin
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Pedmarqsi 80 mg/mL solution for infusion
sodium thiosulfate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 100 mL contains 8 g of sodium thiosulfate.

3. LIST OF EXCIPIENTS

Excipients: boric acid, water for injections, hydrochloric acid, sodium hydroxide
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 vial
8 g/100 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use. For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Pedmarqsi should not be used in neonates under the age of 1 month.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fennec Pharmaceuticals (EU) Limited
Regus House, Harcourt Centre
Block 4 Harcourt Rd, Saint Kevin's
Dublin
D02 HW77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/23/1734/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**VIAL****1. NAME OF THE MEDICINAL PRODUCT**

Pedmarqsi 80 mg/mL solution for infusion
sodium thiosulfate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 100 mL contains 8 g of sodium thiosulfate.

3. LIST OF EXCIPIENTS

Excipients: boric acid, water for injections, hydrochloric acid, sodium hydroxide
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 vial
8 g/100 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use. For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Pedmarqsi should not be used in neonates under the age of 1 month.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Pedmarqsi 80 mg/mL solution for infusion sodium thiosulfate

Read all of this leaflet carefully before you or your child starts receiving this medicine because it contains important information.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor or nurse.
- If you or your child get any side effects, talk to the doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pedmarqsi is and what it is used for
2. What you need to know before you or your child receives Pedmarqsi
3. How Pedmarqsi is given
4. Possible side effects
5. How to store Pedmarqsi
6. Contents of the pack and other information

1. What Pedmarqsi is and what it is used for

Pedmarqsi contains the active substance sodium thiosulfate.

Pedmarqsi is used to reduce the risk of hearing loss from the cancer medicine cisplatin. It is given to children and adolescents aged 1 month to 18 years who are being treated with cisplatin for solid tumours that have not spread to other areas of the body.

2. What you need to know before you or your child receives Pedmarqsi

Do not give Pedmarqsi

if the child is:

- allergic to sodium thiosulfate or any of the other ingredients of this medicine (listed in section 6)
- a baby under the age of 1 month

Warnings and precautions

Talk to a doctor or nurse before you or your child receives Pedmarqsi if the child:

- has had an allergic reaction like a rash, hives or difficulty breathing after a previous dose of sodium thiosulfate
- has a known allergy to chemicals called sulfites – this may mean you or the child is more likely to have an allergic reaction to this medicine
- has poor kidney function or serious kidney disease
- needs a low salt diet because of another medical condition

Other medicines and Pedmarqsi

Tell the doctor or nurse if you or your child is taking, has recently taken or might take any other medicines.

Pregnancy and breast-feeding

This medicine should not be given if you or your child is pregnant (or could be pregnant), or is breast-feeding. This medicine is only given after cisplatin chemotherapy and cisplatin can harm your baby. Discuss with your doctor whether there is a need for contraception both during treatment and for 6 months after treatment.

Pedmarqsi contains boric acid

This medicine contains boric acid which may impair fertility when given chronically.

Pedmarqsi contains sodium

This medicine contains 23 mg sodium (main component of cooking/table salt) in each mL. This is equivalent to 1-2% of the safe dietary intake of sodium for children aged 1 to 17 years and 12% in babies aged 7 to 11 months.

3. How Pedmarqsi is given

Before you or your child will receive this medicine, he/she will be given anti-sickness medicines to help prevent vomiting.

This medicine is a solution that is given as an infusion (drip) into a vein by a doctor or nurse. This is usually done via a tube inserted into a vein in the chest, known as a central line. The infusion is given over 15 minutes. Treatment is started 6 hours after the dose of cisplatin has finished.

The dose of this medicine is worked out based on your size (body surface area) in m^2 , which is calculated from height and weight. The recommended dose for those weighing 10 kg or more is 12.8 g per m^2 ; lower doses are given to those weighing less than 10 kg. Your doctor will work out the dose that is right for you or your child.

If you or your child receives more Pedmarqsi than he/she should

Because the dose is worked out and checked by healthcare professionals, it is unlikely that you or your child will be given the wrong amount. In case of overdose, you or your child may experience nausea, vomiting, changes to levels of sodium, phosphate or potassium in the blood, changes to blood pressure, or acidic blood (metabolic acidosis) which can cause nausea, vomiting, drowsiness and breathlessness. Your doctor may give you or your child symptomatic treatment for these side effects.

If you have any further questions on the use of this medicine, ask the doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

If you or your child has a severe allergic reaction to this medicine with symptoms such as a skin rash, tight chest, wheezing, shortness of breath or feeling cold you or they should tell a doctor or nurse immediately.

