



DATE: SEP 29 2010

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

SUBJECT: CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1497480

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 67-year-old female with endometrioid endometrial adenocarcinoma experienced grade 3 right upper extremity pain while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with megestrol and tamoxifen.

ADVERSE EVENTS ASSESSMENT

IND 61010	ADVERSE EXPERIENCE REPORT NO.
NSC 683864	IND Safety Report: #1
CCI-779 (temsirolimus, Torisel®)	Event: Gr. 3: Pain: Extremity-limb
AE: 1497480	Protocol: GOG-0248

The patient is a 67-year-old female with endometrioid endometrial adenocarcinoma who experienced right upper extremity pain while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with megestrol and tamoxifen. She began the first course of the investigational therapy on July 9, 2009, receiving temsirolimus 25 mg IV over 30 minutes weekly, and megestrol 80 mg PO twice daily x 3 weeks followed by tamoxifen 20 mg PO twice daily x 3 weeks, every 6 weeks. The patient received her last dose of temsirolimus on June 4, 2010 (Cycle 8, Day 29), her last dose of megestrol on January 4, 2010 (Cycle 5, Day 12), and her last dose of tamoxifen on December 24, 2009 (Cycle 5, Day 1).

The patient was diagnosed with endometrioid endometrial adenocarcinoma in August 2007, and is status post total abdominal hysterectomy with bilateral salpingo-oophorectomy, and multiple-agent systemic chemotherapy. She began the investigational therapy on July 9, 2009.

On June 4, 2010 (Cycle 8, Day 29) the patient presented to the clinic with increased right upper extremity swelling and worsening pain over a 2-week period. She had complained of swelling in her hands 1 week earlier necessitating a venous Doppler® study which was negative for DVT. She was afebrile, had a blood pressure of 93/62 mmHg, and a pulse of 90 bpm. The patient had right upper extremity swelling with pitting edema of the right hand extending to a point proximal to the elbow. The investigational treatment was held and she was admitted to the hospital for further evaluation. On June 6, 2010, a CT scan of the upper right extremity showed nonspecific subcutaneous soft tissue edema in the dorsal-medial aspect of the right elbow and proximal forearm without CT evidence of soft tissue abscess or mass. The next day, a right upper extremity venous duplex scan was unremarkable for deep or superficial venous thrombosis. The patient was continued on Vicodin®, fentanyl patch, and Lasix®.

Based on the negative findings of the multiple investigative procedures, it was felt that the patient most likely had lymphedema. On June 11, 2010, the patient was discharged home in stable condition. During a follow-up visit on June 14, 2010, the patient reported continued pain in the right medial portion of her forearm and right breast with associated swelling and warmth. The patient's right upper extremity revealed subcutaneous lymphatic fluid with subcutaneous fibrosis, erythema, and warmth in the forearm. The breast examination also revealed subcutaneous lymphedema and fluid in the right breast with associated warmth, erythema, and tenderness. She was started on a 14-day course of Duricef®.

On June 16, 2010, a mammogram revealed asymmetric edema and skin thickening of the right breast greatest in the upper outer quadrant with a differential diagnosis including cellulitis and edema versus inflammatory carcinoma. On June 23, 2010, a right breast punch biopsy of the skin was consistent with lichen simplex chronicus. On June 24, 2010, the patient presented to the clinic with 4+ edema of the right arm and associated pain. The patient was informed that it was unlikely that the investigational treatment caused unilateral swelling of her right arm. She indicated her desire to continue study participation.

On July 1, 2010, the patient continued to have high output edema of the right upper arm with associated tenderness and pain in her hand. There was no evidence of neurological impairment. The patient had shown no clear signs of infection and had not fully responded to antibiotics. She was started on decongestive therapy to mobilize fluid out of the arm and breast. On July 2, 2010 (Cycle 9, Day 1), the patient resumed the investigational treatment. On July 8, 2010, a bilateral upper extremity venogram was unremarkable for stenosis, intraluminal thrombus, or collateral circulation. An ultrasound of her bilateral

internal jugular veins was also unremarkable. On July 15, 2010, the patient presented to the clinic complaining of worsening right arm swelling, pain, and now with right facial swelling. She also reported swelling in her right breast. The breast examination revealed definite lymphedema and signs of inflammatory changes in the right breast. A right breast skin biopsy on July 21, 2010 described skin with mild dermal fibrosis, and slight increase in dermal vascularity with focal minimal perivascular chronic inflammation. There was no evidence of malignancy. On July 23, 2010 (Cycle 9, Day 22), the patient received the investigational treatment as scheduled.

The patient's past medical/surgical history is significant for morbid obesity, diabetes mellitus, anemia, coronary artery disease status post cardiac catheterization and stent placement, peripheral vascular disease, peripheral neuropathy, hypertension, hypercholesterolemia, hypertriglyceridemia, sick sinus syndrome status post-pacemaker placement, degenerative joint disease of the spine with spinal stenosis, right foot MRSA infection (January 2009), diastolic heart failure, cholecystectomy, and appendectomy. Medications taken at the time of the event included Vicodin[®] extra strength, fentanyl, lisinopril, Lasix[®], hemostatin, Ambien[®], Coreg[®], aspirin, Lantus[®], and Novolog[®].

There have been 6 other cases of pain in the extremity reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Extremity pain (n=6)	4	1 Unlikely
	3	3 Unrelated, 2 Unlikely

To date, a total of 2,213 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and temsirolimus.

	Extremity pain
Temsirolimus	Possible
Megace[®]	Unlikely
Tamoxifen	Unlikely
Endometrioid endometrial adenocarcinoma	Unlikely
Simvastatin	Possible
Tricor[®]	Possible
Peripheral vascular disease	Possible
Peripheral neuropathy	Possible

Date: 9/28/10

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

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

cc: Rafael E. Curiel, Ph.D.
Wyeth GSSE Triage: WASDTRI@wyeth.com
Wyeth Pharmaceuticals, Inc.

Jocelyn Ulrich, R.Ph.
Pfizer, Inc.