




National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** April 21, 2009

**FROM:** S. Percy Ivy, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Sunitinib Malate (SU-011248) Investigator Notification: **Necrotizing Pancreatitis**  
Mfr Report #: 2008013916

**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 MedWatch Report and Dear Investigator Letter, which describes fatal necrotizing pancreatitis in a patient participating in a Pfizer-sponsored clinical 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) according to your local IRB's 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 MedWatch Report that describes the following adverse event is attached.

A 46-year-old female with metastatic adenocarcinoma experienced fatal necrotizing pancreatitis while on a randomized, double-blind, controlled phase 3 study utilizing investigational sunitinib malate with erlotinib. The patient was unblinded and found to be on sunitinib malate.

There have been no cases of necrotizing pancreatitis and 6 cases of pancreatitis reported to the NCI through AdEERS under the sunitinib malate NSC and/or IND. A total of 1778 patients have been enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC.

Attachment: MedWatch Report  
Dear Investigator Letter

Pfizer Inc  
Drug Safety Surveillance  
Safety & Risk Management  
150 East 42<sup>nd</sup> Street  
New York, NY 10017



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## 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 trials<sup>1</sup>, you are being notified of a serious adverse event involving a product that you are investigating.

The attached MedWatch 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.

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

**MEDWATCH**  
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Mfr Report #	04.15.09	2008013916
UF/Importer Report #	<del>XXXXXXXXXX</del>	
send safety letter		
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<b>A. PATIENT INFORMATION</b>			
1. Patient Identifier PRIVACY  In confidence	2. Age at Time of Event: 46 Years or Date of Birth: 06/04/1961	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or 71.0 kgs

<b>B. ADVERSE EVENT OR PRODUCT PROBLEM</b>			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input checked="" type="checkbox"/> Death: 03/08/2008 (mm/dd/yyyy)		<input type="checkbox"/> Disability or Permanent Damage	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly/Birth Defect	
<input checked="" type="checkbox"/> Hospitalization - initial or prolonged		<input type="checkbox"/> Other Serious (Important Medical Events)	
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) 01/30/2008		4. Date of This Report (mm/dd/yyyy) 04/10/2009	

5. Describe Event or Problem  
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)  
necrotizing pancreatitis [Necrotizing pancreatitis]  
DEHYDRATION [Dehydration]  
DIARRHEA [Diarrhea]

Case Description:  
2007-001915-52#A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED PHASE 3, EFFICACY AND SAFETY STUDY OF SUNITINIB (SU011248) IN PATIENTS WITH ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH ERLOTINIB

This is a SU011248 report from a Pfizer clinical trial. This 46-year-old white female patient, with an unknown medical history, was enrolled in the above mentioned study. She started receiving oral erlotinib 150 mg once daily and blinded continued in additional info section...

6. Relevant Tests/Laboratory Data, Including Dates			
#1 02/12/2008 Blood calcium 0.97 mmol/l			
#2 02/26/2008 Blood calcium 2.04 mmol/l			
#3 02/12/2008 Blood lactate dehydrogenase (continued)			
#4 02/26/2008 Blood lactate dehydrogenase (continued)			
#5 02/12/2008 Blood sodium 123 mmol/l			
#6 02/26/2008 Blood sodium 131 mmol/l			
continued in additional info section...			

7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian			
#1 --/--/2001 to UNK, Relevant Med History, Myocardial infarction			
#2 Relevant Med History, Hypercholesterolaemia			

Submission of a report does not constitute an admission that medical personnel, user, facility, distributor, manufacturer or product caused or contributed to an event.

<b>C. SUSPECT PRODUCT(S)</b>			
1. Name (Give labeled strength & mfr/labeler)			
#1. SUNITINIB MALATE;PLACEBO (SUNITINIB MALATE) (Continued)			
#2. *Erlotinib (ERLOTINIB) Unknown			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 37.5 mg, 1x/day, Oral		#1. 10/15/2007 to 02/11/2008	
#2. 150 mg, 1x/day, Oral		#2. 10/15/2007 to 02/11/2008	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. NON-SMALL CELL (Continued)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. NON-SMALL CELL (Continued)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
#1. MINOCYCLINE (MINOCYCLINE) 12/20/2007 to ongoing			
#2. METOCLOPRAMIDE (METOCLOPRAMIDE) 02/04/2008			
continued in additional info section...			

