



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: April 24, 2009
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 (Erlotinib, Tarceva™) Investigator Notification: **Pericardial Effusion**
OSI Pharmaceuticals Report # 2009000831
TO: Investigators of CTEP-sponsored Trials Using OSI-774 (NSC 718781)

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. An investigator notification, which describes pericardial effusion in a patient participating in an OSI Pharmaceuticals-sponsored clinical study utilizing the investigational agent OSI-774/placebo, was recently distributed to investigators.

The following must be completed by all investigators using OSI-774 under NCI IND 63383:

- 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 63383, 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 OSI-774 there does not appear to be a change in the risk-benefit ratio for OSI-774 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 events is attached:

A 66-year-old male with non-small cell lung cancer developed pericardial effusion while participating in a double blind, placebo-controlled, phase 3 study utilizing the investigational agent OSI-774/placebo following tumor resection.

There have been four cases of pericardial effusion reported to the NCI through AdEERS under the OSI-774 NSC and/or IND.

A total of 2787 patients have been enrolled in NCI-sponsored clinical trials under the OSI-774 NSC and/or IND.

Attachment: MedWatch Report

For use by user-facilities,
importers, distributors and manufacturers

Mfr Report # 2009000831
UF/Importer Report #
FDA Use Only

MEDWATCH

FORM FDA 3500A (10/05)

for MANDATORY reporting

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A. PATIENT INFORMATION			
1. Patient Identifier MBG	2. Age at Time of Event: or Date of Birth: 07/25/1942	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 203.6 lbs or kgs
B. ADVERSE EVENT OR PRODUCT PROBLEM			
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 type="checkbox"/> Death: _____ (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) 03/12/2009		4. Date of This Report (mm/dd/yyyy) 04/21/2009	
5. Describe Event or Problem			
VERBATIM TERM (Preferred term) PERICARDIAL EFFUSION (Pericardial effusion) This 66-year-old male was enrolled in OSI protocol OSI-774-302, a multi-center, randomized, double-blind, placebo-controlled, phase 3 study of single-agent Tarceva (erlotinib) following complete tumor resection with or without adjuvant chemotherapy in patients with stage IB-IIIA non small cell lung carcinoma who have EGFR-positive tumors. He was diagnosed with NSCLC on 03-Nov-2008 and underwent right upper lobe resection. No other prior therapy was provided. Medical history and concomitant medications were non-contributory. Therapy with erlotinib/placebo 100mg PO QD was initiated on 22-Jan-2009. On 12-Mar-2009, the patient presented for routine protocol visit and complained of increased dyspnea. On physical exam chest was clear to auscultation bilaterally. Cardiac exam was normal with no rubs or gallops. A chest X-ray showed cardiomegaly with considerable increase in the size of Cont...			
6. Relevant Tests/Laboratory Data, Including Dates			
CXR (3/12/2009): Cardiomegaly ECHOCARDIOGRAM (3/13/2009): Pericardial effusion; minium collapse right ventricle ECHOCARDIOGRAM (3/14/2009): Pericardial effusion; minium collapse right ventricle			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			
Concurrent Disease: Barrett's esophagus Gastroesophageal reflux disease Skin cancer Seizures Hernia repair			

