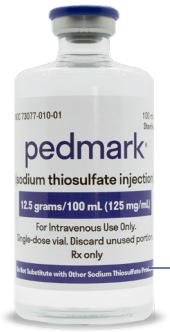
There is only one PEDMARK®

Per the FDA Approved Label, PEDMARK® Is Not Substitutable With Other Sodium Thiosulfate Products.



Do Not Substitute with Other Sodium Thiosulfate Products

Possible Safety Concerns When PEDMARK® Is Substituted Acute Risk Associated With Intravenous (IV) Potassium Chloride (KCl) Excipient Pushed Over 15 Minutes in a Child[1]:

	KCl Concentration (mEq/L)			Rate of KCl Infusion (mEq/kg/h)		
	PEDMARK®[2]	LRS[3]+KCl[a]	Sodium Thiosulfate (STS) Product[4b]	PEDMARK®[2]	LRS[3]+KCl[a]	STS Product[4b]
Infusion for 1-mo-old (BSA=0.25 m^2), weight=4.2 kg	0	14	30	0	0.06	0.6
Infusion for 2-yr-old (BSA=0.54 m^2), weight=12.8 kg		24			0.09	0.8

[a] LRS+KCl=Lactated Ringer's Solution with added KCl, administered according to the CHOP protocol and used independently for electrolyte balance.
[b] STS Product=Compounded STS drug product prepared using Hope STS, diluted 1:1 with water, and administered by 15-minute IV infusion according to PEDMARK® label.

- IV infusion of KCl recommended only for patients with severe hypokalemia (serum levels < 2.0 mEq/L) that cannot be rapidly corrected via the oral route[5]
- High concentration KCl should be administered slowly and guided by continuous electrocardiogram (ECG) monitoring and serum K
- KCl infusion rates for STS Product substantially exceed max. recommended infusion rates for pediatric patients who have severe hypokalemia
- Hyperkalemia can potentially lead to cardiac arrhythmias and sudden cardiac death

Risk of Cardiac Adverse Events Associated With IV KCl[5]

Safety and effectiveness of potassium chloride injection in pediatric patents have not been established by adequate and well-controlled studies.[5]

Risk of Hyperkalemia

- Hyperkalemia can be asymptomatic and manifest only by increased serum potassium concentrations and/or characteristic ECG changes. Cardiac conduction disorders (including complete heart block) and other cardiac arrhythmias, some fatal, can develop at any time during hyperkalemia. Continuous electrocardiogram monitoring may be necessary to aid in the detection of cardiac arrhythmias due to hyperkalemia

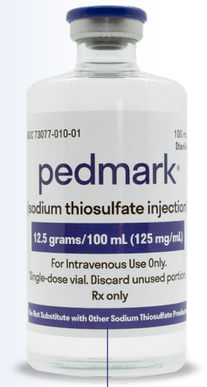
An Increased Infusion Rate of KCl May Cause[5]:

- Hyperkalemia, including disturbances in cardiac conduction and arrhythmias such as bradycardia, heart block, asystole, ventricular tachycardia, and ventricular fibrillation. Presence of any ECG findings suspected to be caused by hyperkalemia should be considered a medical emergency. If hyperkalemia is present or suspected, discontinue the infusion immediately and institute close ECG, laboratory and other monitoring, and, as necessary, corrective therapy to reduce serum potassium concentrations
- Muscle weakness (up to and including muscular and respiratory paralysis, paresthesia of extremities) may occur as a complication of hyperkalemia
- Gastrointestinal symptoms (ileus, nausea, vomiting, abdominal pain)

PEDMARK® contains no KCl as an excipient, which eliminates any potassium infusion risk

Please read the accompanying full Prescribing Information in this booth, including Patient Product Information, or go to PEDMARK.com.

Unique Characteristics of PEDMARK® (sodium thiosulfate injection)



Do Not Substitute with Other Sodium Thiosulfate Products

- PEDMARK® is the only STS formulation that has been evaluated in randomized clinical trials for its safety and efficacy in pediatric patients 1 month and older[2]
- PEDMARK® is designed to be safe at the higher doses required for otoprotection
- PEDMARK® does not contain potassium chloride and has low levels of boron in its formulation
- Ease of use: PEDMARK® is ready to infuse and can be safely administered multiple times as required by chemotherapy treatment protocols
- **According to the PEDMARK® Prescribing Information, PEDMARK® is not substitutable with other sodium thiosulfate products**
- There is no generic version of PEDMARK® available on the market
- The dose of PEDMARK®, including dose modifications for younger and lower-weight patients, are specific to the PEDMARK® formulation
- The PEDMARK® Prescribing Information includes guidance on pre-medication and safety precautions to ensure the product may be safely administered to patients

IMPORTANT SAFETY INFORMATION

- PEDMARK is contraindicated in patients with history of a severe hypersensitivity to sodium thiosulfate or any of its components.
- Hypersensitivity reactions occurred in 8% to 13% of patients in clinical trials. Monitor patients for hypersensitivity reactions. Immediately discontinue PEDMARK and institute appropriate care if a hypersensitivity reaction occurs. Administer antihistamines or glucocorticoids (if appropriate) before each subsequent administration of PEDMARK. PEDMARK may contain sodium sulfite; patients with sulfite sensitivity may have hypersensitivity reactions, including anaphylactic symptoms and life-threatening or severe asthma episodes. Sulfite sensitivity is seen more frequently in people with asthma.
- PEDMARK is not indicated for use in pediatric patients less than 1 month of age due to the increased risk of hypernatremia or in pediatric patients with metastatic cancers.

