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RESEARCH**

APPLICATION NUMBER:

212937Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PEDMARK safely and effectively. See full prescribing information for PEDMARK.

PEDMARK® (sodium thiosulfate injection), for intravenous use
Initial U.S. Approval: 1992

INDICATIONS AND USAGE

PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors. (1)

Limitations of Use:

The safety and efficacy of PEDMARK have not been established when administered following cisplatin infusions longer than 6 hours. PEDMARK may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

DOSAGE AND ADMINISTRATION

PEDMARK is not substitutable with other sodium thiosulfate products. (2)

The recommended dose of PEDMARK is based on surface area according to actual body weight.

- Administer PEDMARK as an intravenous infusion over 15 minutes starting 6 hours after completion of cisplatin infusion.
- For multiday cisplatin regimens, administer PEDMARK 6 hours after each cisplatin infusion but at least 10 hours before the next cisplatin infusion.
- Do not start PEDMARK if less than 10 hours before starting the next cisplatin infusion (2)

Actual Body Weight	PEDMARK Dose
Less than 5 kg	10 g/m ²
5 to 10 kg	15 g/m ²
Greater than 10 kg	20 g/m ²

DOSAGE FORMS AND STRENGTHS

Injection: 12.5 grams/100 mL in a single-dose vial. (3)

CONTRAINDICATIONS

History of severe hypersensitivity to sodium thiosulfate or any components. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity:** Immediately discontinue PEDMARK and institute appropriate care. Administer premedications before each subsequent dose. PEDMARK may contain sodium sulfite; patients with sulfite sensitivity may have hypersensitivity reactions. (5.1)
- Hypermnatremia and Hypokalemia:** PEDMARK is not indicated for use in pediatric patients less than 1 month of age. Monitor serum sodium and potassium at baseline and as clinically indicated. Withhold PEDMARK in patients with serum sodium greater than 145 mmol/L (5.2)
- Nausea and Vomiting:** Administer antiemetics prior to each PEDMARK administration. (5.3)

ADVERSE REACTIONS

- Most common adverse reactions ($\geq 25\%$ with difference between arms of $>5\%$ compared to cisplatin alone) in SIOPEL 6 are vomiting, nausea, decreased hemoglobin, and hypernatremia. (6)
- Most common adverse reaction ($\geq 25\%$ with difference between arms of $>5\%$ compared to cisplatin alone) in COG ACCL0431 is hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Fennec Pharmaceuticals, Inc. at 1-833-336-6321, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Renal Impairment: Monitor for signs and symptoms of hypernatremia and hypokalemia more closely if the glomerular filtration rate (GFR) falls below 60 mL/min/1.73m². (5.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

Limitations of Use

The safety and efficacy of PEDMARK have not been established when administered following cisplatin infusions longer than 6 hours. PEDMARK may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

PEDMARK is not substitutable with other sodium thiosulfate products.

Ensure serum sodium level is within normal range prior to initiating PEDMARK [*see Warnings and Precautions (5.2)*].

2.2 Recommended Dosage and Administration

The recommended dose of PEDMARK is based on surface area according to actual body weight as summarized in Table 1.

Table 1. Recommended Dose for PEDMARK

Actual Body Weight	PEDMARK Dose
Less than 5 kg	10 g/m ²
5 to 10 kg	15 g/m ²
Greater than 10 kg	20 g/m ²

Administer PEDMARK as an intravenous infusion over 15 minutes, following cisplatin infusions that are 1 to 6 hours in duration [*see Indications and Usage (1)*].

Infuse PEDMARK as described below to minimize the potential interference with the antitumor activity of cisplatin [*see Clinical Pharmacology (12.1), Clinical Studies (14)*].

- Administer PEDMARK 6 hours after completion of a cisplatin infusion.
- For multiday cisplatin regimens, administer PEDMARK 6 hours after completion of each cisplatin infusion and at least 10 hours before the next cisplatin infusion. Do not administer PEDMARK if the next cisplatin infusion is scheduled to begin in less than 10 hours [*see Clinical Pharmacology (12.3), Clinical Studies (14)*].

