



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: February 7, 2011
FROM: Pamela Harris, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Sunitinib Malate (SU-011248) Investigator Notification: **Pheochromocytoma**
Mfr Report #: 2011008034
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. A Sponsor's Report, which describes the pheochromocytoma in rats participating in a Pfizer-sponsored preclinical study utilizing the investigational agent sunitinib malate, was recently distributed to investigators.

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

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter 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 Non-clinical Safety Report and a Dear Investigator Letter that describe the following adverse event are attached:

A statistically significant increase in incidence of pheochromocytomas in the adrenal medulla of male rats given 3.0 mg/kg/day, which is comparable to AUC exposure associated with the recommended human dose (RHD) of 50 mg/day, has been observed following >1 year of dosing. While pheochromocytoma represents a new adverse finding associated with sunitinib, duodenal carcinomas and gastric mucous cell hyperplasia were previously observed in rats given ≥ 1.0 mg/kg/day sunitinib malate for 1-6 months in rasH2 transgenic mice.

There have been no cases of pheochromocytoma and one case of secondary malignancy (squamous cell carcinoma) reported to the NCI through AdEERS under the sunitinib malate NSC and/or IND. A total of 2848 patients have been enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC.

Attachments: Dear Investigator Letter
Company Non-Clinical Safety Report

Pfizer Inc
Drug Safety Surveillance
Safety & Risk Management
235 East 42nd Street 150/3/18
New York, NY 10017



Pfizer Global Pharmaceuticals

Subject: Suspected Unexpected Serious Adverse Reaction Report (SUSAR)

Dear Investigator:

In accordance with applicable guidelines and regulations governing the conduct of clinical trials¹, you are being notified of a serious adverse event involving a product that you are investigating.

The attached letter is being provided for your information and we suggest that you file a copy of this document in the labeling section of your study documents. A copy of the document should be provided to your Institutional Review Board (IRB) and confirmation of receipt by your IRB filed in your study file. In addition, please notify your sub-investigators and other appropriate personnel in your clinical trial.

If you have any questions regarding this report, please contact your designated Pfizer medical contact.

¹ Code of Federal Regulations (CFR) 312.32 IND Safety Reports; International Conference on Harmonization (ICH): Good Clinical Practice (CPMP/ICH/135/95)



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Maria Luisa Bonura, MD
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Worldwide Safety and Regulatory Operations
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Subject: Unexpected Non-Clinical Safety Report, for <<Sunitinib malate>>, Sponsor reference number <<2011008034>>.

Dear Investigator:

In accordance with applicable guidelines and regulations governing the conduct of clinical trials¹, you are being notified of an unexpected, non-clinical safety information, regarding observations from the non-clinical toxicology study entitled "2-Year Oral Carcinogenicity Study of SU010398 (SU011248 L-Malate Salt) in Rats", protocol number 6348-495 (08LJ018) conducted by Pfizer Inc in the United States. The observations are described below:

A new adverse nonclinical safety finding has been identified from a recently completed 2-year oral carcinogenicity study with sunitinib malate (SU011248 L-malate salt; SU010398; hereafter referred to as sunitinib). In this 2-year study (Study 6348-495), sunitinib was administered by oral gavage at doses of 0, 0.33, 1.0, and 3.0 mg/kg/day to Sprague-Dawley rats in a cycle of 28 days of dosing followed by a 7-day treatment-free period. No apparent sunitinib-related deaths were observed, and there were no new target organ systems identified from this 2-year rat carcinogenicity study compared to those previously identified from repeat-dose toxicity studies in the rat or monkey of up to 9 months in duration. A statistically significant increase in incidence of pheochromocytomas in the adrenal medulla of male rats given 3.0 mg/kg/day, observed following >1 year of dosing, represents a new adverse finding associated with sunitinib administration. While pheochromocytomas represent a new neoplastic lesion, duodenal carcinomas and gastric mucous cell hyperplasia (identified in rats given ≥ 1.0 mg/kg/day), were previously identified following 1 and 6 months of

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dosing in rasH2 transgenic mice. The neoplastic changes observed in rats occurred at mean combined (ie, SU011248 + SU012662) AUC(0-24) exposures ≥ 1680 ng•h/mL that are comparable to AUC exposure associated with the RHD of 50 mg/day. The no effect level for neoplastic changes was 0.33 mg/kg/day, with sub-therapeutic exposure compared with AUC exposure at the RHD of 50 mg/day.

The Sponsor continues to see a positive benefit versus risk ratio for sunitinib in its current use for the treatment of cancer.

Company Clinical Evaluation

A review of Pfizer's safety database for cases received through 31 December 2010 identified 42 serious cases from solicited cases and clinical studies reporting sunitinib (SU-011,248) or blinded therapy and adverse event encoding to the MedDRA (version 13.1) Lower Level Term "Second primary malignancy." Of these 42 cases, there were 5 cases in which the event (one basal cell carcinoma, two squamous cell carcinoma, one malignant lymphoma and one pharyngeal cancer) was attributed to the subject/Pfizer suspect drug by the investigator and/or sponsor. In addition, 10 cases (colon cancer, breast cancer, skin cancer unspecified, transitional cell carcinoma, basal cell carcinoma, prostate cancer, rectal cancer, lymphoma, gastric cancer, mantle cell lymphoma, one report for each neoplasm type) reported from sources other than clinical studies were identified during this period with sunitinib (SU-011,248). There were no reports of secondary adrenal neoplasms.

While pheochromocytomas represent a new neoplastic lesion, duodenal carcinomas and gastric mucous cell hyperplasia, were previously identified following 1 and 6 months of dosing in another animal model (rasH2 transgenic mice).

Reports of second malignancies associated with the use of sunitinib in humans do not seem to indicate a specific target organ.

The information contained in this report does not materially alter the current benefit/risk assessment for this product nor will it modify the conduct of the study.



Pfizer Inc
235 East 42nd Street
New York, NY 10017

If you have any questions regarding this report, please contact me or your designated Pfizer medical contact.

Sincerely,

Maria Luisa Bonura , MD

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¹Code of Federal Regulations (CFR) 312.32 IND Safety Reports; International Conference on Harmonization (ICH): Good Clinical Practice (CPMP/ICH/135/95); Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (ENTR/CT 3 Rev 1)

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