CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Arsenic Trioxide (Trisenox®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Arsenic Trioxide (Trisenox®)

Note: 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.

Note: 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]

Arsenic trioxide is approved by the Food and Drug Administration (FDA) for the following indications:

1. In combination with tretinoin for the treatment of adults with newly diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression
2. For induction of remission and consolidation in patients with APL 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]

Note:

1. Patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide may experience symptoms of differentiation syndrome, which may be life-threatening or fatal.
2. Arsenic trioxide can cause QTc interval prolongation, complete atrioventricular block, and torsade de pointes, which can be fatal.
3. Serious encephalopathy, including Wernicke's, has occurred with arsenic trioxide. [2]
4. The National Comprehensive Cancer Network (NCCN) endorses arsenic trioxide in the following cancer types: acute myeloid leukemia and T-cell lymphoma. [3,4]

Arsenic Trioxide: 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.

- **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.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two 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 within a timely manner.
- **Retinoic acid receptor (RAR)-** This is the hallmark protein of acute promyelocytic leukemia.
- **Wernicke's Encephalopathy –** This is an acute neurological condition characterized by a clinical triad of ophthalmoparesis with nystagmus, ataxia, and confusion.

Arsenic Trioxide: Policy

Arsenic Trioxide will be considered for coverage when the following 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 EITHER
3. Preferred for treatment 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
4. Preferred for treatment 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
5. For treatment 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
6. Preferred for 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

7. For 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) (preferred regimen)
    b) 5 days per week for 4 weeks every 8 weeks for a total of 4 cycles, in combination with ATRA (preferred regimen)
    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 (preferred regimen)
    d) In combination with gemtuzumab ozogamicin if ATRA was discontinued due to toxicity
    e) In combination with ATRA and daunorubicin; OR
8. For 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
9. 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
10. For additional therapy as single-agent consolidation in patients that are not transplant candidates and are PCR negative following the second remission (morphologic).

T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line or subsequent therapy as a single agent for non-responders to first-line therapy for acute or lymphoma subtypes.

Note: Coverage of arsenic trioxide will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

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

Arsenic Trioxide: References

1. Mechanisms of action of arsenic trioxide. https://pubmed.ncbi.nlm.nih.gov/12124315. Accessed May 16, 2023.
2. Arsenic Trioxide (Trisenox) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021248s019lbl.pdf. Accessed May 17, 2023.
3. National Comprehensive Cancer Network Guidelines. Acute Myeloid Leukemia (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed May 16, 2023.
4. National Comprehensive Cancer Network Guidelines. T-Cell Lymphomas (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 17, 2023.

Arsenic Trioxide: 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
C84.4	Peripheral T-cell lymphoma
C9242	Acute promyelocytic leukemia, in relapse
J9017	Arsenic Trioxide (Trisenox ®)

Arsenic Trioxide: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	5/22/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	6/29/2023
6	Revision Changes:	