



**DATE:** SEP 13 2011

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

**SUBJECT:** CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1309898

**TO:** Investigators Using CCI-779 (temsirolimus, Torisel®) (NSC 683864)

*L. Austin Doyle M.D.*

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 62-year-old female with endometrial adenocarcinoma developed grade 2 injection site reaction/extravasation changes 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> <b>CCI-779 (temsirolimus, Torisel®)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> Event: <b>Gr. 2: Injection site reaction/extravasation changes</b>
AE: <b>1309898</b>	Protocol: <b>GOG-0086P</b>

The patient is a 62-year-old female with endometrial adenocarcinoma who developed an injection site reaction while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with paclitaxel and carboplatin. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 21 days:

No Prior Radiotherapy:

Paclitaxel: 175 mg/m<sup>2</sup> IV over 3 hrs on day 1 x 6 cycles

Carboplatin: AUC = 5 IV over 30 minutes on day 1 x 6 cycles

Temsirolimus: 25 mg IV over 30 minutes on days 1, 8 (starting with cycle 2 for those pts entering post surgery) x 6 cycles

Maintenance Therapy (Cycles 7+)

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 was diagnosed with serous endometrial adenocarcinoma in January 2011. She is status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and paraaortic lymph node dissection. She began the first course of the investigational therapy on April 6, 2011. The patient received her last doses of temsirolimus, paclitaxel, and carboplatin on June 29, 2011 (Cycle 5, Day 1).

On July 2, 2011 (Cycle 5, Day 4), the patient was admitted to the hospital for weakness, dehydration, renal insufficiency, hypokalemia, hyponatremia, and a markedly elevated blood sugar. She also had pain, swelling, tenderness, erythema, and increased warmth of her left arm, which started the day after her last chemotherapy treatment on June 29, 2011. As noted, the patient typically received her chemotherapy through a port located in the distal medial left upper arm. Duplex venous sonograms of the left upper extremity were performed on July 2 and July 4, 2011, but neither of them revealed evidence of deep vein thrombosis in the left arm. Her CPK was elevated at 998 units/L (reference range: 30-135 units/L), which was possibly secondary to rhabdomyolysis. The swelling of the left arm was considered to be an extravasation change. During the hospitalization, the patient was rehydrated with normal saline and potassium chloride; she was also empirically treated with Levaquin® for possible infection, and her Coumadin® was held and then restarted at a lower dosage due to its over-anticoagulation effect. The patient was discharged on July 9, 2010, when she improved. After the discharge, the patient reported that her left arm edema continued to resolve, although it was still painful to palpation and began desquamating.

On July 20, 2011, the patient was admitted to the hospital for the possible left lower arm chemotherapy extravasation. Physical examination revealed non-pitting left forearm edema, desquamation of the forearm extending from the elbow to the wrist, but no underlying ulceration or acute pigmentation, indurated mass on the extensor surface of the forearm with moderate erythema, and normal strength in the arm. Her left arm remained negative for deep venous thrombosis by Doppler exam. Her left forearm ultrasound revealed an area of soft tissue thickening and induration of the left lateral forearm at the site of her chemotherapy extravasation, but with no evidence of abscess or focal fluid collection. The patient

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received a dermatology consult, which felt no further intervention was needed. A surgery consult was also obtained; the symptoms of the patient were considered to represent a questionable compartment syndrome, but no urgent surgical intervention was required. The patient's condition improved, and she was discharged on July 22, 2011.

During a follow-up visit on July 27, 2011, her arm was significantly improved, although there was still a hard, erythematous, indurated area just distal to her left elbow, which was approximately 6-8 cm in diameter.

The patient's past medical/surgical history is significant for pulmonary embolism, breast cancer, hypertension, type 2 diabetes mellitus, dyslipidemia, right mastectomy, and IVC filter placement. Medications taken at the time of the event included metoprolol, hydrochlorothiazide, lisinopril, amlodipine, Coumadin®, metformin, Zofran®, and dexamethasone.

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

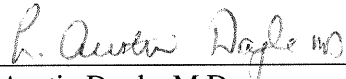
Adverse Event	Grade	Attribution
Injection site reaction (n=5)	3	1 Possible
	2	1 Unlikely, 2 Possible, 1 Probable

To date, a total of 2,826 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.

	Injection site reaction
<b>Temsirolimus</b>	Possible
<b>Carboplatin</b>	Possible
<b>Paclitaxel</b>	Possible
<b>Endometrial adenocarcinoma</b>	Unrelated

Date: 9/1/11

Signature: 

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

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

cc: Julia J. Perkins, M.D.  
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Pfizer, Inc.