



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** August 16, 2010  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1289062  
**TO:** Investigators Using CCI-779 (temsirolimus, Torisel®) (NSC 683864)

*L. Austin Doyle MD*

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 experienced grade 3 dehydration while on a phase 2 trial utilizing the investigational agent temsirolimus.

## ADVERSE EVENTS ASSESSMENT

IND 61010	ADVERSE EXPERIENCE REPORT NO.
NSC 683864	IND Safety Report: #1
CCI-779 (temsirolimus, Torisel®)	Event: Gr. 3: Dehydration
AE: 1289062	Protocol: GOG-0248

The patient is a 68-year-old female with endometrioid endometrial adenocarcinoma who experienced dehydration 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. The patient received her last dose of temsirolimus on March 12, 2010 (Cycle 8, Day 30).

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

On March 10, 2010 (Cycle 8, Day 28), the patient, who had experienced complications including enteritis, diarrhea, and malnutrition as well as a failure to thrive (necessitated PEG tube placement in February 2010), presented to the ER and was admitted to the hospital with severe nausea and vomiting. She also had diarrhea, however, she denied any history of melena or hematochezia. She had experienced a syncopal episode 1 day prior to admission, with no prior history of head trauma, subsequent confusion or shortness of breath associated with this episode. Her physical examination was within normal limits. The patient's potassium was 3.1 mEq/L (reference range: 3.5-5.1 mEq/L), her BUN was 43 mg/dL (reference range: 8-21 mg/dL), and her creatinine was 1.47 mg/dL (reference range: 0.70-1.20 mg/dL). Her ECG showed normal sinus rhythm with nonspecific T-wave abnormality. It was felt that her syncopal episode was likely due to dehydration. The acute abdominal series showed distended loops of small and large bowel with scattered air-fluid levels suspicious of enteritis. There was no evidence of obstruction. She was made NPO and started on Zofran® and IV fluids with potassium replacement.

On March 11, 2010 (Cycle 8, Day 29), a repeat abdominal series was not concerning and the patient's tube feeding was reinstated at 5 cc per hour, which was increased later that day to 30 cc per hour, without any residuals. On March 12, 2010 (Cycle 8, Day 30), the patient's condition improved significantly, and she was discharged home on the same day after receiving the scheduled dose of temsirolimus. She was advised to follow-up at the clinic.

On March 17, 2010, the patient returned to the clinic for follow up and pre-cycle evaluation with no new complaints. She had gained 4 pounds since her last clinic visit, while on PEG tube feeding. Temsirolimus was re-started (Cycle 9, Day 1).

The patient's past medical/surgical history is significant for osteoporosis, radiation-induced diarrhea and enterocolitis, a pulmonary embolism following surgery in 2007 necessitating long-term anticoagulation, vacuum placement in 2007, IV port placement, and incisional hernia repair with mesh placement. Medications taken at the time of the event included magnesium, colestipol, Lipitor®, potassium, Imodium®, lorazepam, Lortab®, Reglan®, Ambien®, Boniva®, Lovenox®, and vitamin D.

There have been 70 other cases of dehydration reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as shown in the table below:

Adverse Event	Grade	Attribution
Dehydration (n=70)	4	1 Unrelated, 1 Possible
	3	11 Unrelated, 31 Unlikely, 5 Possible, 4 Probable, 1 Definite
	2	2 Unrelated, 11 Unlikely, 2 Possible, 1 Probable

To date, a total of 2,147 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 temsirolimus.

	Dehydration
<b>Temsirolimus</b>	Possible
<b>Endometrioid endometrial adenocarcinoma</b>	Unlikely
<b>PEG tube</b>	Possible

Date: 8/17/10

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.  
Wyeth GSSE Triage: [WASDTRI@wyeth.com](mailto:WASDTRI@wyeth.com)  
Wyeth Pharmaceuticals, Inc.