Other side effects

The other side effects seen with this medicine are usually mild. The side effects you or your child may experience are:

Very common (may affect more than 1 in 10 people)

- Feeling sick (nausea)
- Vomiting
- Reduced level of phosphate or potassium seen in blood tests

- Increased level of sodium seen in blood tests

Common (may affect more than 1 in 100 people)

- Increased or reduced blood pressure
- Reduced level of calcium seen in blood tests
- Acidic blood (metabolic acidosis) which can cause nausea, vomiting, drowsiness and breathlessness

Reporting of side effects

If you or your child get any side effects, talk to the doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pedmarqsi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pedmarqsi contains

- The active substance is sodium thiosulfate, in anhydrous form.
- The other ingredients are:
 - boric acid (0.25 mg/mL)
 - water for injections
 - hydrochloric acid and sodium hydroxide for pH adjustment (see section 2; Pedmarqsi contains sodium).

What Pedmarqsi looks like and contents of the pack

This medicine is a solution for infusion.

This medicine is a clear and colourless sterile solution supplied in clear glass vials sealed with a rubber stopper and an aluminium flip-off overseal. Each carton contains one vial.

Marketing Authorisation Holder

Fennec Pharmaceuticals (EU) Limited
Regus House, Harcourt Centre
Block 4 Harcourt Rd, Saint Kevin's
Dublin
D02 HW77
Ireland

Manufacturer

MIAS Pharma Limited
Suite 2, Stafford House
Strand Road
Portmarnock
Co. Dublin
Ireland

This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

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The following information is intended **for healthcare professionals only**:

Posology and method of administration*Time of administration in relation to cisplatin*

The timing of sodium thiosulfate administration relative to cisplatin chemotherapy is critical.
If sodium thiosulfate is administered:

- Less than 6 hours after end of cisplatin infusion: may reduce cisplatin efficacy against the tumour
- More than 6 hours after end of cisplatin infusion: may not be effective in preventing ototoxicity.

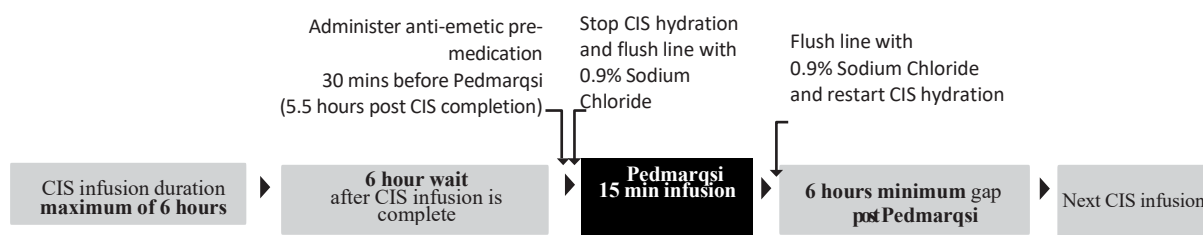
Only use sodium thiosulfate following cisplatin infusion duration of 6 hours or less. Do not use sodium thiosulfate if:

- Cisplatin infusion exceeds 6 hours, or
- A subsequent cisplatin infusion is planned within 6 hours.

When cisplatin is administered on consecutive days, ensure a minimum 6-hour gap after sodium thiosulfate infusion before a subsequent cisplatin infusion is given.

After end of cisplatin infusion:

- Provide highly effective multi-agent intravenous antiemetic therapy 30 minutes prior to administration of sodium thiosulfate i.e. 5.5 hours after completion of cisplatin infusion
- This medicine is a ready to use solution for infusion
- Prepare the required mL of sodium thiosulfate, 80 mg/mL, in a syringe or add to an empty, sterile infusion bag
- Stop cisplatin hydration fluid and flush line with sodium chloride 0.9%
- Infuse sodium thiosulfate over 15 minutes (6 hours after completion of cisplatin infusion)
- Flush line with sodium chloride 0.9% and restart the cisplatin hydration immediately afterwards



CIS = cisplatin

See ‘*Time of administration in relation to cisplatin*’ for critical information regarding timing of sodium thiosulfate administration.

This medicine is provided as a single use vial containing 8 g as 80 mg/mL. The recommended dose of sodium thiosulfate for the prevention of cisplatin-induced ototoxicity is weight based and normalised to body surface area according to the table below:

Body Weight	Dose	Volume
> 10 kg	12.8 g/m ²	160 mL/m ²
5 to 10 kg	9.6 g/m ²	120 mL/m ²
< 5 kg	6.4 g/m ²	80 mL/m ²

Instructions for use and handling, and disposal

This medicine is intended only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

Chemical and physical in-use stability has been demonstrated for 24 hours at controlled room temperature for product stored in polyvinyl chloride, ethylene vinyl acetate and polyolephine intravenous bags.

From a microbial point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.