




DATE: January 6, 2009

FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI 

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) NCI IND Safety Report, AE# **1642009**

TO: Investigators Using Sorafenib (NSC 724772)

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 sorafenib.

The following must be completed by all investigators using sorafenib under NCI IND 69896:

- 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 69896, 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 sorafenib, there does not appear to be a change in the risk-benefit ratio for sorafenib 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 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 55-year-old female with malignant melanoma metastatic to the gastric mucosa, lungs, liver, and subcutaneous sites on the chest and neck died suddenly from cardiac ischemia while on a phase 3 trial utilizing the investigational agent sorafenib or placebo in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) AE: 1642009	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 5: Cardiac ischemia/infarction Protocol: E2603
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The patient was a 55-year-old female with malignant melanoma metastatic to the gastric mucosa, lungs, liver, and subcutaneous sites on the chest and neck who died suddenly from cardiac ischemia while on a phase 3 trial utilizing the investigational agent sorafenib or placebo in combination with paclitaxel and carboplatin. She began her first course of treatment on October 17, 2007, receiving sorafenib 400 mg PO twice daily or placebo 2 tablets twice daily on Days 2-19, paclitaxel 225 mg/m² IV over 3 hours on Day 1, and carboplatin AUC 6 IV over 30 minutes on Day 1, every 21 days, for Cycles 1-4. For Cycles 5-10, the dose of paclitaxel and carboplatin was reduced by 25%, while the sorafenib dose remained unchanged. After completion of or discontinuation of the paclitaxel and carboplatin, responding patients continue to receive sorafenib or placebo continuously until disease progression. She received the last dose of sorafenib or placebo on October 19, 2008 (Cycle 15, Day 13), and the last doses of paclitaxel and carboplatin on March 21, 2008.

The patient was initially diagnosed with malignant melanoma, Breslow depth of 0.64 mm and Clark's level III, in November 2002 and was status post surgical excision of a right knee lesion, and high dose interleukin-2 therapy in July 2007. Unfortunately, restaging scans noted disease progression, and she began the investigational therapy on October 17, 2007, with a good response. Due to persistent cytopenias and a decline in her functional status, however, paclitaxel and carboplatin were discontinued, and she continued on sorafenib or placebo only.

The patient had a history of hypertension controlled by medication. On July 2, 2007, she had a normal Cardiolite[®] myocardial perfusion scan which revealed an ejection fraction of 68%. Restaging scans of May 2, 2008, revealed a slight decline in the subcutaneous nodules and a slight regression of the gastric masses. Further imaging on July 7, 2008, showed stable gastric masses and no evidence of subcutaneous sites of disease. At her clinic appointment on September 5, 2008 (Cycle 13, Day 11), the patient's blood pressure was 118/82 mmHg, her pulse was 87 bpm, her heart rate and rhythm were regular and without murmurs, her lungs were clear, and she had no peripheral edema. She reported worsening diarrhea, abdominal pain, and mild nausea over the previous week that was attributed to the abrupt withdrawal of oxycodone, which she had been using chronically for abdominal pain. She was given a refill prescription for oxycodone, a new prescription for Lomotil[®], and encouraged to increase her fluid intake.

On October 19, 2008 (Cycle 15, Day 13), the patient laid down for a nap, and when her husband checked on her around midnight, he discovered that she had died. He reported that he found her in the same position that she was in when he checked on her earlier that evening. He also reported that nothing eventful had happened since her last clinic appointment prior to her death. She was taken by ambulance to the funeral home. No autopsy was performed. Based on the patient's history the investigator felt that the patient's death was due to cardiac ischemia.

The patient's past medical/surgical history is significant for hypertension, hypothyroidism, anemia, bipolar disorder, rheumatoid arthritis, fibromyalgia, Epstein-Barr infection, Raynaud's phenomenon, tonsillectomy, tubal ligation, and hysterectomy. Medications taken prior to her death included Seroquel[®], Wellbutrin XL[®], triamterene-HCTZ, clonazepam, Neurontin[®], levothyroxine, Nexium[®], Pravachol[®], Lexapro[®], tramadol, Premarin[®], Metroloction[®], metoclopramide, Proair HFA[®], vitamin and mineral supplements, fish oil, calcium, oxycodone, prochlorperazine maleate, Zofran[®], clotrimazole, Finacea[®], desonide, and Lomotil[®].

There have been 21 other cases of cardiac ischemia/infarction reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC, as shown in the table below:

Adverse Event	Grade	Attribution
Cardiac ischemia/infarction (n=21)	5	1 Possible
	4	8 Possible, 1 Unlikely
	3	1 Probable, 7 Possible, 2 Unlikely, 1 Unrelated

A total of 4,660 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib NSC.

In this case, it is considered unlikely that there was a causal relationship between the patient's death and sorafenib or placebo; however, due to the seriousness of the event, it is being reported.

	Cardiac ischemia/infarction
Sorafenib or placebo	Unlikely
Carboplatin	Unrelated
Paclitaxel	Unrelated
Melanoma	Possible

Date: 1/15/09

Signature: John Wright
 John Wright, M.D., Ph.D.
 (IDB Monitor for sorafenib)

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

cc: Diane M. Plateis, PharmD
 Bayer Pharmaceuticals Corporation

Todd J. Yancey, MD
 Onyx Pharmaceuticals, Inc.