CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Arsenic Trioxide (Trisenox®)

Version: 2.0

EFFECTIVE DATE: 5/27/2025

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Arsenic Trioxide (Trisenox®)

Discussion

Arsenic trioxide causes morphological changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells in vitro. Arsenic trioxide also causes damage or degradation of the fusion protein promyelocytic leukemia (PML)-retinoic acid receptor (RAR)-alpha.[1,2]

Adverse reactions associated with arsenic include hepatotoxicity, carcinogenesis, embryo-fetal toxicity, nausea, cough, fatigue, pyrexia, headache, abdominal pain, vomiting, tachycardia, diarrhea, dyspnea, hypokalemia, leukocytosis, hyperglycemia, hypomagnesemia, insomnia, dermatitis, edema, QTc prolongation, rigors, sore throat, arthralgia, paresthesia, and pruritus. Patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide may experience symptoms of differentiation syndrome, serious encephalopathy, including Wernicke's, complete atrioventricular block, and torsade de pointes, which may be life-threatening or fatal.[2]

The Food and Drug Administration (FDA) has approved arsenic trioxide for the treatment of acute promyelocytic leukemia.[2] The National Comprehensive Cancer Network (NCCN) endorses arsenic trioxide in the following cancer types: acute myeloid leukemia and T-cell lymphoma.[3,4]

Definitions

- **Differentiation Syndrome** - This is a complication of all-trans retinoic acid (ATRA) therapy in patients with acute promyelocytic leukemia (APML). It appears clinically as acute end-organ damage with peripheral edema, hypotension, acute renal failure, and interstitial pulmonary infiltrates.[5]
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[6]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than thirty leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated, and NantHealth, Inc. reviews these and updates its policies on time.[7]
- **Retinoic Acid Receptor (RAR)** - This is the hallmark protein of acute promyelocytic leukemia.[8]
- **Wernicke's Encephalopathy** - This is an acute neurological condition characterized by a clinical trial of ophthalmoparesis with nystagmus, ataxia, and confusion.[9]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when all criteria are met:

Acute Myeloid Leukemia - Acute Promyelocytic Leukemia

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage

3. In combination with tretinoin all-trans retinoic acid (ATRA) for newly diagnosed low-risk acute disease, which is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression; OR
4. Induction of remission and consolidation in patients with disease who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression;[2] OR

For **NCCN** required criteria coverage

5. Induction in low-risk disease (white blood cell count ≤ 10,000/mcL) for one of the following:
   a) Daily in combination with tretinoin (ATRA)
   b) On days 1-5 of week 1 and twice weekly in weeks 2-8 in combination with ATRA; OR
6. Induction in high-risk disease (white blood cell count >10,000/mcL) in patients with no cardiac issues for one of the following:
   a) In combination with tretinoin (ATRA) and idarubicin
   b) Daily in combination with ATRA and gemtuzumab ozogamicin
   c) On days 1-5 of week 1 and twice weekly in weeks 2-8 in combination with ATRA and gemtuzumab ozogamicin; OR
7. Induction in high-risk disease (white blood cell count >10,000/mcL) in patients with cardiac issues (low ejection fraction) for one of the following:
   a) Daily in combination with tretinoin (ATRA) and gemtuzumab ozogamicin
   b) On days 1-5 of week 1 and twice weekly in weeks 2-8 in combination with ATRA and gemtuzumab ozogamicin; OR
8. Consolidation therapy in low-risk disease (white blood cell count ≤ 10,000/mcL) for one of the following:
   a) 5 days per week for 4 weeks every 8 weeks for a total of 4 cycles, in combination with tretinoin (ATRA)
   b) On days 1-5 of week 1 followed by twice weekly during weeks 2-4 of consolidation, courses 1-4 in combination with ATRA (first 3 consolidation cycles = 56-day cycles, followed by a 4th consolidation cycle, which = a 28-day cycle); OR
9. Consolidation therapy in high-risk disease (white blood cell count >10,000/mcL) in patients with no cardiac issues for one of the following:
   a) In combination with tretinoin (ATRA)

b) 5 days per week for 4 weeks every 8 weeks for a total of 4 cycles, in combination with ATRA
c) On days 1-5 of week 1 in consolidation courses 1-4 and twice weekly in weeks 2-4 of consolidation courses 1-4, in combination with ATRA
d) In combination with gemtuzumab ozogamicin if ATRA was discontinued due to toxicity
e) In combination with ATRA and daunorubicin; OR

