



**DATE:** March 12, 2010

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**SUBJECT:** Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1710309

**TO:** Investigators Using Bevacizumab (NSC 704865) and Temsirolimus (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 agents bevacizumab and temsirolimus.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and 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 INDs 7921, 11460, and 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 bevacizumab and temsirolimus, there does not appear to be a change in the risk-benefit ratio for bevacizumab and temsirolimus studies; 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 69-year-old male with renal cell adenocarcinoma metastatic to the bone and lungs experienced grade 3 dehydration while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus.

## ADVERSE EVENTS ASSESSMENT

IND <b>7921</b> <b>61010</b> NSC <b>704865</b> <b>683864</b> <b>Bevacizumab</b> <b>CCI-779</b> <b>(rhuMAb VEGF)</b> <b>(temsirrolimus,</b> <b>Torisel®)</b> AE: <b>1710309</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> <b>Gr. 3: Dehydration</b> Protocol: <b>E2804</b>
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The patient is a 69-year-old male with renal cell adenocarcinoma metastatic to the bone and lungs who experienced dehydration while on a phase 2 trial utilizing the investigational agents sorafenib, bevacizumab, and temsirolimus. He did not receive sorafenib. The patient began the first course of the investigational therapy on May 20, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. He received his last doses of bevacizumab and temsirolimus on August 10, 2009 (Cycle 4, Day 1).

The patient was initially diagnosed with renal cell adenocarcinoma in February 2009, and is status post a right radical nephrectomy. He began the investigational therapy on May 20, 2009.

On August 16, 2009 (Cycle 4, Day 5), the patient presented to the emergency room with complaints of progressively worsening weakness, anorexia, nausea, and diffuse abdominal discomfort since his last treatment. He also reported intermittent nose bleeds, non-productive cough, and sleeping 15-18 hours a day. His vital signs were: temperature 100.9° F, pulse 86 bpm; respiration 18 breaths per minute, and blood pressure 164/75 mmHg. On examination, the patient appeared weak, had ulcers on his tongue with no tongue coating, dry mucus membranes, and crusted blood in the nares. Laboratory reports were consistent with dehydration and anemia: hemoglobin 9.2 g/dL (reference range: 14.0-18.0 g/dL) which decreased to 7.8 g/dL the next morning, BUN 25 mg/dL (reference range: 3-29mg/dL), and creatinine 1.36 mg/dL (reference range: 0.5-1.4 mg/dL). The patient received Zofran®, he was started on IV fluids, and he was admitted to the hospital for rehydration and management of his anemia. The study agents were held until the patient was rehydrated and his hemoglobin and hematocrit were stable. He received 2 units of packed red blood cells. The patient was closely monitored and instructed to avoid aspirin and NSAIDS. On August 18, 2009 (Cycle 4, Day 7), the patient's hemoglobin was 10.9 g/dL, he was afebrile, well hydrated, and feeling significantly improved. He was discharged home later that day with instructions to follow up with his primary care physician.

On August 24, 2009, the patient presented to the clinic for a follow-up visit. He reported feeling well and had improved appetite since discharge. His vital signs and a comprehensive metabolic panel report were within normal limits. The investigational treatment was resumed with the temsirolimus at a reduced dose of 15 mg.

The patient's past medical/surgical history is significant for diabetes, back pain, hypertension, gastroesophageal reflux disease, unspecified renal failure, hypercholesterolemia, arthritis, hypochromic/microcytic anemia, cancer of the right shoulder, coronary artery disease status post left heart catheterization and cardiac stent placements × 3, osteoarthritis, , , bilateral total knee arthroplasty, right shoulder surgery with rod, adrenalectomy, nephrectomy lateral, bilateral bunionectomy, left hand surgery, rod placement in right arm, and a remote smoking history. Medications taken at the time of the event included prochlorperazine, valacyclovir, losartan, hydrochlorothiazide, Aleve®, aspirin, metoprolol tartrate, amlodipine, omeprazole, Percocet®, ibuprofen, baclofen, and Neurontin®.

There have been 63 other cases of dehydration reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as summarized in the table below. There have been 526 cases of dehydration (ranging from grades 2 to 3, definite to unrelated) reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND.

Adverse Event	Grade	Attribution
<b>Temsirolimus</b>		
Dehydration (n=63)	4	1 Possible, 1 Unrelated
	3	1 Definite, 4 Probable, 6 Possible, 25 Unlikely, 11 Unrelated
	2	1 Possible, 11 Unlikely, 2 Unrelated

To date, a total of 25,462 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC and 1,935 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.


In this case, it is felt that a probable causal relationship exists between the event and temsirolimus and that an unlikely relationship exists between the event and bevacizumab.

	Dehydration
<b>Bevacizumab</b>	Unlikely
<b>Temsirolimus</b>	Probable
<b>Renal cell carcinoma</b>	Unrelated

Date: 3/15/10

Signature:   
Helen Chen, M.D.  
(IDB Monitor for bevacizumab)

Date: 3/12/10

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

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

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