2.3 Recommended Premedications

Administer antiemetics before each PEDMARK infusion [*see Warnings and Precautions (5.3)*].

For patients who experience a hypersensitivity reaction, administer antihistamines and glucocorticoids (if appropriate) before each subsequent PEDMARK infusion [*see Warnings and Precautions (5.1)*].

2.4 Dosage Modifications for Adverse Reactions

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2. Recommended PEDMARK Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hypersensitivity [<i>see Warnings and Precautions (5.1)</i>]	Grade 3 or 4	Permanently discontinue PEDMARK.
Hypernatremia [<i>see Warnings and Precautions (5.2)</i>]	>145 mmol/L	Withhold PEDMARK until sodium is within normal limits. Resume at the same dose.
Hypokalemia [<i>see Warnings and Precautions (5.2)</i>]	Grade 3 or 4	Withhold PEDMARK until potassium is within normal limits. Resume at the same dose.
Other Adverse Reactions [<i>see Adverse Reactions (6.1)</i>]	Grade 3	Withhold until \leq Grade 1. Resume at the same dose.
	Grade 4	Permanently discontinue PEDMARK.

2.5 Preparation

- Calculate the dose (grams) and determine the number of vial(s) needed.
- Visually inspect the contents of the vial for particulate matter and discoloration. Discard the vial(s) if discolored or contains visible particulates.
- Withdraw the calculated dose from the vial(s) into a syringe or transfer the calculated dose into an empty infusion bag.
- Use immediately after withdrawing into a syringe or transferring to an empty infusion bag. If not used immediately, PEDMARK can be stored in an infusion bag for no more than 18 hours at 20°C to 22°C (68°F to 72°F). Discard unused portion.

No incompatibilities have been observed between PEDMARK with infusion bags made of polyvinyl chloride, ethylene vinyl acetate, or polyolephin.

3 DOSAGE FORMS AND STRENGTHS

Injection: 12.5 grams/100 mL (125 mg/mL) clear, colorless solution in a single-dose vial

4 CONTRAINDICATIONS

PEDMARK is contraindicated in patients with history of a severe hypersensitivity to sodium thiosulfate or any of its components [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions occurred in 8% to 13% of patients in clinical trials [*see Adverse*

Reactions (6.1)].

PEDMARK is contraindicated in patients with a history of severe hypersensitivity to sodium thiosulfate or its components [see *Contraindications (4)*].

Monitor patients for hypersensitivity reactions. Immediately discontinue PEDMARK and institute appropriate care if a hypersensitivity reaction occurs [see *Dosage and Administration (2.4)*]. Administer antihistamines or glucocorticoids (if appropriate) before each subsequent administration of PEDMARK [see *Dosage and Administration (2.3)*].

PEDMARK may contain sodium sulfite. Sulfite exposure can cause hypersensitivity reactions, including anaphylactic symptoms and life-threatening or severe asthma episodes, in patients with sulfite sensitivity. The overall prevalence of sulfite sensitivity in the general population is unknown; sulfite sensitivity is seen more frequently in people with asthma compared to people without asthma.

5.2 Hypernatremia and Hypokalemia

At the recommended dosage of PEDMARK, a 20 g/m² dose delivers a sodium load of 162 mmol/m², a 15 g/m² dose delivers a sodium load of 121 mmol/m² and a 10 g/m² dose delivers a sodium load of 81 mmol/m².

Hypernatremia occurred in 12% to 26% of patients in clinical trials, including a single Grade 3 case. Hypokalemia occurred in 15% to 27% of patients in clinical trials, with Grade 3 or 4 occurring in 9% to 27% [see *Adverse Reactions (6.1)*].

