

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Arsenic trioxide

Product: arsenic trioxide (ATO; Trisenox®)

Class of Drugs: antineoplastic

Reason for Use: acute promyelocytic leukemia (APL)

Manufacturer: Lundbeck Canada Inc.

Date of Review: March 12, 2014

CED Recommendation

The CED recommended arsenic trioxide (ATO; Trisenox®) be funded for the treatment of acute promyelocytic leukemia (APL) according to specific criteria. The available evidence suggests a net clinical benefit with ATO and the treatment is considered to be cost-effective.

Executive Officer Decision*

Based on the CED's recommendation and an agreement with the manufacturer, the Executive Officer decided to fund arsenic trioxide (ATO; Trisenox®) for the treatment of acute promyelocytic leukemia (APL) according to specific criteria.

Funding Status*

Funded through Cancer Care Ontario's New Drug Funding Program according to specific criteria.

** This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.*

Highlights of Recommendation:

- Two randomized controlled trials in patients with previously untreated acute promyelocytic leukemia (APL) showed that the addition of arsenic trioxide (ATO) to a standard treatment improved outcomes.
- Eleven observational studies in patients with APL whose disease has not responded to or has returned after front-line treatment showed benefit with ATO.
- The overall safety of ATO was considered to be acceptable as the drug will be used by clinicians familiar with managing its adverse events.
- At the list price, ATO costs \$15,582 per 28-day course for induction treatment and \$11,130 per 28-day course for consolidation treatment. Based on analyses conducted by the pan-Canadian Oncology Drug Review, ATO was considered to be cost-effective.

Background:

Acute promyelocytic leukemia (APL) is a type of acute myeloid leukemia, a cancer of the blood and bone marrow.

Patients with APL may be grouped into three risk categories, low-, intermediate-, or high-risk, based on the patient's white blood cell count and platelet count.

Treatment is divided into stages: induction, consolidation and maintenance therapy. The first phase is remission induction where treatments are used to clear leukaemia cells from the bone marrow. Consolidation treatment is then used to maintain patients in remission. The final phase of treatment is maintenance therapy used to prevent the return of the disease.

The standard first-line treatment (i.e., in newly diagnosed patients) has been all-trans retinoic acid (ATRA) plus anthracycline-based chemotherapy. For patients whose disease has come back (relapsed) or has not responded (refractory) to the treatment, ATRA and anthracycline-based chemotherapy are used for re-induction followed by further chemotherapy consolidation with or without stem cell transplantation.

Detailed Discussions:

- For this evaluation, the CED considered:
 - Findings from the pan-Canadian Oncology Drug Review (pCODR) and the recommendation of the pCODR Expert Review Committee;
 - Information in the manufacturer's submission;
 - One patient group submission received by pCODR;
 - Feedback from Cancer Care Ontario's Hematology Disease Site Group.
- In the **first-line setting**, the CED evaluated two randomized controlled trials.
- Lo-Coco 2013 was an open-label, non-inferiority trial comparing ATRA plus chemotherapy with ATRA plus ATO for induction and consolidation treatment of APL in low- and intermediate-risk patients. The primary endpoint was 2-year event-free survival (EFS). Secondary endpoints included overall survival (OS), disease-free survival, APL differentiation syndrome, and hematologic and non-hematologic toxicity.

- The study showed that the 2-year EFS rate was significantly greater in the ATRA plus ATO group compared with the ATRA plus chemotherapy group (97% vs. 86%, respectively; $p < 0.001$ for non-inferiority and $p = 0.02$ for superiority). The 2-year OS rate was also greater in patients on ATO compared with the control group (99% vs. 91%, respectively; $p = 0.02$).
- Powell 2010 was a two-arm randomized trial examining the use of ATO in early consolidation treatment (following achievement of complete remission in induction and prior to chemotherapy in consolidation), in low-, intermediate- and high-risk patients. Patients were randomized to receive ATRA plus chemotherapy or ATRA plus chemotherapy plus ATO. The primary endpoint was 3-year EFS, and secondary endpoints included 3-year disease-free survival and safety.
- The study showed that the 3-year EFS rate was greater in the ATO group compared with the non-ATO group (80% vs. 63%, respectively; $p < 0.001$). The 3-year OS was 86% and 81% in the ATO and non-ATO arms, respectively ($p = 0.07$).
- Although randomized controlled trials did not include high-risk APL patients receiving induction therapy, the CED felt that ATO was an acceptable therapeutic option for this small subgroup of patients.
- With respect to the use of ATO in the **relapsed or refractory setting**, the CED considered 11 prospective cohort studies that were included in the pCODR systematic review. The lack of randomized controlled trials in this setting was deemed acceptable due to the small number of relapsed/refractory patients with APL. The key efficacy outcome in these 11 studies was complete remission. Complete remission rates ranged from 71% to 100% with a median rate of 85%.
- Quality of life was not reported in any of the above studies.
- The safety profile of ATO was considered to be acceptable and distinct from the toxicities associated with ATRA and anthracycline-based chemotherapies. The most frequent side effects resulting in dose modifications were neuropathy, cardiac effects, retinoic acid syndrome, APL differentiation and major organ dysfunction, which could be managed by oncologists when detected.
- At the submitted price, ATO costs \$15,582 per 28-day course during induction and \$11,130 per 28-day course during consolidation. ATO was considered cost-effective in both the first-line and relapsed/refractory settings.
- The CED discussed the use of ATO in children and older adults. The use of ATO was deemed appropriate for both of these age groups.
- The CED considered one patient group submission. The submission highlighted the burden of the disease and its impact on patients' quality of life. Patients value effective treatments with fewer and less toxic side effects and longer remission rates.
- Overall, the CED noted that randomized controlled trials and uncontrolled trials show a net clinical benefit with ATO in patients with low- to intermediate-risk APL as an induction and consolidation treatment, in patients with high-risk APL as consolidation treatment, and in patients of all risk categories with relapsed/refractory APL. Although randomized controlled trials did not include high-risk APL patients receiving induction therapy, the Committee felt that ATO was an acceptable therapeutic option for this small subgroup of patients. The

safety profile of ATO was considered to be acceptable and distinct from the toxicities associated with ATRA and anthracycline-based chemotherapies. ATO was found to be cost-effective.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

For more information, please contact:

Ministry of Health and Long-Term Care

Ontario Public Drug Programs

Hepburn Block, 9th Floor

80 Grosvenor Street, Queen's Park

Toronto, Ontario M7A 1R3

www.health.gov.on.ca/en/pro/programs/drugs/