10. Consolidation therapy in high-risk disease (white blood cell count >10,000/mcL) in patients with cardiac issues (low ejection fraction [EF]) for one of the following:
    a) 5 days per week for 4 weeks every 8 weeks for a total of 4 cycles, in combination with tretinoin (ATRA)
    b) On days 1-5 of week 1 in consolidation courses 1-4 and twice weekly in weeks 2-4 of consolidation courses 1-4, in combination with ATRA
    c) In combination with gemtuzumab ozogamicin, if ATRA was discontinued due to toxicity; OR
11. Therapy for first relapse (morphologic or molecular) for one of the following:
    a) In combination with tretinoin (ATRA) and idarubicin, as part of an anthracycline-based regimen in patients with early relapse (<6 months) after ATRA and arsenic trioxide (no anthracycline)
    b) With or without ATRA, with or without gemtuzumab ozogamicin, in patients with no prior exposure to arsenic trioxide or early relapse (<6 months) after ATRA + anthracycline-containing regimen
    c) With or without ATRA, with or without anthracycline, or gemtuzumab ozogamicin, in patients with late relapse (≥6 months) after arsenic trioxide-containing regimen; OR
12. For additional therapy as single-agent consolidation in patients that are not transplant candidates and are PCR negative following the second remission (morphologic).[3]

T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage

3. Second-line or subsequent therapy as a single agent for non-responders to first-line therapy in chronic high risk, acute, or lymphoma subtypes.[4]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD 10 and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C91.5	Adult T-cell lymphoma/leukemia (HTLV-1 associated)
C92.40	Acute promyelocytic leukemia, not having achieved remission
J9017	Injection, arsenic trioxide

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	6/29/2023
2	Policy Annual Review Dates:	5/22/2023, 5/28/2024, 5/16/2025
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	6/29/2023, 6/18/2024, 5/27/25
5	Revision Changes:	5/16/2025 Added adverse reactions and 2 FDA indications for APL; v.2.0

References

[1] Miller WH Jr, Schipper HM, Lee JS, Singer J, Waxman S. Mechanisms of action of arsenic trioxide. *Cancer Res*. 2002;62(14):3893-3903. https://pubmed.ncbi.nlm.nih.gov/12124315/. Accessed April 16, 2025.

[2] Trisenox (Arsenic Trioxide) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021248s019lbl.pdf. Accessed May 2, 2025.

[3] National Comprehensive Cancer Network. NCCN Guidelines: Acute Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed May 2, 2025.

[4] National Comprehensive Cancer Network. NCCN Guidelines: T-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 2, 2025.

[5] Reyhanoglu G, Hughes B, King KE, Cambridge R. Differentiation Syndrome, a Side Effect From the Therapy of Acute Promyelocytic Leukemia. *Cureus*. 2020;12(12):e12042. Published 2020 Dec 12. https://pmc.ncbi.nlm.nih.gov/articles/PMC7802406/. Accessed April 30, 2025.

[6] U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed April 23, 2025.

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[8] Saeed S, Logie C, Stunnenberg HG, Martens JH. Genome-wide functions of PML-RARα in acute promyelocytic leukaemia. *Br J Cancer*. 2011;104(4):554-558. https://pubmed.ncbi.nlm.nih.gov/21245861/. Accessed April 23, 2025.

[9] Vasan S, Kumar A, Doerr C. Wernicke Encephalopathy (Nursing). In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; August 14, 2023. https://pubmed.ncbi.nlm.nih.gov/33760557/. Accessed April 23, 2025.