Pediatric patients younger than 1 month have less well-developed sodium homeostasis compared to other pediatric patients. PEDMARK is not indicated and not recommended for use in pediatric patients younger than 1 month of age.

Monitor serum sodium and potassium levels at baseline and as clinically indicated. Do not initiate PEDMARK infusions in patients with baseline serum sodium greater than 145 mmol/L [see *Clinical Pharmacology (12.2)*, *Dosage and Administration (2.3)*].

Withhold PEDMARK in patients with serum sodium greater than 145 mmol/L [see *Clinical Pharmacology (12.2)*, *Dosage and Administration (2.4)*].

Monitor for signs and symptoms of hypernatremia and hypokalemia. Provide supportive care and supplementation as appropriate.

5.3 Nausea and Vomiting

Nausea occurred in 8% to 40% of patients in clinical trials, with Grade 3 or 4 in 3.8 to 8%. Vomiting occurred in 7% to 85% of patients in clinical trials, with Grade 3 or 4 in 7% to 8% [see *Adverse Reactions (6.1)*].

Administer antiemetics prior to each PEDMARK administration [see *Dosage and Administration (2.3)*]. Provide additional antiemetics and supportive care as appropriate.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Warnings and Precautions (5.1)*]
- Hypernatremia and Hypokalemia [see *Warnings and Precautions (5.2)*]
- Nausea and Vomiting [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

SIOPEL 6

The safety of PEDMARK was evaluated in SIOPEL 6 [see *Clinical Studies (14)*]. Patients received cisplatin-based chemotherapy with or without PEDMARK administered at a dose of 10 g/m², 15 g/m², or 20 g/m² (depending on body weight) as an intravenous infusion over 15 minutes starting 6 hours after completion of each cisplatin infusion. Patients received PEDMARK for a median of 6 cycles (range: 2 to 8 cycles) during a median of 94 days (range: 2.1 to 5.2 months) of cisplatin-based chemotherapy.

Serious adverse reactions occurred in 40% of patients who received PEDMARK in combination with cisplatin-based chemotherapy. Serious adverse reactions in >5% of patients who received PEDMARK included infection, decreased neutrophil count, and pyrexia.

PEDMARK was permanently discontinued due to an adverse reaction in 1 patient; this patient discontinued PEDMARK for Grade 2 hypersensitivity.

The most common adverse reactions ($\geq 25\%$ with difference between arms of $>5\%$ compared to cisplatin alone) were vomiting, nausea, decreased hemoglobin, and hypernatremia.

Table 3 summarizes the adverse reactions reported in SIOPEL 6.

Table 3. Adverse Reactions ($\geq 10\%$) in Patients Who Received PEDMARK and Cisplatin with a Difference Between Arms of $>5\%$ Compared to Cisplatin Alone in SIOPEL 6

Adverse Reaction	PEDMARK + Cisplatin (N = 53)		Cisplatin Alone (N = 56)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Vomiting	85	8	54	3.6
Nausea	40	3.8	30	5
Investigations				
Decreased Hemoglobin	34	19	29	16
Metabolism and nutrition disorders				
Hypernatremia	26	1.9	3.6	0
Hypokalemia	15	9	1.8	0
Hypophosphatemia	15	9	1.8	0
Hypermagnesemia	11	9	5	3.6
General disorders				
Pyrexia	15	0	9	0

COG ACCL0431

The safety of PEDMARK was evaluated in COG ACCL0431 [see *Clinical Studies (14)*]. Patients received cisplatin-based chemotherapy with or without PEDMARK, administered at a dose that is bioequivalent to the recommended dose as an intravenous infusion over 15 minutes starting 6 hours after completion of each cisplatin infusion. Patients who received PEDMARK were treated for a median of 3 cycles (range: 1 to 6) during a median of 15 weeks of cisplatin-based chemotherapy.

