IMPORTANT PRESCRIBING INFORMATION

cti

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T 206.282.7100 F 206.284.6206

March 2001

Dear Health Care Provider,

An article published recently in *Blood* (Unnikrishnan, et al, 1 March 2001;97:1514–1516) describes prolonged QT interval and torsade de pointes in 3 patients being treated with arsenic trioxide for acute myeloid leukemia (AML). In one patient, the torsade resolved upon correction of serum potassium to 3.1 mEq/L and magnesium to 1.7 mg/dL. The other two patients died from cardiac arrhythmia. All 3 patients had been intubated due to respiratory distress. The arsenic trioxide used in the reported study was not Cell Therapeutics' Trisenox™ (arsenic trioxide) injection.

QT prolongation is a well described toxic effect of arsenic trioxide. Of 40 patients evaluated in the trial that was the basis of approval of Trisenox, 16 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. One case of torsade de pointes had occurred in these 40 patients. Prolongation of the QTc was observed between 1 and 5 weeks of daily Trisenox infusion, and then returned to baseline by the end of 8 weeks after Trisenox infusion. These observations led to the boxed warning in the Trisenox label regarding the importance of ECG and electrolyte monitoring in patients given arsenic trioxide (shown below, and in the package insert enclosed with this letter).

No cardiac deaths have been reported in post-marketing surveillance to date. Based on available data on > 360 patients treated in clinical investigations, the safety of administration of Trisenox can be optimized with appropriate monitoring and management of ECG abnormalities as described in the label.

WARNING

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.

For complete boxed warning, see full package insert enclosed with this letter.

Health care providers are encouraged to report any adverse events related to Trisenox to

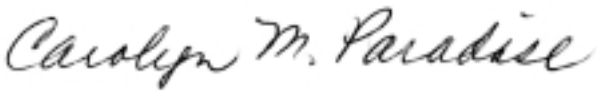
Cell Therapeutics: Telephone 1-800-368-1377 or Fax 1-206-270-8418

or to the FDA using MedWatch by one of the following methods:

Telephone 1-800-FDA-1088; Fax 1-800-FDA-0178
Internet: https://www.accessdata.fda.gov/scripts/medwatch/
Print form to send prepaid form by mail: http://www.fda.gov/medwatch/safety/3500.pdf

cti would appreciate receiving a copy of MedWatch forms when they are submitted to the FDA to ensure that our safety database is as complete as possible.

Sincerely,



Carolyn M. Paradise, MD
Vice President, Clinical Development
Cell Therapeutics, Inc.