<b>G. ALL MANUFACTURERS</b>			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Pfizer Inc. 150 East 42nd Street New York, NY 10017 UNITED STATES		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/06/2009		5. (A)NDA # IND # 62,382 STN # PMA/510(k) #	
6. If IND, Give Protocol # A6181087		7. Type of Report (Check all that apply)	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day		Combination Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic		Pre-1938 <input type="checkbox"/> Yes	
<input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial		OTC Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #			
9. Manufacturer Report Number 2008013916		8. Adverse Event Term(s) Necrotizing pancreatitis, Dehydration, Diarrhea	

<b>E. INITIAL REPORTER</b>	
1. Name and Address NETHERLANDS Name and address withheld.	Phone # Withheld

2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation Physician	4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Unk
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**ADDITIONAL INFORMATION****B5. EVENT DESCRIPTION (Continued)**

therapy (SU011248 or placebo) once daily in a continuous regimen, (expressed as 4-week cycles on an unknown date). The patient suffered from diarrhea since 30Jan2008 and dehydration since 09Feb2008. She was hospitalized for both events on 11Feb2008. Blinded therapy was interrupted on an unknown date in response to both events. Action taken with erlotinib in response to the events was unknown. At the time of this report the outcome of both events was unknown.

The investigator considered that there was a reasonable possibility that both events were related to blinded therapy but not to a clinical trial procedure.

The investigator assessment of the causal relationship of the events with erlotinib was not provided at the time of this report. Efforts are being made to obtain such final determination. Since no determination was received, the case is managed as if the investigator's assessment was that a reasonable possibility exists that the event was related to the study product, as a cautionary measure and for reporting purposes.

**Follow-up (29Feb2008):**

This subject, diagnosed with adenocarcinoma stage 4 since May2006, for which she was treated with unspecified chemotherapy and radiation and which relapsed in Sep2007, had a medical history of a myocardial infarction. Concomitant drugs included minocycline 100mg once daily, metoclopramide 10mg as needed, pantozole 40mg once daily and Imodium 2mg as needed. According to the reporter the events dehydration and diarrhea were possibly related to erlotinib. She started blinded therapy and erlotinib on 15Oct2007. Erlotinib and blinded therapy were interrupted on 12Feb2008 following both the events dehydration and diarrhea. The events were treated with no oral intake started on 12Feb2008, sodium chloride / glucose 4L / 24 hours intravenously started on 12Feb2008 and calcium gluconate 2g three times intravenously started on 12Feb2008. It was stated that on 15Feb2008 the subject suffered from dyspnea (not reported as serious adverse event), for which she was treated with 2L O<sub>2</sub>. On 18Feb2008 Augmentin intravenously was started. Results of sodium, calcium, lactate dehydrogenase and C-reactive protein were provided. At the time of the follow-up the event diarrhea was considered ongoing. The event dehydration was considered resolved on 18Feb2008.

**Follow-up (10Mar2008)**

The last dose administration for blinded therapy and erlotinib was 11Feb2008. They were not restarted. It was stated that pancreatitis (not reported as serious adverse event) was diagnosed in the hospital. On 07Mar2008 the patient went home where she died on 08Mar2008. Cause of death was unknown at the time of this report. No further information was provided.

The investigator considered that there was a reasonable possibility that the event death cause unknown was related to blinded therapy, to erlotinib and to a clinical trial procedure.

This follow-up report is being submitted to amend previously reported information (i.e. to add expectedness call for the event "death cause unknown"):

The serious adverse event "death cause unknown" is expected versus the Investigator's Brochure of SU011248.

**Follow-up (06Apr2009):**

This follow-up contains medically significant information.

The information has been received from a draft publication of a Case Report.

The patient was confirmed to be a 46-year-old female, with metastatic NSCLC (adenocarcinoma). One year before enrollment in the trial she had received 3 cycles cisplatin and gemcitabine for locally advanced disease, followed by radiotherapy to the tumor in the right lung and mediastinal lymph nodes. She had then developed metastases in the right side retroclavicular lymph nodes, left second rib, both suprarenal glands and left kidney. Her medical history included myocardial infarction and hypercholesterolemia 6 years before. Since then, she had stopped smoking, and used aspirin, metoprolol and atorvastatin as medication. She used no alcohol.

