



DATE: December 17, 2009

FROM: Pamela J. Harris, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Sunitinib Malate (SU011248 L-malate; Sutent[®]) NCI IND Safety Report #2, AE# 1168449

TO: Investigators Using Sunitinib Malate (NSC 736511)

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 sunitinib malate.

The following must be completed by all investigators using sunitinib malate under NCI IND 74019:

- 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 74019, 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 sunitinib malate, there does not appear to be a change in the risk-benefit ratio for sunitinib malate studies; 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 Assessments describe 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 52-year-old female with metastatic endometrioid endometrial adenocarcinoma experienced a grade 4 pulmonary embolism while on a phase 2 trial utilizing the investigational agent sunitinib malate.

This Adverse Events Assessment 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 74019 NSC 736511 Sunitinib malate (SU011248 L-malate; Sutent®) AE: 1168449	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #2 Event: Gr. 4: Thrombosis/thrombus/embolism Protocol: 7713
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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 52-year-old female with metastatic endometrioid endometrial adenocarcinoma who experienced a pulmonary embolism while on a phase 2 trial utilizing the investigational agent sunitinib malate. She began the first course of treatment on May 4, 2009, receiving sunitinib malate 50 mg PO daily for 4 weeks, every 6 weeks. She received her last dose of sunitinib malate on July 3, 2009 (Cycle 2, Day 19).

The patient was diagnosed with endometrioid endometrial adenocarcinoma in January 2008, and is status post total abdominal hysterectomy, bilateral salpingo-oophorectomy and chemotherapy with multiple systemic agents. She was found to have lesions in the lung in February 2008. She began the investigational treatment on May 4, 2009.

On July 21, 2009 (Cycle 2, Day 37), the patient had a staging CT scan which revealed multiple right-sided pulmonary emboli involving the right lower lobe pulmonary artery, and the right lower lobe posterior and lateral segmental branches. The patient was asymptomatic. She had a history of chronic leg swelling which had not changed and had not had any leg pain apart from intermittent left foot cramping. She had no previous personal or family history of venous thromboembolism. She had never been on oral contraceptives and was not receiving any hormonal therapy. She did not have any recent travel or period of immobilization, and she has been a non-smoker. The patient was started on Tinzaparin®, and the investigational agent was discontinued. It was decided on July 27, 2009, to remove her from the protocol.

The patient's past medical/surgical history is significant for hypertension, tonsillectomy/adenoidectomy (age 6), tubal ligation, morbid obesity, right knee surgery (age 13), and total thyroidectomy for thyroid cancer in 2008 with re-implantation of two parathyroid glands. Medications taken at the time of the event included calcium, Norvasc®, Adalat®, L-thyroxine, ramipril, Rocaltrol®, and ferrous gluconate.


There have been 25 other cases of thrombosis/thrombus/embolism reported to the NCI as serious adverse events through AdEERS under the sunitinib malate NSC and/or IND as shown in the table below:

Adverse Event	Grade	Attribution
Thrombosis/thrombus/embolism (n=25)	5	1 Possible
	4	1 Probable, 7 Possible, 1 Unlikely, 5 Unrelated
	3	6 Possible, 2 Unlikely
	2	2 Possible

There have been 2066 patients enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC. In this case, it is thought that a causal relationship between the event and sunitinib malate cannot be excluded.

	Pulmonary embolism
Sunitinib malate	Possible Unlikely
Endometrioid endometrial adenocarcinoma	Probable

Date: 12/17/09

Signature: 
Pamela Harris, M.D.
(IDB Monitor for sunitinib malate)

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

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