



**DATE:** 3/7/11  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
*L. Austin Doyle MD*  
**SUBJECT:** CCI-779 (temsirolimus, Torisel<sup>®</sup>) IND Safety Report, AE# 1737163  
**TO:** Investigators Using CCI-779 (temsirolimus, Torisel<sup>®</sup>) (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 this letter to your Institutional Review Board (IRB) of record according to your 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 59-year-old female with endometrial adenocarcinoma developed grade 4 hyperuricemia while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with paclitaxel and carboplatin.

## ADVERSE EVENTS ASSESSMENT

IND <b>61010</b> NSC <b>683864</b> CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: <b>Gr. 4: Uric acid, serum-high (hyperuricemia)</b>
AE: <b>1737163</b>	Protocol: <b>GOG-0086P</b>

The patient is a 59-year-old female with endometrial adenocarcinoma who developed hyperuricemia while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with paclitaxel and carboplatin. She began the first course of the investigational therapy on October 13, 2010, receiving temsirolimus 25 mg IV over 30 minutes on Days 1 and 8 (starting with cycle 2 for those patients entering post surgery) × 6 cycles, and paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours on Day 1 × 6 cycles followed by carboplatin AUC = 5 IV over 30 minutes on Day 1 × 6 cycles, every 21 days. She is to begin maintenance therapy starting with Cycles 7+, receiving temsirolimus 25 mg IV over 30 minutes weekly on Days 1, 8, and 15 (Note: Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy). The patient received her last dose of temsirolimus on November 11, 2010 (Cycle 2, Day 8), and the last doses of paclitaxel and carboplatin on November 4, 2010 (Cycle 2, Day 1).

The patient was diagnosed with poorly differentiated endometrial adenocarcinoma in March 2009. She is status post total abdominal hysterectomy with bilateral salpingo-oophorectomy, and pelvic radiation therapy with adjuvant high-dose-rate (HDR) brachytherapy. The patient began the investigational therapy on October 13, 2010.

On November 24, 2010 (Cycle 3, Day 1), the patient presented to the clinic for reassessment, and her uric acid was 11.9 mg/dL (reference range: 2.4-6.0 mg/dL) as compared to a baseline value of 8.1 mg/dL on September 30, 2010. On December 8, 2010 (Cycle 3, Day 15), the patient called the clinic complaining of a painful left toe. She was uncertain if her toe pain was a symptom of gout or related to her bunions. On December 9, 2010 (Cycle 3, Day 16), during a clinic visit, her left bunion and left big toe were red, swollen, and slightly warm. A repeat laboratory report showed a uric acid of 9 mg/dL. The patient was started on indomethacin and advised to follow-up with her primary care physician (PCP). She was removed from the protocol due to progression of disease.

On December 10, 2010, a follow-up visit with her PCP showed improved symptoms, though she had erythema in the left great toe which was localized to the area of her bunion. It was felt that her symptoms were more likely from the bunion than true gout. There are no medical records to support the diagnosis of gout. On December 16, 2010, the patient had a uric acid of 11.2 mg/dL, on December 23, 2010, she had a uric acid of 9.5 mg/dL, and on January 13, 2011, she had a uric acid of 6.2 mg/dL.

The patient's past medical/surgical history is significant for deep venous thrombosis, cystoscopy, and excision of medial and lateral knee cartilage. Medications taken at the time of the event included ciprofloxacin, Lasix®, metolazone, multivitamin, potassium chloride, Coumadin®, Zofran®, and Compazine®.

There have been 3 other cases of hyperuricemia (grade 4, 2 unlikely and 1 possible) reported as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as shown in the table below.


To date, a total of 2,519 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.

	<b>Hyperuricemia</b>
<b>Temsirolimus</b>	Possible
<b>Carboplatin</b>	Possible
<b>Paclitaxel</b>	Possible
<b>Endometrial adenocarcinoma</b>	Possible

Date: 3/7/11

Signature:

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

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

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