As previously reported, she was enrolled in this phase 3 multicenter clinical trial on the efficacy and safety of sunitinib in patients with NSCLC treated with erlotinib and received oral erlotinib 150 mg once daily and oral sunitinib 37.5 mg once daily, both continuously. After 12 weeks on this treatment she presented to the emergency department because of abdominal pain, nausea and vomiting. Physical examination revealed an acutely ill dehydrated woman with decreased bowel sounds, abdominal distension and tenderness at palpation. She had no fever. Laboratory examination showed hemoglobin 8.0 (normal range 7.4-9.9 mmol/L), Leukocytes 12.2 (normal range 3.5-11.0 10<sup>9</sup>/L), creatinine 273 (normal range 50-80 μmol/L), calcium ionised 0.62 (normal range 1.10-1.32 mmol/L), calcium total 1.00 (2.10-2.55 mmol/L), magnesium 0.41 (0.65-1.05 mmol/L), bilirubin 22 (normal range 0-17 μmol/L), alkaline phosphatase 119 (normal range 0-120 U/L), aspartate aminotransferase 84 (1-40 U/L), alanine aminotransferase 35 (normal range 0-45 U/L), lactate dehydrogenase 1781 (normal range 1-450 U/L), amylase 1011 (normal range 1-220 U/L), C-reactive protein 265 (normal range 0-9 mg/L), albumin 24.8 (35-50 g/L).

Most remarkable were the extreme low serum calcium, and the increased serum amylase. At ultrasonography there were no gallstones nor biliary duct dilatation. An abdominal CT scan showed an enlarged pancreas and ascites. The treating physicians

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concluded that the patient was suffering from acute non-biliary pancreatitis, with secondary extreme low serum calcium. Since she had no risk factors for pancreatitis, such as alcohol abuse, bile duct obstruction, familiar history of pancreatitis or hypertriglyceridemia, it was considered most probably related to the medication she used.

At admission, all medication was stopped. The patient was rehydrated, received intravenous calcium and magnesium supplementation, and parenteral nutrition. The clinical situation however deteriorated. She developed high fever, and a second CT scan was consistent with necrotizing pancreatitis. Despite maximal supportive care, the patient died 4 weeks after admission.

Post-mortem confirmed the diagnosis of necrotizing pancreatitis with extended peripancreatic fat necrosis. Vital tumor was not found anywhere in the body. There were no additional findings.

Since this patient had no classic risk factors for pancreatitis, and since elevated serum amylase is being observed in a minority of patients during treatment with sunitinib, the investigator concluded that it is probable that sunitinib, either alone or in combination with erlotinib, was involved in the occurrence of this pancreatitis.

On 20Aug2008 the Investigator decided to unblind this patient and the patient was found to be on Sunitinib.

This is a final report for initial notification of a fatal/life threatening event to regulators and to investigators/ethics committees as required; no additional information is anticipated prior to the 15-day reporting timeline.

**Case Comment:**

Fatal necrotising pancreatitis is unlisted in the sunitinib Investigator's Brochure and in the erlotinib UK SPC.

A review of Pfizer's safety database for cases received through 15 March 2009 identified 47 serious cases from solicited cases and clinical studies reporting sunitinib (SU-011,248) or blinded therapy and adverse events encoding to the MedDRA (version 11.1) High Level Term "Acute and chronic pancreatitis" or the Preferred Term, "Pancreatic necrosis." None of these events had a fatal outcome. Twenty-eight cases were attributed to the Pfizer suspect drug by the investigator and/or the Sponsor. In addition, 21 cases reported from sources other than clinical studies were identified during this period with sunitinib (SU-011,248); one of the relevant events (Pancreatitis necrotising) had a fatal outcome.

In light of a plausible drug-event temporal association, the post-mortem findings, and the patient's negative medical history, a reasonable possibility that diarrhea, dehydration and necrotizing pancreatitis are related to the study drugs sunitinib and erlotinib cannot be excluded.

The events are considered not related to any clinical trial procedure.

Erlotinib is not a Pfizer product. The Company does not have access to the data to provide a benefit/risk assessment for erlotinib.

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

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
3	02/12/2008	Blood lactate dehydrogenase	1805 IU/l	
4	02/26/2008	Blood lactate dehydrogenase	708 IU/l	
7	02/12/2008	C-reactive protein	257 mg/l	
8	02/26/2008	C-reactive protein	162 mg/l	

**C1. NAME (Continued)**

Suspect Medication #1: SUNITINIB MALATE;PLACEBO(SUNITINIB MALATE) Unknown

**C4. DIAGNOSIS FOR USE (Continued)**

#1:NON-SMALL CELL LUNG CANCER (Non-small cell lung cancer)

#2:NON-SMALL CELL LUNG CANCER (Non-small cell lung cancer)

**C10. CONCOMITANT MEDICAL PRODUCTS (Continued)**

to ongoing

#3. PANTOZOL (PANTOPRAZOLE SODIUM) 02/04/2008 to ongoing

#4. LOPERAMIDE (LOPERAMIDE) 02/04/2008 to ongoing

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