Why Not Nithiodote STS from Hope Pharma?

- In 2011, FDA approved Hope's New Drug Application (NDA) #201444 for Nithiodote® (co-packaged sodium nitrite and STS) for sequential use for the treatment of acute cyanide poisoning that is judged to be life-threatening. Any other use of this product would be considered "off-label".[6]
- In 2012, FDA approved Hope's NDA #203923 for STS alone for sequential use with sodium nitrite for the same indication[7]
- The separation of Nithiodote® components was intended only to provide flexibility in managing supply stocks due to different expiration dates and not to provide an avenue for using STS independently of the combination product[8]
- "There are no randomized controlled clinical trials" for this product, including trials with children. Rather, "[a]vailable human safety information is based largely on anecdotal case reports and case series of limited scope"[4]
- In 2018, Hope announced the submission of a supplemental NDA for STS "to prevent a potential complication associated with the administration of a chemotherapeutic agent" which to date has not been approved[9]
- There are currently no published data in the literature or FDA approvals related to reducing the risk of chemotherapy-induced ototoxicity

Overview When Substituting PEDMARK® With Nithiodote STS from Hope Pharma

Formulation Component	PEDMARK®[2]	STS from Hope Pharmaceuticals[4]
STS Pentahydrate Equivalent Concentration	125 mg/mL	250 mg/mL
KCl Concentration	0	0.06 mEq K/mL
Boric Acid Concentration	0.25 mg/mL	2.8 mg/mL
Infusion Rate	15 min	"slow"

- PEDMARK® formulation does not contain KCl
- When using the Hope STS according to the PEDMARK® label, boron exposure may result in exposures higher than the National Institutes of Health specified tolerable upper intake levels for boron
- PEDMARK® is formulated for pediatric use: it does not contain KCl and has minimal boron
- Compounding STS from Hope Pharmaceuticals according to the PEDMARK® label may result in boron exposures higher than tolerable upper intake levels specified by the National Institutes of Health

There Is No Substitute for PEDMARK®

Why the FDA-approved Labeling Recommends Against Substitution for PEDMARK®

Formulation Component	PEDMARK®[2]	STS from Hope Pharmaceuticals
FDA-approved STS formulation for cisplatin-induced ototoxicity	Yes	No
Unique formulation specifically developed for pediatric use	Yes	No
Clinically tested in children in two phase 3 randomized trials	Yes	No
No potassium chloride and low levels of boron	Yes	No
Ready to administer	Yes	No
Can be safely administered multiple times as required by chemotherapy treatment protocols	Yes	No

IMPORTANT SAFETY INFORMATION (CONT'D)

- 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% of patients. Monitor serum sodium and potassium at baseline and as clinically indicated. Withhold PEDMARK in patients with baseline serum sodium greater than 145 mmol/L.
- Monitor for signs and symptoms of hypernatremia and hypokalemia more closely if the glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m^2.
- Administer antiemetics prior to each PEDMARK administration. Provide additional antiemetics and supportive care as appropriate.
- The most common adverse reactions (≥25% with difference between arms of >5% compared to cisplatin alone) in SIOPEL 6 were vomiting, nausea, decreased hemoglobin, and hypernatremia.

Please see full Prescribing Information for PEDMARK.

References: 1. Data on file. Fennec Pharmaceuticals, Inc. **2.** PEDMARK [package insert]. Hoboken, NJ: Fennec Pharmaceuticals, Inc.; September 2022. **3.** Lactated Ringer's Injection, USP [package insert]. Deerfield, IL: Baxter Healthcare Corporation; October 2019. **4.** Nithiodote [package insert]. Scottsdale, AZ: Hope Pharmaceuticals; 2017. **5.** Potassium Chloride Injection in Plastic Container. [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2019. **6.** Center for Drug Evaluation and Research. Approval package for 2014440rig1s000. Accessed August 23, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201444_nithiodote_toc.cfm. **7.** Center for Drug Evaluation and Research. Approval package for 2039230rig1s000. Accessed August 23, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203923_sodium_thiosulfate_toc.cfm **8.** Center for Drug Evaluation and Research. Summary Review. Accessed August 23, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203923_sodium_thiosulfate_toc.cfm. **9.** Hope Pharmaceuticals. Hope Pharmaceuticals files new supplemental application to the Food and Drug Administration for sodium thiosulfate solution for injection. Press Release. June 7, 2018. Accessed August 23, 2023. https://www.globenewswire.com/news-release/2018/06/07/1518202/0/en/Hope-Pharmaceuticals-Files-Supplemental-New-Drug-Application-to-the-Food-and-Drug-Administration-for-Sodium-Thiosulfate-Injection.html#:~:text=SCOTTSDALE%2C%20Ariz.%2C%20June%2007,complication%20associated%20with%20the%20administration

pedmark® (sodium thiosulfate injection)

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