Serious adverse reactions occurred in 36% of patients who received PEDMARK in combination with cisplatin-based chemotherapy. Serious adverse reactions in >5% of patients who received PEDMARK included febrile neutropenia, decreased neutrophil count, decreased platelet count, decreased white blood cell count, anemia, stomatitis, infections, decreased lymphocyte count, and increased alanine aminotransferase (ALT).

PEDMARK was permanently discontinued due to an adverse reaction in 1 patient; this patient discontinued PEDMARK for Grade 2 hypersensitivity.

The most common adverse reaction ($\geq 25\%$ with difference between arms of >5% compared to cisplatin alone) was hypokalemia.

Table 4 summarizes the adverse reactions reported in COG ACCL0431.

Table 4. Adverse Reactions ($\geq 10\%$) in Patients Who Received PEDMARK and Cisplatin with a Difference Between Arms of >5% Compared to Cisplatin Alone in COG ACCL0431

Adverse Reaction	PEDMARK + Cisplatin (N = 59)		Cisplatin Alone (N = 64)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders				
Hypokalemia	27	27	20	20
Hypophosphatemia	20	20	11	11
Hyponatremia	14	12	6	6
Hypernatremia	12	0	6	0
Gastrointestinal disorders				
Stomatitis	14	14	6	6

6.2 Postmarketing Experience/Spontaneous Reports

The following adverse reactions have been identified from spontaneous reports based on medical literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Disorders: hypertension, hypotension

Metabolic and Nutritional Disorders: metabolic acidosis, hypocalcemia

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on PEDMARK used in pregnant women to evaluate for a drug-associated risk. Oral or intravenous administration of sodium thiosulfate during the period of organogenesis resulted in no signs of malformations or lethality, but at doses and exposures that were lower than those in humans (*see Data*).

PEDMARK is administered following cisplatin infusions, which can cause embryo-fetal harm. Refer to cisplatin prescribing information for additional information.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In animal studies, sodium thiosulfate was not embryotoxic or teratogenic in pregnant mice, rats, hamsters, or rabbits at daily (5 to 13 daily doses during the period of organogenesis) oral maternal doses of up to 550, 400, 400, and 580 mg/kg/day (0.08 to 0.35 times the highest clinical dose of 20 g/m² based on body surface area [BSA]), respectively, of sodium thiosulfate; exposure in these animals compared to humans may be much lower due to poor oral bioavailability. Sodium thiosulfate was not embryotoxic or teratogenic in hamsters following a total daily dose of 1500 mg/kg (0.38 times the highest clinical dose of 20 g/m² based on BSA). Additionally, an intravenous pharmacokinetic study in gravid ewes indicated that sodium thiosulfate does not cross the placenta.

8.2 Lactation

There are no data on the presence of sodium thiosulfate in human milk or its effects on the breastfed child or on milk production.

PEDMARK is administered in combination with cisplatin. Refer to cisplatin prescribing information for additional information.

8.4 Pediatric Use

The safety and effectiveness of PEDMARK have been established to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

The safety and effectiveness of PEDMARK have not been established in pediatric patients younger than 1 month old or in pediatric patients with metastatic cancer.

PEDMARK is not recommended in pediatric patients younger than 1 month old due to the increased risk of hypernatremia [*see Warnings and Precautions (5.2)*].

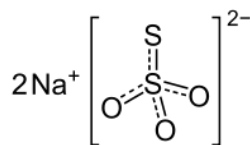
8.6 Renal Impairment

Sodium thiosulfate is substantially excreted by the kidney [*see Clinical Pharmacology (12.3)*]. No dose adjustment is recommended for patients with renal impairment or end-stage renal disease. Monitor for signs and symptoms of hypernatremia and hypokalemia more closely if the GFR falls below 60 mL/min/1.73 m² [*see Warnings and Precautions (5.2)*].

