



DATE: September 4, 2009
FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1986402
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 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 50-year-old female with endometrioid endometrial adenocarcinoma developed grade 3 dehydration and grade 3 hyponatremia while on a phase 2 trial utilizing the investigational agent temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®) AE: 1986402	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Dehydration Gr. 3: Sodium, serum-low (hyponatremia) Protocol: NCIC-160
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The patient is a 50-year-old female with endometrial adenocarcinoma who developed dehydration and hyponatremia while on a phase 2 trial utilizing the investigational agent temsirolimus. She began the first course of the investigational therapy on September 26, 2006, receiving temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. She received her last dose of temsirolimus on November 7, 2006 (Cycle 1, Day 43).

The patient was diagnosed with endometrioid endometrial adenocarcinoma in July 2004, and is status post total abdominal hysterectomy with bilateral salpingo-oophorectomy, and multi-agent systemic chemotherapy until January 2005. She later developed right sided pleural effusion and liver metastasis. She began the investigational therapy on September 26, 2006.

On October 15, 2006 (Cycle 1, Day 20), the patient presented to the emergency room complaining of diarrhea, nausea, vomiting, and abdominal cramping. She also complained of flu-like symptoms for more than 1 week with decreased appetite. She was afebrile, and the remainder of her examination was unremarkable. The patient was treated for hypokalemia [potassium of 2.4 mmol/L (reference range: 3.5-5.1 mmol/L)] with IV fluids and electrolytes, and released after 12 hours. On October 17, 2006 (Cycle 1, Day 22), the patient presented to clinic complaining of weakness. The physical examination revealed a temperature of 36.3°C, heart rate of 104 bpm, blood pressure of 110/84 mmHg and respiratory rate of 18 bpm. The laboratory findings showed a potassium of 2.7 mmol/L (reference range: 3.6-5.1 mmol/L), sodium of 128 mmol/L (reference range: 136-144mmol/L), and chloride of 96 mmol/L (reference range: 101-111 mmol/L) with a normal anion gap. Please see the table below. The investigational agent was held, and she was admitted to the hospital for further evaluation and emergent treatment of dehydration and hyponatremia with IV fluids and electrolytes.

On October 18, 2006 (Cycle 1, Day 23), a CT scan of the chest, which was performed to evaluate progression of a pre-existing right pleural effusion, showed a large right pleural effusion which occupied approximately half of the hemithorax. There was no study for comparison and the scan was otherwise unremarkable.

On October 20, 2006, an abdominal X-ray revealed the possibility of an early bowel or partial small bowel obstruction, but the findings were nonspecific. Her potassium was 3.7 mmol/L and sodium was 130 mmol/L. She was discharged on October 22, 2006 with plans to restart the investigational therapy.

Pertinent laboratory values are shown below:

	9/14/2006 Baseline	10/15/2006 C1, D20	10/17/2006 C1, D22	10/18/2006 C1, D23	10/19/2006 C1, D24	10/20/2006 C1, D25
Sodium (reference range: 136-145 mmol/L)	140	127-133	128	124 - 129	128	130
Potassium (reference range: 3.6-5.1mmol/L)	3.9	2.4 - 2.9	2.7	3.2 - 3.4	4.0	3.7
Chloride (reference range: 101-111 mmol/L)	*	97 [98-107 mmol/L]	96	94 - 96	103	96
Total CO₂ (reference range: 22-32 mmol/L)	*	*	23	23 - 24	22	25
Osmolality (reference range: 283-292 mM/Kg)	*	274	*	*	270	*
Urea (reference range: 2.9-9.3 mmol/L)	*	5.6	3.7	3.1	*	2.1
Creatinine (reference range: 35-88 µmol/L)	*	71	55	61	*	53

*=not done

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The patient's past medical/surgical history is significant for tonsillectomy. Medications taken at the time of the event include Imodium.

There have been 56 other cases of dehydration and 19 other cases of hyponatremia reported as a serious adverse event through AdEERS under the temsirolimus NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Dehydration (n=56)	4	1 Possible, 1 Unrelated
	3	2 Probable, 7 Possible, 21 Unlikely, 10 Unrelated
	2	1 Possible, 11 Unlikely, 2 Unrelated
Hyponatremia (n=19)	4	1 Unlikely, 2 Unrelated
	3	5 Possible, 8 Unlikely, 3 Unrelated

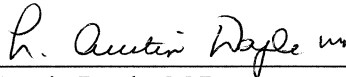
To date, a total of 1,720 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a definite relationship exists between the investigational agent and the dehydration, while a possible relationship exists between the investigational agent and hyponatremia.

	Dehydration	Hyponatremia
<u>Temsirolimus</u>	Definite	Possible
<u>Endometrial adenocarcinoma</u>	Unlikely	Unlikely
<u>Virus</u>	Possible	Possible

Date: 9/8/09

Signature:


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

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

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