ABBREVIATED PACKAGE INSERT – See Product Monograph for complete product information.

PrArsenic Trioxide for Injection

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous infusion	Solution, 10 mg/ 10 mL (1 mg/mL) Arsenic Trioxide	Hydrochloric acid to adjust pH, sodium hydroxide, water for injection.

INDICATIONS AND CLINICAL USE

Arsenic Trioxide for Injection is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL), which is refractory to or has relapsed from retinoid and anthracycline therapy, and whose APL is characterized by the presence of the t(15;17) translocation or promyelocytic leukemia-retinoic-acid-receptor alpha (PML-RARα) gene expression.

The indication is based on complete response rate. The duration of remission induced by Arsenic Trioxide for Injection has not been determined.

The response rate of other acute myelogenous leukemia subtypes to Arsenic Trioxide for Injection has not been examined.

Geriatrics (> 65 years of age):
There is limited clinical data on the use of arsenic trioxide in geriatric patients with relapsed or refractory APL. Caution is needed in these patients.

Pediatrics (< 18 years of age):
Safety and effectiveness in relapsed APL pediatric patients below the age of 5 years have not been studied.

There is limited clinical data on the use of arsenic trioxide in pediatric patients > 5 years and < 18 years of age with relapsed or refractory APL.

Caution is advised in the use of Arsenic Trioxide for Injection in pediatric patients. All pediatric patients should be closely monitored for toxicities as the exposure to Arsenic Trioxide for Injection is expected to be higher than in adult patients. Dosage adjustments are necessary when administering in obese pediatric patients (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**).

CONTRAINDICATIONS

Arsenic Trioxide for Injection is contraindicated in patients who are hypersensitive to arsenic or any of the non-medicinal ingredients in this product. For a complete listing, see the **DOSAGE FORMS**, **COMPOSITION AND PACKAGING** section.

Arsenic Trioxide for Injection is contraindicated during pregnancy and in nursing mothers.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **APL Differentiation Syndrome**
  This syndrome can be fatal. At the first signs or symptoms that could suggest the syndrome, high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated.
- **Acute Cardiac Toxicities (Rhythm Disturbance)**
  - o Arsenic trioxide can cause QT prolongation and complete atrioventricular block. QT prolongation can lead to torsade de pointes, a polymorphic ventricular tachyarrhythmia, which can be fatal.
  - o Patients with syncope, rapid or irregular heartbeat should be hospitalized for monitoring. Serum electrolytes should be assessed and Arsenic Trioxide for Injection interrupted (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).
  - o Special electrocardiogram and electrolyte monitoring is required.
    - ▪ Prior to initiating therapy with Arsenic Trioxide for Injection, a 12-lead electrocardiogram (ECG) should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; preexisting electrolyte abnormalities (including hypokalaemia, hypocalcaemia or hypomagnesaemia) should be corrected.
    - ▪ For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using Arsenic Trioxide for Injection. Arsenic Trioxide for Injection therapy may be started at QTc values of less than 430 msec for males, and less than 450 msec for females.
  - o Concomitant use of drugs that prolong the QT interval or disrupt electrolyte levels should be avoided.
- Encephalopathy, including fatal outcomes.
- Arsenic Trioxide for Injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Arsenic Trioxide for Injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia. The special monitoring procedures described in **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests** of the Product Monograph should be followed.

Pre-existing electrolyte abnormalities should be corrected prior to initiating therapy with Arsenic Trioxide for Injection.

Arsenic Trioxide for Injection should not be administered to patients with baseline QT/QTc interval greater than 500 msec unless corrective measures are completed and the QT/QTc interval is reassessed with serial ECGs.

Dosing of obese patients based on total body weight may result in higher than expected plasma and tissue concentration of arsenical species. Obese patients should be closely monitored for signs of serious acute arsenic toxicity.

Total number of Arsenic Trioxide for Injection doses should not exceed the maximum number of doses recommended for the induction and consolidation treatments.

Recommended Dose and Dosage Adjustment

Arsenic Trioxide for Injection is recommended to be given according to the following schedule:

- **Induction Treatment Schedule**:
  Arsenic Trioxide for Injection should be administered intravenously at a dose of 0.15 mg/kg daily until bone marrow remission. It should be stopped at any time if substantial toxicity occurs. Total induction dose should not exceed 60 doses.
- **Consolidation Treatment Schedule**:
  Consolidation treatment should begin 3 to 6 weeks after completion of induction therapy. Arsenic Trioxide for Injection should be administered intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period up to 5 weeks.

Obese pediatric patients should be dosed based on ideal body weight.

Patients who reach an absolute QT/QTc interval value > 500 msec while on Arsenic Trioxide for Injection therapy should be reassessed and immediate action should be taken to correct concomitant risk factors. Interruption of Arsenic Trioxide for Injection therapy should be considered.

During therapy with Arsenic Trioxide for Injection, potassium concentrations should be kept above 4 mEq/L and magnesium concentrations should be kept above 1.8 mg/dL.

If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring and serum electrolytes should be assessed, Arsenic Trioxide for Injection therapy should be interrupted until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease.

Administration
Arsenic Trioxide for Injection should be diluted with 100 to 250 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, using proper aseptic technique, immediately after withdrawal from the vial. Arsenic Trioxide for Injection vials are single-use and do not contain any preservatives. Unused portions of each vial should be discarded properly. Do not save any unused portions for later administration.

Arsenic Trioxide for Injection must not be mixed with or concomitantly administered in the same intravenous line with other medicinal products.

Arsenic Trioxide for Injection should be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed. A central venous catheter is not required.

OVERDOSAGE

If symptoms suggestive of serious acute arsenic toxicity (e.g., convulsions, muscle weakness and confusion) appear, Arsenic Trioxide for Injection should be immediately discontinued and chelation therapy should be considered. A conventional protocol for acute arsenic intoxication includes dimercaprol administered at a dose of 3 mg/kg intramuscularly every 4 hours until immediate life-threatening toxicity has subsided. Electrocardiogram monitoring is recommended in the event of overdosage.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

STORAGE AND STABILITY

Store at controlled room temperature (15°C - 30°C).

After dilution in 5% Dextrose or 0.9% Sodium chloride, Arsenic Trioxide for Injection is chemically and physically stable when stored for 24 hours at room temperature and 48 hours when refrigerated.

For single use only. Unused portions of each vial must be discarded properly. Do not save any unused portions for later administration.

SPECIAL HANDLING INSTRUCTIONS

Use caution during handling and preparation. Use of gloves and safety glasses is recommended to avoid exposure.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Arsenic Trioxide for Injection contains 1 mg/mL arsenic trioxide. Non-medicinal ingredients: hydrochloric acid (used to adjust pH), sodium hydroxide, and water for injection.

Arsenic Trioxide for Injection is supplied as a sterile, clear, colourless solution in 10 mL glass, single-use vials in packages of 10 vials.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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