11 DESCRIPTION

Sodium thiosulfate anhydrous is an inorganic salt with a molecular formula of Na₂S₂O₃ and a

molecular weight of 158.11 g/mol. The structural formula is:



It is a white to off-white crystalline solid that is soluble in water, but insoluble in alcohol. The aqueous solution has a pH ranging from 6.5 to 8.0.

PEDMARK (sodium thiosulfate injection) is a sterile, preservative-free, clear, colorless solution in a single-dose vial for intravenous use with a pH between 7 and 9. Each vial contains the equivalent of 12.5 grams of sodium thiosulfate pentahydrate (provided as sodium thiosulfate anhydrous 8 grams) in 100 mL solution (125 mg/mL). Each mL contains the equivalent of 125 mg of sodium thiosulfate pentahydrate (provided as sodium thiosulfate anhydrous 80 mg) and 0.25 mg boric acid. Sodium hydroxide and hydrochloric acid may have been used for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cisplatin-induced ototoxicity is caused by irreversible damage to hair cells in the cochlea hypothesized to be due to a combination of reactive oxygen species (ROS) production and direct alkylation of DNA leading to cell death. Sodium thiosulfate interacts directly with cisplatin to produce an inactive platinum species. In addition, sodium thiosulfate can enter cells through the sodium sulfate cotransporter 2 and cause intracellular effects such as the increase in antioxidant glutathione levels and inhibition of intracellular oxidative stress. Both activities may contribute to the ability of sodium thiosulfate to reduce the risk of ototoxicity.

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

12.2 Pharmacodynamics

Serum Sodium Level

A 20 g/m² dose delivers a sodium load of 162 mmol/m², a 15 g/m² dose delivers a sodium load of 121 mmol/m², and a 10 g/m² dose delivers a sodium load of 81 mmol/m². In SIOPEL 6, the recommended dosage resulted in an average transient increase in serum sodium levels of approximately 6 mmol/L at 1 hour after infusion [*see Warnings and Precautions (5.2)*] and levels had returned to baseline by 18 hours or 24 hours after administration.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of thiosulfate was assessed in pediatric patients. At the recommended dosage, the mean (±SD) maximum concentration (C_{max}) was 13 ± 1.2 mM. The C_{max} of thiosulfate increased proportionally to dose over the range of 4 g/m² to 20 g/m². No accumulation of thiosulfate is expected following administration of PEDMARK on two consecutive days.

Distribution

Sodium thiosulfate does not bind to human plasma proteins. Sodium thiosulfate is an inorganic salt and thiosulfate anions do not readily cross cell membranes. The mean volume of distribution of thiosulfate is 0.23 L/kg.

Elimination

The mean half-life ($t_{1/2}$) of thiosulfate is approximately 20 minutes to 50 minutes. The mean total clearance of thiosulfate is 2.2 mL/min/kg in patients with fully developed renal function (age approximately 1 year). Renal clearance accounts for approximately 50% of total clearance in patients with fully developed renal function.

Metabolism

Thiosulfate is an endogenous intermediate product of sulfur-containing amino acid metabolism. Thiosulfate is metabolized through thiosulfate sulfur transferase and thiosulfate reductase to sulfite, which is oxidized to sulfate.

Excretion

After administration of sodium thiosulfate, approximately 50% of the administered sodium thiosulfate was excreted unchanged in urine and >95% of the dose excreted in urine occurs within the first 4 hours after administration.

Specific Populations

Patients with Renal Impairment

Thiosulfate C_{max} increased approximately 25% and AUC increased approximately 2-fold in subjects on hemodialysis (GFR 0 to 6 mL/min/1.72 m², estimated by the modification of diet in renal disease [MDRD] equation) compared to subjects with normal renal function (GFR >70 mL/min/1.72 m², MDRD).

Drug Interaction Studies

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 or CYP3A4 at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the potential carcinogenicity of sodium thiosulfate. In an in vitro Bacterial Reverse Mutation Assay (Ames Assay), sodium thiosulfate was not mutagenic in the absence of metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538, nor in the presence of metabolic activation in strains TA98, TA1535, TA1537, or TA1538 or *E. coli* strain WP2. Sodium thiosulfate at up to 1000 µM did not increase the frequency of sister chromatid exchanges in human lymphocytes in vitro.