C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#1 Erlotinib / Placebo(Erlotinib HCl) (Tablet) (Erlotinib HCl)	
#2 Cont...	
2. Dose, Frequency & Route Used	
#1 (100 mg, QD), Oral	
#2	
3. Therapy Dates (If unknown, give duration from/to (or best estimate))	
#1 01/22/2009 - 03/12/2009	
#2	
4. Diagnosis for Use (Indication)	
#1 Lung cancer	
#2	
5. Event Abated After Use Stopped or Dose Reduced?	
#1 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	
#1	
#2	
7. Exp. Date	
#1	
#2	
8. Event Reappeared After Reintroduction?	
#1 <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#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) PROTONIX (PANTOPRA-ZOLE)	
2) SIMVASTATIN (SIMVA-STATIN)	
3) ALLI	
4) VIAGRA (SILDENAFIL)	
Cont...	
G. ALL MANUFACTURERS	
1. Contact Office - Name/Address (and Manufacturing Site for Devices)	
OSI Pharmaceuticals Boulder Safety 2860 Wilderness Place Boulder, CO 80301 USA (Initial Unit)	
2. Phone Number	
303-546-7600	
3. Report Source (Check all that apply)	
<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____	
4. Date Received by Manufacturer (mm/dd/yyyy)	
04/13/2009	
5. (A)NDA #	
21-743	
IND #	
53,728	
6. If IND, Give Protocol #	
OSI-774-302	
7. Type of Report (Check all that apply)	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up # 1	
8. Adverse Event Term(s)	
1) PERICARDIAL EFFUSION	
Cont...	
E. INITIAL REPORTER	
1. Name and Address	
R.J. Cerfolio University of Alabama at Birmingham AL	
Phone # 205-934-5938	
2. Health Professional?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
3. Occupation	
Study Cont...	
4. Initial Reporter Also Sent Report to FDA	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unk	

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

B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

the cardiac silhouette since 19-Feb-2009. Also small bilateral effusions were present but the lungs were clear. The patient was asked to have an echocardiogram done but he refused and was asked to obtain one from his regular physician. On 13-Mar-2009, an echocardiogram (ECG) at an outside facility revealed pericardial effusion with minimal compression of the right atrium and right ventricle. Left and right ventricle ejection fractions were normal (greater than 55%). Also noted was mild mitral, tricuspid and pulmonic regurgitation. Albumin was 3.3 g/dL (3.4-5.0 g/dL) and creatinine kinase was 54 units/L (35-250 units/L). He returned to the investigative hospital and was admitted to the thoracic surgery service for management of the effusion. A cardiology consult was obtained and due to the minimal amount of fluid with no hemodynamic compromise a pericardiocentesis was not recommended. The cardiologist felt the event may have been caused by the study medication and the patient requested stopping the medication temporarily to see if the symptoms improved. His last dose of study medication was on 13-Mar-2009 with plans to restart in 21 days. On 14-Mar-2009 an ECG showed normal sinus rhythm with left axis deviation and nonspecific ST-T abnormality. A repeat ECG six and a half hours later showed no significant change. Later that day the patient was discharged home. The effusion resolved after stopping study drug. On 02-Apr-2009, study drug was restarted at 50mg PO QD. As of 09-Apr-2009 the effusion had not recurred and was considered completely resolved.

No further information is expected.

The event is serious, unexpected in the erlotinib IB and considered by the investigator to be related to study drug and possibly related to the 03-Nov-2008 surgery.

Follow up received 13-Apr-2009: The effusion resolved after stopping study drug. On 02-Apr-2009, study drug was restarted at 50mg PO QD. As of 09-Apr-2009 the effusion had not recurred and was considered completely resolved.

Follow up received 20-Apr-2009: Albumin was 3.3 g/dL (3.4-5.0 g/dL) and creatinine kinase was 54 units/L (35-250 units/L). On 14-Mar-2009 an ECG showed normal sinus rhythm with left axis deviation and nonspecific ST-T abnormality. A repeat ECG six and a half hours later showed no significant change.

C. SUSPECT PRODUCT(S) (Cont...)

Seq No.	: 1
C.1 Suspect Product	: Erlotinib / Placebo(Erlotinib HCl) (Tablet) (Erlotinib HCl)
C.2 Dose, Frequency & Route Used	: 2) (50 mg, QD), Oral
C.3 Therapy Dates (or duration)	: 2) 04/02/2009 -

C.10 Concomitant Medical Products and Therapy Dates

Seq No.	: 4
Concomitant Medical Product	: VIAGRA (SILDENAFIL CITRATE)

E. INITIAL REPORTER (Cont...)

Occupation: Study investigator

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

1) PERICARDIAL EFFUSION (Pericardial effusion)