



DATE: AUG 3 1 2010

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

SUBJECT: Sunitinib Malate (SU011248 L-malate; Sutent®) NCI IND Safety Report, AE# 1842265

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.

The patient was an 8-year-old male with thalamic/midbrain glioblastoma multiforme who experienced a grade 4 cerebral hemorrhage while on a phase 1 trial utilizing the investigational agent sunitinib.

ADVERSE EVENTS ASSESSMENT

IND 74019 NSC 736511 Sunitinib malate (SU011248 L-malate; Sutent®) AE: 1842265	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Hemorrhage, CNS Protocol: ADVL0612
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The patient was an 8-year-old male with thalamic/midbrain glioblastoma multiforme who experienced a cerebral hemorrhage while on a phase 1 trial utilizing the investigational agent sunitinib malate. He began the first course of treatment on June 8, 2010, receiving sunitinib malate 15 mg/m² PO daily as powder on Days 1- 28 (Cycle=42 days). Note that the patient switched to a capsule formulation on June 10, 2010. He received his last dose of sunitinib malate on June 23, 2010 (Cycle 1, Day 16).

The patient was diagnosed with thalamic/midbrain glioblastoma multiforme in November 2009 and was status post craniotomy with ventriculo-peritoneal shunt placement in November 2009, single-agent systemic chemotherapy and radiotherapy from December 2009 to February 2010, and multiple-agent systemic chemotherapy from March to May 2010. He began the investigational therapy with sunitinib malate on June 8, 2010.

On June 21, 2010 (Cycle 1, Day 14), the patient was neurologically stable during a routine clinic visit; however, he developed a pentamidine reaction with asymptomatic hypotension which necessitated hospitalization and IV fluids. The patient responded to therapy, and he was discharged the next day.

On June 24, 2010 (Cycle 1, Day 17), the patient developed a headache, became less responsive and dyspneic, and was brought to the emergency room where he was hypopneic, had poor swallowing function, and was unable to control his secretions. His arterial blood gas showed a pH of 7.23 (reference range: 7.35 – 7.45), PO₂ of 106 mmHg (reference range: 80-100 mmHg), and a pCO₂ of 73 mmHg (reference range: 35-45 mmHg). He was intubated and placed on mechanical ventilation due to respiratory failure then admitted to the pediatric ICU. A CT scan of the head revealed interval increase in size of known left thalamic mass with new calcifications, a new mass in the fourth ventricle, and an acute hemorrhage filling most of the fourth ventricle and extending inferiorly to the base of the skull and superiorly to the level of the foramen of Monro. The patient was removed from the protocol. He was started on Unasyn[®] empirically, midazolam, and fentanyl infusions.

By June 27, 2010 (Cycle 1, Day 20), the patient's condition deteriorated as he had no cough or gag reflex, and multiple family meetings had occurred regarding withdrawal of technological support. The patient was extubated and placed on high-flow oxygen by nasal cannula. His secretions, pain and anxiety were addressed. On July 1, 2010 (Cycle 1, Day 24), the patient expired due to disease progression.

The patient's past medical was significant for sinusitis one week prior to becoming less responsive. Medications taken at the time of the event included Keppra[®], Colace[®], dexamethasone, and Kytril[®].

There have been 2 other cases of cerebral hemorrhage reported to the NCI as serious adverse events through AdEERS under the sunitinib malate NSC and/or IND as summarized in the following table:

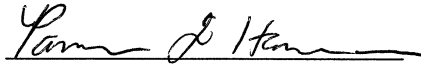
Adverse Event	Grade	Attribution
Cerebral hemorrhage (n = 2)	5	1 Unlikely
	4	1 Unlikely

There have been 2645 patients enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC.

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

	Cerebral hemorrhage
Sunitinib	Possible
Glioblastoma multiforme	Definite

Date: 8/31/2010

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

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

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