



DATE: 3/30/11
FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (temsirolimus, Torisel®) and AZD6244 Hydrogen sulfate IND Safety Report, AE# 1651103
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 71-year-old male with liposarcoma experienced grade 3 syncope while on a phase 2 trial utilizing the investigational agents temsirolimus and AZD6244 Hydrogen sulfate.

ADVERSE EVENTS ASSESSMENT

IND 77782 NSC 748727 AZD6244 Hydrogen sulfate AE: 1651103	61010 683864 CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 3: Syncope Protocol: 8412
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The patient is a 71-year-old male with liposarcoma who experienced syncope while on a phase 2 trial utilizing the investigational agents temsirolimus and AZD6244 Hydrogen sulfate. He began the first course of the investigational therapy on February 2, 2011, receiving temsirolimus 25 mg IV over 30-60 minutes on Days 1, 8, 15, and 22, and AZD6244 Hydrogen sulfate 50 mg PO twice daily, every 28 days. He received his last dose of temsirolimus on February 9, 2011 (Cycle 1, Day 8), and his last dose of AZD6244 Hydrogen sulfate on February 14, 2011 (Cycle 1, Day 13).

The patient was diagnosed with liposarcoma in July 2007, and is status post surgery, single agent systemic chemotherapy, and radiation therapy. The patient started the investigational treatment on February 2, 2011.

On February 14, 2011 (Cycle 1, Day 13), the patient visited his oncologist for follow-up of worsening sore throat, difficulty swallowing, and bilateral ear pain for which he was started on Augmentin® 2 days prior. The patient appeared tired, had significant mucositis with pain from several oral ulcers likely due to treatment, and significant bilateral ear wax. He was given one liter of IV fluid with plans for daily fluid infusions for the remainder of the week. The patient was to follow-up in 3 days for re-evaluation. Later that day, the patient was brought to the emergency room via ambulance after being found on the floor at home. He was unable to recall the events of what happened, and he had questionable mental status changes and slight confusion. He had a blood pressure of 196/96 mmHg, and a pulse rate of 103 bpm. The patient, who has a history of mild to moderate chronic dyspnea on exertion and used oxygen at home, had an oxygen saturation of 96% on 2 liters of oxygen. An ECG showed sinus tachycardia, right bundle branch block, and T-wave inversions in the anterior and inferior leads. His troponin I was 0.153 ng/mL (reference range: 0-0.390 ng/mL). A chest X-ray was unremarkable for evidence of pneumonia. A CT scan of the head showed mild microangiopathic white matter changes, and no evidence of intracranial hemorrhage, acute territorial infarction, mass effect, or fracture. The patient was admitted to the hospital for possible syncope associated with dehydration. He was started on IV fluids, IV Rocephin®, and Tylenol®.

A cardiology evaluation on February 16, 2011, revealed that the patient did not have any acute cardiac issues. Blood and urine cultures were negative. By this day, the patient's condition improved and he was discharged home in stable condition with instructions to follow-up in 1-2 days.

The patient's past medical/surgical history is significant for diabetes, hypertension, hypoxemia, hypercholesterolemia, gastritis, sigmoid resection for desmoids tumors and prostate cancer (treated with primary radiation). Medications taken at the time of the event included Actos®, Altace®, Byetta®, Coreg®, Levoxyl®, Maxzide®, Nexium®, and Vytorin®.

There have been 5 other cases of syncope (grade 3, 2 unrelated and 3 unlikely related) reported to the NCI as a serious adverse event through AdEERS under the temsirolimus NSC and/or IND, and no other cases of syncope reported to the NCI as a serious adverse event through AdEERS under the AZD6244 Hydrogen sulfate NSC and/or IND.

To date, a total of 2490 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC, and a total of 339 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 therapy temsirolimus, but that an unlikely causal relationship exists between the event and the investigational therapy AZD6244 Hydrogen sulfate.

	Syncope
Temsirolimus	Possible
AZD6244 Hydrogen sulfate	Unlikely
Liposarcoma	Possible
Dehydration	Probable

Date: 3/30/11

Signature: AE for LAD

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(IDB Monitor for temsirolimus and
AZD6244 Hydrogen sulfate)

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

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