Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Sodium thiosulfate injection (Pedmark)	MP-RX-FP-160-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Sodium thiosulfate injection (Pedmark®), an agent approved by the Food and Drug Administration (FDA) ndicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

Background Information

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.

On September 20, 2022, the U.S. Food and Drug Administration (FDA) approved Pedmark (sodium thiosulfate) for the prevention of cisplatin-induced ototoxicity in pediatric patients aged 1 month and older with localized, non-metastatic solid tumors. This approval was based on data from two multicenter, open-label, randomized controlled trials: SIOPEL 6 and COG ACCL0431, which evaluated its efficacy in children undergoing cisplatin-based chemotherapy (FDA, 2022).

The SIOPEL 6 trial involved 114 patients with standard-risk hepatoblastoma undergoing six cycles of perioperative cisplatin-based chemotherapy. Participants were randomly assigned (1:1) to receive either cisplatin alone (n=53) or cisplatin combined with Pedmark (n=61). 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). Pedmark was administered intravenously over 15 minutes, starting 6 hours after completing each cisplatin infusion, with dosing based on body weight: 10 g/m² for patients under 5 kg, 15 g/m² for those between 5 kg and 10 kg, and 20 g/m² for those over 10 kg. The primary outcome was the incidence of Brock Grade ≥ 1 hearing loss, evaluated via pure tone audiometry after treatment or when patients reached at least 3.5 years of age. The study showed a reduced rate of hearing loss in the Pedmark group (39%) compared to the cisplatin-only group (68%), with an unadjusted relative risk of 0.58 (95% CI: 0.40–0.83) (FDA, 2022; Fennec Pharmaceuticals, 2022).

The COG ACCL0431 (NCT00716976) was a multicenter, randomized, controlled, open-label trial that included 125 pediatric patients (the median age was 8 years [range: 1 to 18]) receiving cisplatin-based chemotherapy for solid tumors, with cumulative doses of at least 200 mg/m². Patients were randomized (1:1) to receive cisplatin with Pedmark (n=61) or cisplatin alone (n=64). Hearing loss was assessed in a subset of 77 patients with localized, non-

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metastatic solid tumors using the American Speech-Language-Hearing Association (ASHA) criteria, measured at baseline and four weeks after the last cisplatin dose. Results showed that hearing loss occurred less frequently in the Pedmark group (44%) compared to the cisplatin-alone group (58%), with an unadjusted relative risk of 0.75 (95% CI: 0.48–1.18) (FDA, 2022; Fennec Pharmaceuticals, 2022).

Current strategies to reduce the risk of ototoxicity in patients receiving cisplatin include modifications of treatment protocols and hearing tests during oncology treatment. In 2016 a Cochrane review concluded the data were insufficient to make any definite conclusions as to amifostine efficacy or lack thereof. The 2008 American Society of Clinical Oncology also concluded that the data were insufficient to support the routine use of amifostine to prevent cisplatin ototoxicity.

An international clinical practice guideline published in The Lancet (2019) summarized the following regarding the use of sodium thiosulfate in the prevention of ototoxicity due to cisplatin chemotherapy: “Regarding systemic sodium thiosulfate, the panel made a strong recommendation for administration in non-metastatic hepatoblastoma, a weak recommendation for administration in other non metastatic cancers, and a weak recommendation against its routine use in metastatic cancers. Amifostine, sodium diethyldithiocarbamate, and intratympanic therapy should not be routinely used. Cisplatin infusion duration should not be altered as a means to reduce ototoxicity. Further research to determine the safety of sodium thiosulfate in patients with metastatic cancer is encouraged.” The panel did review the two trials (SIOPEL 6 and ACCL0431) used for the FDA approval of Pedmark as evidence regarding these recommendations for sodium thiosulfate.

Other Uses

The National Comprehensive Cancer Network® (NCCN) currently provides category 2A evidence-based recommendations for the use of generic sodium thiosulfate (not interchangeable with Pedmark) as renal protection during hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer. According to NCCN guidelines, HIPEC with cisplatin (100 mg/m^2) can be considered at the time of interval debulking surgery (IDS) for stage III disease. Sodium thiosulfate is recommended to be administered at the start of the perfusion, followed by a continuous infusion, to mitigate potential renal toxicity during the HIPEC procedure.

Definitions and Measures

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.
Cytotoxic: Treatment that is destructive to cells, preventing their reproduction or growth.

Approved Indications

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

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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.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J0208	Injection, sodium thiosulfate, 100 mg [pedmark]

ICD-10	Description
D3A.00	Benign carcinoid tumor of unspecified site
D3A.01	Benign carcinoid tumors of the small intestine
D3A.02	Benign carcinoid tumors of the appendix, large intestine, and rectum
D3A.09	Benign carcinoid tumors of other sites

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Sodium thiosulfate injection (Pedmark®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

I. Individual has a diagnosis of localized, non-metastatic solid tumor; **AND**
II. Individual is using to reduce the risk of ototoxicity associated with cisplatin; **AND**
III. Pedmark will be administered starting 6 hours after completion of cisplatin infusion, OR for multiday cisplatin regimens, Pedmark will be administered 6 hours after each cisplatin infusion but at least 10 hours before the next cisplatin infusion; **AND**
IV. Individual has a baseline serum sodium less than 145 mmol/L; **AND**
V. Individual is 1 month of age and older

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Sodium thiosulfate injection (Pedmark®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when all approval criteria are met.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
Sodium thiosulfate injection (Pedmark®)	Weight-based I.V. infusion: • Less than 5 kg: 10 gm^2. • 5 to 10 kg: 15 g/m^2 • Greater than 10 kg: 20 g/m^2
Exceptions	
• For multiday cisplatin regimens, Pedmark should be administered 6 hours after each cisplatin infusion but at least 10 hours before the next cisplatin infusion. • Pedmark should not be started if less than 10 hours before starting the next cisplatin infusion	

Reference Information

1. Brock PR, Maibach R, Childs M, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. *N Engl J Med.* 2018;378(25):2376-2385. doi:10.1056/NEJMoa1801109. Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1801109?articleTools=true. Accessed October 4, 2023.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
3. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 4, 2023
4. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.

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5. Freyer DR, Chen L, Krailo MD, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open- label, phase 3 trial [published correction appears in Lancet Oncol. 2017 Jun;18(6):e301]. *Lancet Oncol*. 2017;18(1):63-74. doi:10.1016/S1470-2045(16)30625-8. Available at:
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520988/pdf/nihms835502.pdf. Accessed October 4, 2023
7. Freyer DR, Brock PR, Chang KW, et al. Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. *The Lancet Child & Adolescent Health.* 2020;4 (2): 141-150. https://doi.org/10.1016/S2352-4642(19)30336-0. Accessed on October 4, 2023.
8. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
9. NCCN Clinical Practice Guidelines in Oncology™. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on October 4, 2023.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception 07/30/2024	Elevance Health Medical Policy Adoption. Added Authorization and Reauthorization Duration Criteria; Added Reauthorization approval criteria; Added dosing recommendations to the Quantity Limitations section; added clinical trial information to the Background section.	12/9/2024	12/17/2024

Revised: 07/30/2024