



**DATE:** 6/1/11  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
*L. Austin Doyle M.D.*  
**SUBJECT:** CCI-779 (temsirolimus, Torisel®) and AZD6244 Hydrogen sulfate IND Safety Report, AE#  
**1631273**  
**TO:** Investigators Using Temsirolimus (NSC 683864) and AZD6244 (NSC 748727)

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 temsirolimus and AZD6244 Hydrogen sulfate.

The following must be completed by all investigators using temsirolimus under NCI IND 61010 and AZD6244 Hydrogen sulfate under NCI IND 77782:

- 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 INDs 61010 or 77782, 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 and AZD6244 Hydrogen sulfate, there does not appear to be a change in the risk-benefit ratio for temsirolimus or AZD6244 Hydrogen sulfate, 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 55-year-old female with recurrent pelvic sarcoma experienced grade 4 colitis and expired while on a phase 2 trial utilizing the investigational agents temsirolimus and AZD6244 Hydrogen sulfate.

## ADVERSE EVENTS ASSESSMENT

IND 77782 NSC 748727 <b>AZD6244 Hydrogen sulfate</b> AE: 1631273	61010 683864 <b>CCI-779</b> <b>(temsirolimus, Torisel®)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 4: Colitis</b> Protocol: <b>8412</b>
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The patient was a 55-year-old female with metastatic follicular dendritic cell sarcoma who experienced grade 4 colitis, and expired while on a phase 2 trial utilizing the investigational agents temsirolimus and AZD6244 Hydrogen sulfate. She began the study treatment on February 10, 2011. The planned protocol therapy was as follows:

Cycle = 28 days:  
 AZD6244 Hydrogen sulfate: 50 mg PO BID  
 Temsirolimus: 25 mg IV over 30-60 min on days 1, 8, 15, and 22

She received the last dose of temsirolimus on May 5, 2011 (Cycle 4, Day 1), and the last dose of AZD6244 Hydrogen sulfate on May 7, 2011 (Cycle 4, Day 3).

The patient was diagnosed with sarcoma of the neck in December 2002 and was status post multiple-agent systemic chemotherapy (April 2003-July 2003), radiation and soft-neck mass resection (dates not provided), and multiple-agent systemic chemotherapies (July 2010-October 2010). She began the investigational therapy on February 10, 2011.

At a follow-up visit on May 5, 2011 (Cycle 4, Day 1), the patient's physical examination was unremarkable. Her blood pressure was 98/64 mmHg, pulse was 105 bpm, temperature was 36.6 °C, and respiration was 18 breaths/minute. The patient's hemoglobin was 13.7 g/dL (reference range: 12-16 g/dL) and the hematocrit was 40.5 % (reference range: 37-47%). On May 7, 2011 (Cycle 4, Day 3), the patient presented to the ER with a 2-day history of bloody diarrhea, rectal bleeding, abdominal cramps, and pain. She was given fresh frozen plasma, blood transfusions, platelets, and was transferred to the ICU. A colonoscopy (date not provided) revealed a diffusely inflamed and friable necrotic colon. On May 11, 2011, the patient underwent a subtotal colectomy with end ileostomy for ischemic colitis. On May 14, 2011, the patient was extubated and transferred to hospice care. On May 18, 2011, the patient died at home from progressive disease.

The patient's past medical/surgical history was significant for diabetes mellitus, hypertension, thyroid cancer, hypothyroidism, hyperlipidemia, pulmonary embolism, C-section, and bilateral tubal ligation. Medications taken at time of the event included Actos®, Ativan®, Colace®, Glucophage®, K-Dur®, Lasix®, MiraLax®, oxycodone, OxyContin®, and Imodium®.

There have been 4 other cases of colitis reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND, and no other cases of colitis reported to the NCI as serious adverse events through AdEERS under the AZD6244 Hydrogen sulfate NSC and/or IND as summarized in the table below:

Adverse Event	Grade	Attribution
<b>Temsirolimus</b>		
Colitis (n=4)	4	1 Unlikely
	3	1 Unlikely, 1 Possible
	2	1 Unrelated


To date, a total of 2727 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC, and a total of 418 patients have been enrolled in NCI-sponsored clinical trials under the AZD6244 hydrogen sulfate IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the investigational therapies temsirolimus and AZD6244 Hydrogen sulfate.

	<b>Colitis</b>
<b>Temsirolimus</b>	Possible
<b>AZD6244 hydrogen sulfate</b>	Possible
<b>Soft tissue neoplasm, NOS</b>	Probable

Date: 6/1/11

Signature:

  
L. Austin Doyle, M.D.  
(IDB Monitor for temsirolimus and  
AZD6244 Hydrogen sulfate)

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

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