There are no animal studies examining the effects of sodium thiosulfate on fertility.

14 CLINICAL STUDIES

The efficacy of PEDMARK in reducing the risk of cisplatin-associated ototoxicity was evaluated in two multicenter studies: SIOPEL 6 and COG ACCL0431.

SIOPEL 6

SIOPEL 6 (NCT00652132) was a multicenter, randomized, controlled, open-label study. Eligible patients were between 1 month and 18 years of age and were receiving cisplatin-based chemotherapy for standard-risk hepatoblastoma. Patients were randomized 1:1 to receive 6 cycles of perioperative cisplatin-based chemotherapy without (cisplatin alone arm) or with PEDMARK (PEDMARK + cisplatin arm). Patients received PEDMARK at a dose based on body weight administered intravenously over 15 minutes, beginning 6 hours after completion of each cisplatin infusion. Doses of PEDMARK were 10 g/m² for patients weighing <5 kg; 15 g/m² for patients weighing 5 kg to 10 kg; and 20 g/m² for patients weighing >10 kg. Randomization was stratified by country, age (above vs below 15 months), and PRETEXT (I and II vs III). The major efficacy outcome measure was hearing loss defined as a Brock Grade ≥1; hearing was assessed using pure tone audiometry after study treatment or at an age of at least 3.5 years, whichever was later.

A total of 114 patients were randomized, 61 patients to the PEDMARK + cisplatin arm and 53 patients to the cisplatin alone arm. The median age was 1.1 years (range: 1.2 months to 8.2 years); 55% were male; 60% were White, 11% were Asian, and 1.8% were Black or African American.

The incidence of hearing loss was lower in the PEDMARK + cisplatin arm compared with the cisplatin alone arm. Efficacy results are provided in Table 5.

Table 5: Efficacy Results for SIOPEL 6

	PEDMARK + Cisplatin (N = 61^b)	Cisplatin Alone (N = 53^b)
Patients Who Experienced Hearing Loss		
Yes, n (%)	24 (39)	36 (68)
No, n (%)	37 (61)	17 (32)
Unadjusted relative risk (95% CI)	0.58 (0.40, 0.83)	
Adjusted relative risk (95% CI) ^a	0.58 (0.41, 0.81)	

^a From Cochran-Mantel-Haenszel test stratified by country group, age group, and PRETEXT group

^b 6 patients who received PEDMARK + cisplatin and 7 patients who received cisplatin alone did not have hearing assessed and were assumed to have hearing loss.

COG ACCL0431

COG ACCL0431 (NCT00716976) was a multicenter, randomized, controlled, open-label study. Eligible patients were between 1 and 18 years of age and were receiving a chemotherapy regimen that included a cumulative cisplatin dose of 200 mg/m² or higher, with individual cisplatin doses to be infused over 6 hours or less. Patients were randomized 1:1 to receive cisplatin-based chemotherapy without (cisplatin alone arm) or with PEDMARK (PEDMARK + cisplatin arm). Cisplatin was administered according to each site's disease-specific treatment protocols. Patients received PEDMARK intravenously starting 6 hours after the completion of

each cisplatin infusion, at a dose bioequivalent to the recommended dose. The PEDMARK infusion must have been completed at least 10 hours before the next cisplatin infusion if the treatment protocol required multiple daily doses of cisplatin. Randomization was stratified by prior cranial radiation (yes vs no); for patients without prior cranial radiation, randomization was further stratified by age (<5 years vs ≥5 years) and duration of cisplatin infusion (<2 hours vs ≥2 hours). The major efficacy outcome measure was hearing loss assessed by American Speech-Language-Hearing Association (ASHA) criteria; hearing was assessed at baseline and 4 weeks after the final course of cisplatin.

