

media fact sheet

TRISENOX® (arsenic trioxide) injection

What is TRISENOX?

TRISENOX (arsenic trioxide) injection is indicated for the treatment of patients with relapsed or refractory acute promyelocytic leukemia (APL) whose disease returned after, or did not respond to, initial treatment (also called relapsed or refractory disease).

In clinical trials, TRISENOX has delivered high rates of complete remission for APL patients whose disease returned after, or did not respond to, initial treatment.

What is APL?

According to the National Cancer Institute, acute promyelocytic leukemia (APL) is a serious and aggressive (fast-growing) form of leukemia. It can affect people of any age. The annual incidence of newly diagnosed APL in the U.S. is approximately 1,000 to 1,500 cases.

APL is a subtype of the cancer known as acute myeloid leukemia (AML), and accounts for approximately 10% of AML patients. In APL, two genes involved in the prevention of disease trade places or translocate (RAR-alpha gene and PML gene). Normally, these genes help to restrict tumor growth and to control the aging of white blood cells. In patients with APL, these genes combine to form a mutant gene that makes it difficult for normal genes to do their job. Because of this, APL cells may not age as they are supposed to, and can increase in number to an unhealthy degree.

How does TRISENOX work?

The mechanism of action of TRISENOX is not fully understood but it appears to target the underlying genetic causes of APL. TRISENOX helps to break down the mutant proteins created by the gene translocation, enabling white blood cells to age properly. TRISENOX may also help APL cells to actually eliminate themselves through a natural process called apoptosis or programmed cell death.

What is known about the efficacy and safety of TRISENOX?

The Food and Drug Administration (FDA) approved TRISENOX for the treatment of relapsed or refractory APL based on the safety and efficacy data from a multi-center clinical trial involving 40 patients who received arsenic trioxide infusions. In this study, 85 percent of patients responded to therapy, with complete remission of their disease within a median of 59 days. The published remission data have been adjusted based on the International Working Group revised definition of remission. The definition given in the Prescribing Information, which requires a confirmatory bone marrow, is no longer current.

What is known about the safety and efficacy of TRISENOX? (cont'd)

Serious adverse events, grade 3 or 4, were common. Those events attributable to TRISENOX in the phase 2 study of 40 patients with refractory or relapsed APL included QTc interval prolongation (n=16), APL differentiation syndrome (n=3), hyperleukocytosis (n=3), atrial dysrhythmias (n=2), and torsade de pointes (n=1). In clinical trials, most patients taking TRISENOX experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible, nor do they usually require interruption of therapy.

In what form is TRISENOX supplied, and what is the recommended dosage?

TRISENOX is an intravenous therapy usually administered over one to two hours, and may be extended up to four hours if acute vasomotor reactions are observed. TRISENOX is available in 10 milliliter, single-use ampules containing 10 milligrams of arsenic trioxide.

The induction dose of TRISENOX in relapsed/refractory APL is 0.15 mg/kg daily until bone marrow remission (up to 60 doses). During consolidation (a second phase following induction) TRISENOX is administered at a dose of 0.15 mg/kg daily for 25 doses over a period of up to five weeks. Between phases patients are given three to six weeks of rest from treatment.

Where is TRISENOX available?

TRISENOX was approved in the United States in 2000 and in Europe in 2002. In addition to the U.S., TRISENOX is currently marketed in the European Union member states, Norway, Japan and South Korea (through an agreement with Nippon Shinyaku); Mexico, Colombia, Uruguay, Argentina, Brazil, Panama and Venezuela (through an agreement with Tecnofarma); and Israel (through an agreement with Medison Pharma, Ltd.).

Who makes TRISENOX?

Cephalon, Inc. (Nasdaq: CEPH), Frazer, PA, an international biopharmaceutical company, owns worldwide rights to market and develop TRISENOX. Through the CephalonCaresSM Foundation, Cephalon helps patients who do not have prescription drug coverage get the Cephalon medicine they need. For more information about Cephalon or the CephalonCares Foundation, visit www.cephalon.com.

See following page for important safety information and full boxed warning for TRISENOX.

WARNING

Experienced Physician and Institution: TRISENOX (arsenic trioxide) injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

APL Differentiation Syndrome: Some patients with APL treated with TRISENOX have experienced symptoms similar to a syndrome called the retinoic-acid-Acute Promyelocytic Leukemia (RA-APL) or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal. The management of the syndrome has not been fully studied, but high-dose steroids have been used at the first suspicion of the APL differentiation syndrome and appear to mitigate signs and symptoms. At the first signs that could suggest the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated, irrespective of the leukocyte count, and continued for at least 3 days or longer until signs and symptoms have abated. The majority of patients do not require termination of TRISENOX therapy during treatment of the APL differentiation syndrome.

ECG Abnormalities: Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of torsade de pointes, preexisting QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. One patient (also receiving amphotericin B) had torsade de pointes during induction therapy for relapsed APL with arsenic trioxide.

ECG and Electrolyte Monitoring Recommendations: Prior to initiating therapy with TRISENOX, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; preexisting electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using TRISENOX. During therapy with TRISENOX, potassium concentrations should be kept above 4 mEq/L and magnesium concentrations should be kept above 1.8 mg/dL. Patients who reach an absolute QT interval value > 500 msec should be reassessed and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending TRISENOX therapy should be considered. If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring, serum electrolytes should be assessed, TRISENOX therapy should be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of TRISENOX on the QTc interval during the infusion.

TRISENOX® (arsenic trioxide) injection: Indicated for the 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.

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A differentiation syndrome, like retinoic acid syndrome, has been reported with the use of TRISENOX for the treatment of malignancies other than APL from postmarketing surveillance. Due to unknown population size, it is not possible to provide precise estimates of frequency.

TRISENOX [full prescribing information](#), including boxed warning, is available from Cephalon Medical Information (800-896-5855) or at www.trisenox.com.

Note that the prescribing information may vary in other countries where TRISENOX is marketed.