



**DATE:** June 2, 2010  
**FROM:** Pamela J. Harris, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** Sunitinib Malate (SU011248 L-malate; Sutent®) NCI IND Safety Report, AB# 1788898  
**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 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 58-year-old male with metastatic adenocarcinoma of the esophagus experienced grade 4 cerebrovascular ischemia while on a phase 1 trial utilizing the investigational agent sunitinib malate.

**ADVERSE EVENTS ASSESSMENT**

|  |  |
|--|--|
| IND 74019<br>NSC 736511<br>Sunitinib malate (SU011248 L-malate;<br>Sutent®)<br>AE: 1788898 | ADVERSE EXPERIENCE REPORT NO.<br>IND Safety Report: #1<br>Event: Gr. 4: CNS cerebrovascular ischemia<br><br>Protocol: 7898 |
|--|--|

The patient is a 58-year-old male with metastatic adenocarcinoma of the esophagus who experienced cerebrovascular ischemia while on a phase 1 trial utilizing the investigational agent sunitinib malate. He began the first course of treatment on June 10, 2009, receiving sunitinib 50 mg PO daily on Weeks 1, 2, 4, and 5, every 6 weeks. He received his last dose of sunitinib malate on September 1, 2009 (Cycle 2, Day 22).

The patient was diagnosed with metastatic adenocarcinoma of the esophagus in October 2007 and has had no prior therapy. He began the investigational therapy on June 10, 2009.

On September 2, 2009 (Cycle 2, Day 23), the patient was admitted to the hospital with confusion, ataxia, and blurred vision. An MRI of the brain revealed a markedly increased signal involving the left occipital lobe in a gyriform-like pattern and no hemorrhage. The patient was transferred to the research hospital on September 3, 2009. Laboratory findings were significant for a hemoglobin of 9.7 g/dL (reference range: 13.8-17.2 g/dL), hematocrit of 30% (reference range: 40-52%), and platelets of 81 K/uL (reference range: 160-370 K/uL). The patient received 2 units of packed red blood cells. An MRI of the head revealed an acute left posterior cerebral artery (PCA) ischemic infarct and multiple areas of abnormal contrast enhancement within the scalp worrisome for metastatic disease. MR perfusion of the head revealed an uncompensated perfusion defect within the left PCA territory which correlates with the area of infarction. An MRA of the head and neck showed occlusion of the left PCA at the quadrigeminal segment and unremarkable neck vessels. The patient was removed from the protocol that day. The consulting neurologist recommended an echocardiogram with bubble study, lower extremity Doppler® ultrasound, and initiation of aspirin therapy. The patient's symptoms began to improve, and he was discharged on September 4, 2009.

The patient's past medical/surgical history is significant for peripancreatic adenopathy status post ERCP with stent (7/2009), secondary malignancy of the liver status post liver biopsy (2007), an axillary mass status post left axillary biopsy (2009), and anemia. Medications taken at the time of the event included oxycodone, Compazine®, Tylenol®, Carafate®, Nexium®, Claritin®, Ativan®, and Senokot S®.

There have been 15 other cases of cerebrovascular ischemia reported to the NCI as serious adverse events through ADEERS under the sunitinib malate NSC and/or IND. The attributions are summarized in the following table:

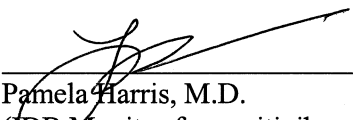
| Adverse Event                     | Grade | Attribution                         |
|-----------------------------------|-------|-------------------------------------|
| Cerebrovascular ischemia (n = 15) | 4     | 4 Possible, 1 Unlikely, 1 Unrelated |
|                                   | 3     | 8 Possible, 1 Unlikely              |

There have been 2,501 patients enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC.

In this case, it is thought that a possible relationship exists between the adverse event and sunitinib malate.

|                                  | <b>Cerebrovascular ischemia</b> |
|----------------------------------|---------------------------------|
| <b>Sunitinib malate</b>          | Possible                        |
| <b>Esophageal adenocarcinoma</b> | Unlikely                        |

Date: 6/3/2016

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

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

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