A total of 125 pediatric patients were randomized, 61 patients to the PEDMARK + cisplatin arm and 64 patients to the cisplatin alone arm. The efficacy was evaluated in patients with localized disease in the ITT population (n = 77). The median age was 8 years (range: 1 to 18); 61% were male; 62% were White, 14% were Black or African American, and 2.6% were Asian. The median Karnofsky or Lansky performance status was 90 (range: 50 to 100). Underlying diagnosis included medulloblastoma (27%), osteosarcoma (26%), germ cell tumor (23%), neuroblastoma (10%), hepatoblastoma (8%), atypical teratoid/rhabdoid tumor (2.6%), choroid plexus carcinoma (1.3%), and anaplastic astrocytoma (1.3%); 7% had prior cranial radiation.

The incidence of hearing loss was lower in the PEDMARK + cisplatin arm compared with the cisplatin alone arm. Efficacy results are provided in Table 6.

Table 6: Efficacy Results for COG ACCL0431 – Patients with Localized Disease

Patients Who Experienced Hearing Loss	PEDMARK + Cisplatin (N = 39^b)	Cisplatin Alone (N = 38^b)
Yes, n (%)	17 (44)	22 (58)
No, n (%)	22 (56)	16 (42)
Unadjusted relative risk (95% CI)	0.75 (0.48, 1.18)	
Adjusted relative risk (95% CI) ^a	0.84 (0.53, 1.35)	

^a From Cochran-Mantel-Haenszel test stratified by prior cranial irradiation, age group, and duration of cisplatin infusion

^b 8 patients who received PEDMARK + cisplatin and 5 patients who received cisplatin alone did not have hearing assessed and were assumed to have hearing loss.

16 HOW SUPPLIED/STORAGE AND HANDLING

PEDMARK (sodium thiosulfate injection) is a clear, colorless, sterile solution in a flint glass single-dose vial with rubber stopper and capped with aluminum overseal, supplied as:

- 12.5 grams/100 mL (125 mg/mL) single-dose vial, NDC 73077-010-01

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity

Inform patients and caregivers that PEDMARK can cause hypersensitivity reactions [*see Warnings and Precautions (5.1)*].

Hypernatremia and Hypokalemia

Inform patients and caregivers that PEDMARK can cause hypernatremia and hypokalemia, and to promptly report signs and symptoms consistent with these electrolyte abnormalities [*see Warnings and Precautions (5.2)*].

Nausea and Vomiting

Inform patients and caregivers that PEDMARK can cause nausea and vomiting [*see Warnings and Precautions (5.3)*].

Distributed by Fennec Pharmaceuticals, Inc., 221 River Street, Hoboken, NJ 07030

PEDMARK is a registered trademark of Fennec Pharmaceuticals Inc.

US PATENTS 10,596,190; 10,792,363; 11,291,728

Patient Information
PEDMARK® (ped-mark)
(sodium thiosulfate injection)
for intravenous use

What is PEDMARK?

PEDMARK is a prescription medicine used to decrease the risk of hearing loss in children 1 month of age and older who are receiving cisplatin for solid tumors (cancer) that have not spread to other parts of the body.

It is not known if PEDMARK is safe and effective when given after cisplatin infusions longer than 6 hours.

It is not known if PEDMARK is safe and effective in children less than 1 month of age. PEDMARK is not recommended in children younger than 1 month of age.

Who should not receive PEDMARK?

Do not allow your child to receive PEDMARK if they have had a severe allergic reaction to sodium thiosulfate or any of the other ingredients in PEDMARK. See the end of this leaflet for a complete list of ingredients in PEDMARK.

Before receiving PEDMARK, tell your healthcare provider about all of your child's medical conditions, including if your child:

- is allergic to sulfites
- has asthma
- has kidney problems
- is on a low salt diet
- is pregnant or plans to become pregnant. It is not known if PEDMARK will harm the unborn baby.
- is breastfeeding or plans to breastfeed. It is not known if PEDMARK passes into the breastmilk.

