IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME AND CARDIAC CONDUCTION ABNORMALITIES

Differential Syndrome: Patients with acute promyelocytic leukemia (APL) treated with TRISENOX® (arsenic trioxide) injection in combination with tretinoin experienced the development of differentiation syndrome, which can be fatal if untreated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, weight gain or peripheral edema, hypotension, and renal, hepatic, or multi-organ dysfunction, in the presence or absence of leukocytosis. If differentiation syndrome is suspected, immediately initiate high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Temporary discontinuation of TRISENOX® may be required.

Cardiac Conduction Abnormalities: Arsenic trioxide can cause QTc interval prolongation, complete atrioventricular block, and a torsade de points-type ventricular arrhythmia, which can be fatal. Before initiating therapy, assess the QTc interval, correct pre-existing electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer TRISENOX® to patients with ventricular arrhythmia or prolonged QTc.

Contraindications: TRISENOX® is contraindicated in patients who are hypersensitive to arsenic trioxide.

Differential Syndrome: In clinical trials, 36-23% of patients treated with TRISENOX® for APL developed differentiation syndrome. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, and it has occurred as early as day 1 of induction to as late as the second month induction therapy. When TRISENOX® is used in combination with tretinoin, prednisone prophylaxis is advised.

Cardiac Conduction Abnormalities: In the clinical trials of patients with newly-diagnosed low-risk APL treated with TRISENOX® in combination with tretinoin, 12% experienced QTc prolongation >450 msec for men and >460 msec for women throughout the treatment cycles. In the clinical trial of patients with relapsed or refractory APL treated with TRISENOX® monotherapy, 40% had at least one ECG tracing with a QTc interval greater than 500 msec. A prolonged QTc was observed between 1 and 5 weeks after start of TRISENOX® infusion, and it usually resolved by 8 weeks after TRISENOX® infusion. There are no data on the effect of TRISENOX® on the QTc interval during the infusion of the drug.

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 points, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. The risk may be increased when TRISENOX® is co-administered with medications that can lead to electrolyte abnormalities (such as diuretics or amphotericin B).

Hepatotoxicity: In the clinical trials, 44% of patients with newly-diagnosed low-risk APL treated with TRISENOX® (arsenic trioxide) injection in combination with tretinoin experienced elevated serum alanine aminotransferase (AST), alkaline phosphatase, and/or serum bilirubin. These abnormalities resolved with temporary discontinuation of TRISENOX® and/or tretinoin. During treatment with TRISENOX® and/or tretinoin, patients with severe renal impairment (creatinine clearance less than 30 mL/min) should be monitored for toxicity when these patients are treated with TRISENOX® and/or tretinoin or if elevations in AST, alkaline phosphatase, and/or serum bilirubin occur to greater than 5 times the upper limit of normal.

Long-term liver abnormalities can occur in APL patients treated with TRISENOX® in combination with tretinoin. In a published series, mild liver dysfunction and hepatic steatosis were seen in 15% and 43%, respectively, of patients at a median of 7 years (range 0-14 years) after treatment with arsenic trioxide in combination with tretinoin.

Carcinogenesis: The active ingredient of TRISENOX® is arsenic trioxide, a human carcinogen. Monitor patients for the development of secondary malignancies.

Embryo-Fetal Toxicity: TRISENOX® can cause fetal harm when administered to a pregnant woman. One patient who became pregnant while receiving arsenic trioxide had a miscarriage. Conduct pregnancy testing prior to initiating treatment and advise pregnant women of the potential risk to a fetus. Advise patients of reproductive potential to use effective contraception during treatment with TRISENOX® and after treatment for 6 months in females and 3 months in males. TRISENOX® may also impair fertility in males.

Lactation: TRISENOX® is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, discontinue breastfeeding during treatment with TRISENOX® and for two weeks after the final dose.

Patients with Renal Impairment: Exposure of arsenic trioxide may be higher in patients with severe renal impairment. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) should be monitored for toxicity when these patients are treated with TRISENOX® and a dose reduction may be warranted. The use of TRISENOX® in patients on dialysis has not been studied.

Patients with Hepatic Impairment: Since limited data are available across all hepatic impairment groups, caution is advised in the use of TRISENOX® in patients with hepatic impairment. Monitor patients with severe hepatic impairment (Child-Pugh Class C) who are treated with TRISENOX® for toxicity.

Most Common Adverse Reactions: The most common adverse reactions (greater than 30%) were leukocytosis, neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, abdominal pain, hepatic toxicity, fever, rigors, fatigue, insomnium, tachycardia, QTc prolongation, edema, hyperglycemia, hypokalemia, hypomagnesemia, dyspnea, cough, rash or itching, sore throat, arthralgia, headaches, paresthesia, and dizziness.