

POLICY: Oncology – Arsenic Trioxide injection for intravenous use (Trisenox® – Teva Pharmaceuticals, generics)

APPROVAL DATE: 09/25/2019

OVERVIEW

The mechanism of action of arsenic trioxide has not been entirely elucidated, however it has been demonstrated *in vitro* that it causes morphologic changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells.¹ In addition, arsenic trioxide has been shown to damage or degrade the fusion protein promyelocytic leukemia (PML)-retinoic acid receptor (RAR)-alpha.

Arsenic trioxide is indicated:

- 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,
- 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.¹

Guidelines

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Acute Myeloid Leukemia (version 2.2020 – September 3, 2019) recommends arsenic trioxide for induction and consolidation therapy in low-risk (white blood cell [WBC] count < 10,000/ μ L) and in high risk (WBC > 10,000/ μ L) APL with or without cardiac issues.^{2,3} NCCN also recommends arsenic trioxide for the first relapse (either morphologic or molecular) and as single agent consolidation therapy in patients that are not transplant candidates and are polymerase chain reaction (PCR) negative following second remission (morphologic). In addition to the FDA approved dosing for arsenic trioxide, NCCN also recommends the following dosing regimen:

- Induction phase: 0.3 mg/kg administered intravenously (IV) on Days 1 through 5 of Week 1, followed by 0.25 mg/kg IV twice weekly in Weeks 2 through 8,
- Consolidation phase: 0.3 mg/kg IV on Days 1 through 5 of Week 1, followed by 0.25 mg/kg IV twice weekly in Weeks 2 through 4 of each 8 week cycle.^{3,4}

The NCCN Clinical Practice Guidelines for T-Cell Lymphoma (version 2.2019 – December 17, 2018) recommends arsenic trioxide in combination with interferon alfa-2b for the second-line or subsequent treatment of nonresponders to first-line therapy for adult T-cell leukemia/lymphoma, acute or lymphoma subtypes.⁵

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of arsenic trioxide. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with arsenic trioxide as well as the monitoring required for adverse events and long-term efficacy, approval requires

arsenic trioxide to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of arsenic trioxide is recommended in those who meet one of the following criteria:

FDA-Approved Indications

- 1. Acute Promyelocytic Leukemia.** Approve for 1 year if arsenic trioxide is prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosing regimens (A or B):

A) FDA approved dose (i, ii, and iii):

- i. Each individual dose must not exceed 0.15 mg/kg administered by intravenous infusion; AND
- ii. During the induction phase, the dose is administered once daily for a maximum of 60 days; AND
- iii. During the consolidation phase, the dose is administered once daily on Days 1 through 5 in the first 5 weeks of each 8 week cycle.¹

B) National Comprehensive Cancer Network recommended dosing (i, ii, and iii):

- i. Each individual dose must not exceed 0.3 mg/kg administered by intravenous infusion; AND
- ii. During the induction phase, the dose is administered on Days 1 through 5 of Week 1 and then twice weekly in Weeks 2 through 8; AND
- iii. During the consolidation phase, the dose is administered on Days 1 through 5 of Week 1 and then twice weekly in Weeks 2 through 4 of each 8 week cycle.^{3,4}

Other Uses with Supportive Evidence

- 2. Adult T-Cell Leukemia/Lymphoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is \geq 18 years of age; AND

B) The patient has acute or lymphoma subtype; AND

C) Patient has tried chemotherapy.

(Note: Examples include CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CHOEP [cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone]); AND

D) Arsenic trioxide will be used in combination with interferon alfa-2b.

(Note: Includes Intron A); AND

E) Arsenic trioxide is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen (A, B, and C):

A) Each individual dose must not exceed 0.15 mg/kg administered by intravenous infusion; AND

B) During the induction phase, the dose is administered once daily for a maximum of 60 days; AND

C) During the consolidation phase, the dose is administered once daily on Days 1 through 5 in the first 5 weeks of each 8 week cycle.¹

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Arsenic trioxide has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Trisenox® injection for intravenous use [prescribing information]. North Wales, PA: Teva Pharmaceuticals; June 2019.
2. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on September 3, 2019. Search term: arsenic trioxide.
3. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – September 3, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on September 3, 2019.
4. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-*trans* retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomized, controlled, phase 3 trial. *Lancet Oncol.* 2015;16:1295-1305.
5. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://nccn.org>. Accessed on September 3, 2019.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	02/06/2019
Early Annual	No change to the criteria	09/25/2019