You should also read the cisplatin Prescribing Information for important pregnancy and breastfeeding information.

Tell your healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines your child takes. Keep a list of them to show to your healthcare provider or pharmacist when your child gets a new medicine.

How will your child receive PEDMARK?

- PEDMARK will be given to your child as an intravenous (IV) infusion into a vein, usually over 15 minutes.
- PEDMARK is given 6 hours after the end of a cisplatin treatment. Your healthcare provider may decide not to treat your child with PEDMARK if it is too soon before the next cisplatin treatment.
- Your healthcare provider may temporarily stop or completely stop your child's treatment with PEDMARK if your child develops certain side effects.

What are the possible side effects of PEDMARK?

PEDMARK may cause serious side effects, including:

- **Allergic reactions.** Allergic reactions can happen with PEDMARK and can be serious and life-threatening. Your healthcare provider will monitor your child for allergic reactions during the PEDMARK infusion. Your healthcare provider will stop the infusion and provide treatment if your child has an allergic reaction. If your child has an allergic reaction, your healthcare provider will give your child certain medicines before each PEDMARK infusion.

Tell your healthcare provider right away if your child develops any of these signs of an allergic reaction:

- rash
- hives (raised bumps)
- chest tightness
- wheezing
- trouble breathing
- swelling of the face, lips, tongue, or throat

- **Increased salt (sodium) and decreased potassium levels in the blood.** Changes in these levels are common with PEDMARK but can also be serious. Your healthcare provider will do blood tests to check your child's sodium and potassium levels before starting and as needed during treatment with PEDMARK. Tell your healthcare provider right away if your child develops any of the following signs or symptoms:

- feeling tired or weak
- feeling restless
- muscle weakness
- seizures

- **Nausea and vomiting.** Nausea and vomiting are common with PEDMARK but can also be serious. Your healthcare provider will give your child medicines before each PEDMARK infusion to help prevent nausea and vomiting.

The most common side effects of PEDMARK include decreased red blood cells (anemia).

These are not all the possible side effects of PEDMARK.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Fennec Pharmaceuticals, Inc. at 1-833-336-6321.

General information about the safe and effective use of PEDMARK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about PEDMARK that is written for health professionals.

What are the ingredients in PEDMARK?

Active ingredient: sodium thiosulfate anhydrous

Inactive ingredients: boric acid. Sodium hydroxide and hydrochloric acid may have been used for pH adjustment.

Distributed by Fennec Pharmaceuticals, Inc., 221 River Street, Hoboken, NJ 07030

PEDMARK is a registered trademark of Fennec Pharmaceuticals, Inc.

For more information, go to www.fennecpharma.com or call 1-833-336-6321.

US PATENTS 10,596,190; 10,792,363; 11,291,728

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: 9/2022

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 1, 2022
Container label- received on March 23, 2022

LOT: #####
EXP: MMYYY

NDC 73077-010-01

100 mL
Sterile

Each mL contains the equivalent of sodium thiosulfate pentahydrate 125 mg (provided as sodium thiosulfate anhydrous 80 mg), 0.25 mg boric acid, NF and water for injection, USP. May contain sodium hydroxide and hydrochloric acid for pH adjustment.

Recommended Dosage:
See prescribing information

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

Distributed by:
Fenneo Pharmaceuticals, Inc.
221 River Street 9th Floor
Hoboken, NJ 07030
L100218.01 Rev. 07/2020

pedmarkTM
(sodium thiosulfate injection)

12.5 grams/100 mL (125 mg/mL)

For Intravenous Use Only.
Single-dose vial. Discard unused portion.
Rx only

Do Not Substitute with Other Sodium Thiosulfate Products



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA B DONOGHUE
09/20/2022 01:59:40 PM