



DATE: February 17, 2010

FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI LAD

SUBJECT: CCI-779 (temsirolimus, Torisel[®]) IND Safety Report, AE# **1763564**

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 68-year-old female with endometrioid endometrial adenocarcinoma developed grade 4 hypomagnesemia while on a phase 2 trial utilizing the investigational agent temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Magnesium, serum-low (hypomagnesemia)
AE: 1763564	Protocol: GOG-0248

The patient is a 68-year-old female with endometrioid 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 April 23, 2009, receiving temsirolimus 25 mg IV over 30 minutes weekly, every 6 weeks. She received her last dose of temsirolimus on November 19, 2009 (Cycle 6, Day 1).

The patient was diagnosed with Stage IIIC endometrioid endometrial adenocarcinoma in May 2007, and is status post a radical abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, radiation therapy, and chemotherapy. She began the investigational therapy on April 23, 2009.

On October 21, 2009 (Cycle 5, Day 2), the patient presented to the clinic for a routine blood draw which showed a magnesium level of 0.6 mg/dL (reference range: 1.6-2.6 mg/dL). Note that she had a baseline value of 1.5 mg/dL on April 17, 2009, and a later level of 1.2 mg/dL on both September 16 and October 7, 2009. The patient was not given magnesium replacement. Repeat laboratory evaluations revealed a magnesium level of 1.2 mg/dL on October 28, 2009, 1.3 mg/dL on November 4, 2009, 2.1 mg/dL on November 11, 2009, and 1.8 mg/dL on November 18, 2009. On December 9, 2009, the patient's magnesium was again normal at 1.7 mg/dL. The patient continues on study.

The patient's past medical/surgical history is significant for radiation-induced diarrhea/enteritis, osteoporosis, pulmonary embolus, and wound revision with VAC placement and IV port placement in 2007. Her father has throat cancer, sister has multiple myeloma, first cousin has breast cancer, and maternal uncle has lung cancer. Medications taken at the time of the event were not included in the medical records.

There have been 2 other cases of hypomagnesemia (grade 4, possible, and grade 3, unrelated) reported as serious adverse events through AdEERS under the temsirolimus NSC and/or IND.

To date, a total of 1,918 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that because the magnesium drop spontaneously corrected without magnesium replacement therapy, and because the event did not recur with subsequent temsirolimus therapy, a possible relationship exists between the event and the investigational agent, but the possibility of a lab error also exists.

	Magnesium, serum-low (hypomagnesemia)
Temsirolimus	Possible
Endometrioid endometrial adenocarcinoma	Unrelated
Laboratory error	Possible

Date: 2/16/10

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

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

cc: Rafael E. Curiel, Ph.D.
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