



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: March 16, 2010
FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# **1548651**
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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 75-year-old male with mantle cell lymphoma developed grade 4 testicular atrophy while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with rituximab.

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Sexual/Reproductive Function-Other: Testicular Atrophy
AE: 1548651	Protocol: N038H

The patient is a 75-year-old male with mantle cell lymphoma who experienced testicular atrophy while on a phase 2 trials using the investigational agent, temsirolimus in combination with rituximab. He began the first course of the investigational therapy on September 12, 2008, receiving temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, and rituximab 375 mg/m² IV at an initial rate of 50 mg/hour, increasing by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour on Day 1, followed by then rituximab 375 mg/m² IV at an initial rate of 100 mg/hour, increasing by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour on Days 8, 15, and 22 in Cycle 1. For Cycle 2 and beyond, the patient received temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, and rituximab 375 mg/m² IV at an initial rate of 100 mg/hour, increasing by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour on Day 1 of Cycles 3, 5, 7, 9, and 11 only, every 4 weeks. The patient received his last doses of temsirolimus and rituximab on August 18, 2009 (Cycle 13, Day 1).

The patient was initially diagnosed with mantle cell lymphoma in September 2008, and is status post splenectomy at time of diagnosis and multiple-agents systemic chemotherapy. He began the investigational therapy on September 12, 2008.

On February 3, 2009 (Cycle 6, Day 1), the patient reported that he was getting weaker and was losing muscle mass. He also noted that his testicles appeared smaller. Neurological examination revealed normal motor strength bilaterally. On March 3, 2009 (Cycle 7, Day 1), the testosterone level was 440 ng/dL (reference range: 270-1070 ng/dL). When reviewed by the attending physician, it was felt that the testicular atrophy would be monitored because at that range of testosterone level, the patient was not eligible for hormonal replacement.

On April 28, 2009 (Cycle 9, Day 1), the patient reported lower extremity edema, cracking finger nails, and persistence of testicular atrophy. He was treated with Lasix® and potassium supplement. On July 21, 2009 (Cycle 12, Day 1), he reported worsening of his testicular atrophy, as well as the persistence of lower extremity edema. The patient denied associated pain, night sweat, fever, or chills. The laboratory report on that day revealed a testosterone level of 112 ng/dL. By September 2, 2009, the patient had completed the investigational study, and during a surveillance visit, was started on AndroGel® three times weekly.

On December 8, 2009, a follow-up visit revealed improvement in his general well being and the building of muscle mass. The patient was asked to continue with the AndroGel® and to return for follow-up in 1 month.

The patient has no significant past medical/surgical history. Medications taken at the time of the event included Lasix® and potassium supplement.

There have been no other cases of testicular atrophy reported to the NCI as a serious adverse event through AdEERS under the temsirolimus NSC and/or IND.

To date, a total of 1935 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 relationship exists between the event and the investigational agent.

	Testicular Atrophy
Temsirolimus	Probable
Rituximab	Unrelated
Mantle cell lymphoma	Unrelated

Date: 3/18/10

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

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

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