



DATE: SEP 20 2011

FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: AZD6244 Hydrogen sulfate and CCI-779 (temsirolimus, Torisel®) IND Safety Report #2, AE# 1396035

TO: Investigators Using AZD6244 Hydrogen sulfate (NSC 748727) 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 AZD6244 Hydrogen sulfate and temsirolimus.

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

- 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 AZD6244 Hydrogen sulfate and temsirolimus, there does not appear to be a change in the risk-benefit ratio for AZD6244 Hydrogen sulfate or 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 69-year-old female with metastatic endometrial stromal sarcoma experienced grade 3 paronychia while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and temsirolimus.

This report has been amended to reflect a change in assessment. Changes to the attached report are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

ADVERSE EVENTS ASSESSMENT

IND 77782	61010	ADVERSE EXPERIENCE REPORT NO.
NSC 748727	683864	IND Safety Report: # 2
AZD6244 Hydrogen sulfate	CCI-779 (temsirolimus, Torisel®)	Event: Gr. 3: Paronychia
AE: 1396035		Protocol: 8412

This report has been amended to reflect a change in assessment. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

The patient is a 69-year-old female with metastatic endometrial stromal sarcoma who experienced paronychia while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and temsirolimus. The planned protocol therapy the patient was assigned to is follows:

Cycle = 28 Days
 AZD6244 Hydrogen sulfate: 50 mg PO BID
 Temsirolimus: 20 mg IV over 30-60 min on Days 1, 8, 15, and 22

The patient was diagnosed with endometrial stromal sarcoma in April 2008, and is status post chemotherapy, radiation, and surgery. She began the investigational therapy on March 17, 2011. She started the investigational treatment on a treatment arm receiving only AZD6244 Hydrogen sulfate but crossed over to a treatment arm receiving both AZD6244 Hydrogen sulfate and temsirolimus on May 12, 2011. She received the last dose of AZD6244 Hydrogen sulfate on July 19, 2011 (Cycle 5, Day 13), and the last dose of temsirolimus on July 14, 2011 (Cycle 5, Day 8).

At a follow-up visit on July 14, 2011, the patient was noted to have paronychia of the left thumb. She refused an incision and drainage at that time, and the event was managed with salt water baths. On July 16, 2011, she presented to urgent care due to progression in the size of the lesion and increased tenderness of the left thumb. She was referred to the emergency room to be managed by a hand specialist. She was admitted and started on IV antibiotics. No further information has been provided.

The patient's past medical/surgical history is unavailable. Medications taken at time of the event are unavailable.

There have been no other cases of infection in general reported to the NCI as serious adverse events through AdEERS under the AZD6244 Hydrogen sulfate and AZD6244 NSC and/or IND. Although infection is an expected adverse event for temsirolimus, paronychia specifically has not been described previously.

To date, a total of 475 patients have been enrolled in NCI-sponsored clinical trials under the AZD6244 Hydrogen sulfate IND and/or NSC, a total of 183 patients have been enrolled in NCI-sponsored clinical trials under the AZD6244 IND and/or NSC, and a total of 2,802 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~~ **possible** causal relationship exists between the event and the investigational therapy AZD6244 Hydrogen sulfate, and ~~an unlikely~~ **a possible** relationship exists between temsirolimus and the event.

	Paronychia
AZD6244 Hydrogen sulfate	Probable Possible
Temsirolimus	Unlikely Possible
Endometrial stromal sarcoma	Unlikely

Date: 9/19/11

Signature: 

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

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

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