



**DATE:** MAR 22 2011  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1487991  
**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 this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter 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 69-year-old female with metastatic endometrioid endometrial adenocarcinoma experienced a grade 3 small bowel obstruction and grade 2 infectious colitis while on a phase 2 trial utilizing the investigational agent temsirolimus.

**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. 3: Obstruction : Small bowel NOS</b>  <b>Gr. 2: Colitis, infection (e.g., Clostridium difficile)</b>
AE: <b>1487991</b>	Protocol: <b>GOG-0248</b>

The patient is a 69-year-old female with stage II metastatic endometrioid endometrial adenocarcinoma who experienced a small bowel obstruction and infectious colitis while on a phase 2 trial utilizing the investigational agent temsirolimus. She began the first course of treatment on October 27, 2010, receiving temsirolimus 25 mg IV over 30 minutes weekly, every 6 weeks. She received her last dose of temsirolimus on January 7, 2011 (Cycle 2, Day 24).

The patient was diagnosed with endometrioid endometrial adenocarcinoma in December 2008, and is status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, upper vaginectomy, pelvic and paraaortic lymph node dissection, infracolic omentectomy, peritoneal biopsies, and radiation therapy. She began the investigational therapy on October 27, 2010.

On December 27, 2010 (Cycle 2, Day 13), the patient presented to the ER with a 2-day history of nausea, vomiting green bile, diarrhea, and abdominal pain. She was given Compazine®, and was discharged. On December 29, 2010, the patient presented to the clinic with persistent nausea, vomiting, diarrhea, and epigastric pain. Her abdomen was soft, distended, and tender with palpation, with hypoactive bowel sounds. She was admitted, IV fluids were started, and she was made NPO. An NG tube was inserted with an immediate output of 700 mL of bilious drainage, and it was left in place with low suction. A proton pump inhibitor (PPI), anti-emetics, and morphine sulfate for pain were also ordered. An abdominal X-ray showed possible partial small bowel obstruction. A CT scan of the abdomen and pelvis revealed new moderate abdominal pelvic ascites, new moderate dilatation of the stomach, and small bowel with long segment, mild decrease in caliber and wall thickening in the distal ileum; probably representing enteritis causing partial small bowel obstruction. A small hiatal hernia with new circumferential wall thickening of the distal esophagus was noted; possibly representing esophagitis.

On December 30, 2010, the patient's NG tube continued to drained large amounts of greenish fluid. She was started on IV Cipro® and Flagyl®. On January 1, 2011 (Cycle 2, Day 18), the patient's NG tube was clamped and a clear liquid diet was started, with no complaints of nausea, vomiting, or abdominal pain; however, she did have multiple loose stools. Later that day, she tolerated removal of her NG tube. By January 4, 2011 (Cycle 2, Day 21), the patient's condition improved, and she was discharged.

On January 10, 2011 (Cycle 2, Day 27), the patient presented to the ER, and was admitted for nausea, vomiting, diarrhea, abdominal pain, and weakness. On January 12, 2011, the patient's stool specimen was positive for *Clostridium difficile*, and she was started on Flagyl®. On January 13, 2011, the patient was discharged, with orders to continue the antibiotic course. The last week of her treatment for Cycle 2 was held pending her follow-up clinic visit scheduled for January 26, 2011, at which time, treatment for Cycle 3, Day 1 would be considered.

The patient's past medical/surgical history is significant for coronary artery disease, hypertension, sinus bradycardia, hypercholesterolemia, chronic obstruction pulmonary disease (COPD), cataracts, osteoporosis, tubal ligation, triple coronary artery bypass, and wedge resection of the left upper lobe. Medications taken at the time of the event included Tenormin®, Niaspan®, Flonase®, pravastatin, Compazine®, Imodium®, Centrum® Silver® multivitamins, Citracal®, and aspirin.

There have been 33 other cases of small bowel obstruction and 5 other cases of infectious colitis reported as serious adverse events through AdEERS under the temsirolimus NSC and/or IND, as summarized in the table below:

Adverse Events	Grade	Attribution
Small bowel obstruction (n=33)	4	1 Unlikely
	3	7 Unrelated, 20 Unlikely, 4 Possible
	2	1 Unlikely
Colitis, infection, e.g. <i>Clostridium difficile</i> (n=5)	3	1 Unrelated, 1 Unlikely, 2 Possible
	2	1 Unrelated

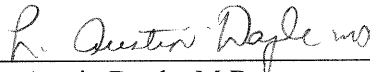
To date, a total of 2,558 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a possible relationship exists between the events and the investigational therapy temsirolimus.

	Obstruction: Small bowel NOS	Colitis, infection (e.g., <i>Clostridium difficile</i> )
<b>Temsirolimus</b>	Possible	Possible
<b>Endometrioid endometrial adenocarcinoma</b>	Possible	Unrelated

Date: 3/18/11

Signature:

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

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

cc: Subramanian Hariharan, M.D.  
 Jocelyn Ulrich, R.Ph.  
 ADVEXP@pfizer.com  
 Pfizer, Inc.