



DATE: JAN 31 2011
FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1666032
TO: Investigators Using CCI-779 (temsirolimus, Torisel®) (NSC 683864)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent temsirolimus.

The following must be completed by all investigators using temsirolimus under NCI IND 61010:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 61010, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with temsirolimus, there does not appear to be a change in the risk-benefit ratio for temsirolimus, therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 66-year-old female with stage III endometrial cancer developed grade 4 hypomagnesemia while on a phase 2 trial utilizing the investigational agent temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirrolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Magnesium, serum-low (hypomagnesemia)
AE: 1666032	Protocol: GOG-0248

The patient is a 66-year-old female with stage IIIC endometrial adenocarcinoma who developed hypomagnesemia while on a phase 2 trial utilizing the investigational agent temsirolimus. She began the first course of the investigational therapy on November 11, 2010, receiving temsirolimus 25 mg IV over 30 minutes weekly, every 6 weeks. The patient received her last dose of temsirolimus on December 9, 2010 (Cycle 1, Day 29).

The patient was diagnosed with Stage IIIC endometrial adenocarcinoma in March 2008, and is status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, radiation therapy, and multiple agent systemic chemotherapy. She was found to have recurrent metastatic adenocarcinoma by a positive right inguinal biopsy in November 2010. She began the investigational therapy on November 11, 2010.

On September 20, 2010, the patient, who was admitted to the hospital for preoperative testing for a pericardial window, was found to have electrolyte abnormalities with calcium of 6.5 mg/dL (reference range: 8.6-10.2 mg/dL) and magnesium of 0.6 mg/dL (reference range: 1.8-2.4 mg/dL). She was given calcium gluconate which improved her calcium to 9.3 mg/dL. The patient was treated with Slow-Mag® and IV magnesium. The more magnesium the patient received the more urinary excretion of magnesium she experienced. It was felt that the chemotherapy had likely induced an injury to her renal tubule causing her to excrete more magnesium. On October 7, 2010, her magnesium was 1.1 mg/dL; she was given 2 grams of IV magnesium, and discharged home on calcium with vitamin D and Slow-Mag®. Despite the supplements, a repeat laboratory result on October 27, 2010, showed magnesium 0.8 mg/dL and calcium 7.1 mg/dL.

On December 11, 2010 (Cycle 1, Day 31), the patient called the clinic complaining of nausea and vomiting. She was given a prescription for Compazine® which was helpful. On December 14, 2010 (Cycle 1, Day 34), the patient presented to the emergency room with nausea, a 2-day history of vomiting, and confusion. As a result of her symptoms, she was unable to take her medications, especially magnesium tablets, for the past 3 days. Her magnesium was 0.3 mg/dL, her troponin I was 0.30 ng/mL (reference: <0.04 ng/mL), her calcium was 5.0 mg/dL, and her albumin was 2.7 g/dL (reference range: 3.4-5.0 g/dL) which corrected her calcium level to 6.0 mg/dL. An ECG showed wide complex tachycardia, ventricular bigeminy, and an old left bundle branch block. The patient was given Zofran® and Ativan®, and she was started on IV magnesium and calcium, and IV Nexium®. She was admitted to the hospital for telemetry.

On December 15, 2010 (Cycle 1, Day 35), during a consult assessment, she was found to be hyper-reflexic and it was recommended to continue the IV and oral supplementation of magnesium. The patient was given multiple transfusions of magnesium with close monitoring. On December 16, 2010, a repeat laboratory evaluation showed magnesium of 1.3 mg/dL, calcium of 5.7 mg/dL, and a troponin I of 0.20 ng/mL. Despite attempts at IV repletion, her magnesium continued to be low. On December 20, 2010, the patient's magnesium was 1.4 mg/dL and her calcium was 7.4 mg/dL with a corrected value of 8.7 mg/dL. She was discharged home that day with follow-up instructions for a recheck of her magnesium in 2 days, and to follow-up with nephrology within 1-2 weeks as well as her primary care physician.

The patient's past medical/surgical history is significant for hypertension, hyperlipidemia, iron deficiency anemia, coronary artery disease, pericardial effusion, left bundle branch block, removal of basal cell

carcinoma of the nose and temporal area, thrombocytopenia, depression with some cognitive impairment, benign colonic polyp, osteoporosis with fractures the metatarsals of her right foot, peripheral neuropathy secondary to chemotherapy, hypokalemia, polymyalgia rheumatica, and polypectomy. Medications taken at the time of the event included simvastatin, Lexapro®, amlodipine, aspirin, amiloride, Norvasc®, multivitamin, Slow-Mag®, calcium with vitamin D, and Compazine®.

There have been 5 other cases of hypomagnesemia reported as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Hypomagnesemia (n=5)	4	2 Possible
	3	1 Unrelated
	2	1 Probable
	1	1 Unlikely

To date, a total of 2,442 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a possible relationship exists between the event and the investigational agent.

	Hypomagnesemia
<u>Temsirolimus</u>	Possible
<u>Endometrial adenocarcinoma</u>	Unrelated

Date: 1/26/11

Signature:

L. Austin Doyle M.D.
L. Austin Doyle, M.D.
(IDB Monitor for temsirolimus)

If this assessment is changed, we will notify your office.

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