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**Operations Office**

Telephone (507) 266-3853

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**Date:** March 28, 2003

**To:** NCCTG Primary Clinical Research Associates

**From:** Linda S. Long

**Re:** N0177, Pilot and Phase II Trial of OSI-774 and Radiation in Glioblastoma Multiforme Patients

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with OSI-774 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE\_2003000295\_F1

Please note that all risks currently cited in the NCCTG consent form can not be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

**Please submit this adverse event to your Institutional Review Board.**

If you have any questions concerning this communication, please contact Linda S. Long at 507-266-3853.

lsl  
enclosure



**DATE:** March 20, 2003  
**FROM:** Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** OSI-774 IND Safety Report, Follow-up #1 ~~A~~  
**TO:** Investigators Using OSI-774, IND 63,383

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 by OSI Pharmaceuticals for the CTEP-sponsored investigational agent, OSI-774 (IND 63,383).

Please complete the following:

- 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.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

CTEP's evaluation of this IND Safety Report in light of previous experience with OSI-774 does not require a change in the clinical protocols for this agent at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The MedWatch form and OSI Pharmaceuticals safety letter that describe the following adverse event are attached:

A 55-year-old male with glioblastoma multiforme experienced pulmonary fibrosis after being treated with OSI-774. Approximately 3 months after treatment initiation, the patient was diagnosed with pneumonia and treatment was withheld. A chest computerized tomography (CT) scan was performed to rule out any pulmonary pathology prior to resuming treatment with OSI-774. Approximately 1 month later, a chest CT scan showed mediastinal lipomatosis and extensive bilateral pulmonary fibrosis with a confluent area of pulmonary fibrosis suggested involving the left lung.

**Follow-up:** The patient developed an upper respiratory infection and was treated with cephalexin. Six days later, he developed a fever (101°F) and was started on co-trimazole. The following day, a chest X-ray showed mild cardiomegaly, evidence of interstitial pneumonitis throughout the right hemithorax and probable early interstitial pneumonitis within the left upper lobe. A pulmonologist diagnosed the patient with pneumonia. The patient became more short of breath and was hospitalized. He was treated with antibiotics and oxygen and later intubated. A bronchoscopy revealed a few mucous plugs in the lower trachea, but was otherwise normal. A fungal culture of the bronchial washings showed a light growth of *Candida albicans*. The pulmonologist assessed the patient's disorder as adult respiratory distress syndrome (ARDS), which had improved. The patient was extubated and discharged. A follow-up chest CT scan revealed extensive bilateral pulmonary fibrosis with a possible confluent area of pulmonary fibrosis involving the left lung base, as well as mediastinal lipomatosis as noted above. During a follow-up visit a few weeks later, the patient was asymptomatic, and a chest CT scan showed signs of improvement but still clear cut pulmonary fibrosis and multiple pulmonary emboli. The patient was hospitalized for intravenous anticoagulation.

**CONFIDENTIAL**

OSI Pharmaceuticals  
For use by user-facilities,  
distributors and manufacturers for  
MANDATORY reporting

Mfr report #	2003000295
UI/Out report #	
FDA Use Only	

# MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

<b>A. Patient information</b>			
1. Patient identifier RJG	2. Age at time of event: 55 Years	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight ____ lbs or 94 ____ kg
In confidence	Date of birth: 09/29/1947		

<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 type="checkbox"/> death	<input type="checkbox"/> disability	<input type="checkbox"/> congenital anomaly	
<input type="checkbox"/> life-threatening	<input type="checkbox"/> required intervention to prevent permanent impairment/damage		
<input type="checkbox"/> hospitalization - initial or prolonged	<input checked="" type="checkbox"/> other: <u>Medica-Cont...</u>		
3. Date of event (month/day) 01/23/03	4. Date of this report (month/day) 03/07/03		

5. Describe event or problem

**PULMONARY FIBROSIS (Pulmonary fibrosis)**

This 55-year-old male was enrolled in OSI2510s, a phase II study of erlotinib in subjects with recurrent/progressive glioblastoma multiforme. The subject was diagnosed with glioblastoma multiforme of the right parietal lobe. From June 2002 through August 2002, he was treated with whole brain radiation therapy. Other significant history includes stable angina, tobacco use (primarily second-hand smoke) and hypertension. Protocol therapy consisted of erlotinib 150 mg PO, QD commencing on 27-Sep-2002. Protocol therapy was held on 27-Dec-2002.

On 19-Dec-2002, the subject was diagnosed with an upper respiratory infection and treated with cephalexin. On 25-Dec-2002, the subject developed a fever of 101 degrees Fahrenheit. He was evaluated by his primary physician and started on co-trimoxazole. The following day, 26-Dec-2002, he was re-evaluated because his condition had not improved. A chest x-ray showed mild cardiomegaly, evidence of interstitial

Cont...

6. Relevant test/laboratory data, including dates

26-Dec-2002, chest x-ray showed mild cardiomegaly, evidence of interstitial pneumonitis throughout the right hemithorax and probable early interstitial pneumonitis within the left upper lobe.

30-Dec-2002, a pulmonologist read the chest x-ray as diffuse consolidation, then diagnosed pneumonia.

Cont...

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)	
Past Disease: STABLE ANGINA TOBACCO ABUSE	
Concurrent Disease: HYPERTENSION	

<b>C. Suspect medication(s)</b>			
1. Name (give labeled strength & mfr/labeler, if known)			
#1 Erlotinib HCl (Tablets)		Cont...	
#2			
2. Dose, frequency & route used		3. Therapy dates (if unknown, give duration)	
#1 150 mg (QD), Oral		#1 09/27/02 - 12/27/02	
#2		#2	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced	
#1 GLIOBLASTOMA MULTIFORME		#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
6. Lot# (if known)		7. Exp. date (if known)	
#1 Unk		#1 Unk	
#2		#2	
8. Event reappeared after reintroduction			
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
9. NDC # - for product problems only (if known)			

10. Concomitant medical products and therapy dates (exclude treatment of event)	
1) MINOXIDIL	
2) VERAPAMIL	
3) GLYCERYL TRINITRATE	
4) ACETYSALICYLIC	
Cont	

<b>G. All manufacturers</b>			
1. Contact office - name/address (& mailing site for devices)		2. Phone number	
OSI Pharmaceuticals Boulder Safety 2860 Wilderness Place Boulder, CO 80301 USA ( Informing Unit )		303-444-5893	
4. Date received by manufacturer (month/day) 02/25/03		5. ANDA # IND # 53,728	
6. If IND, protocol # OSI2510s		PLA #	
7. Type of report (check all that apply)		pre-1938 <input type="checkbox"/> yes	
<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day		OTC product <input type="checkbox"/> yes	
<input type="checkbox"/> 10-day <input type="checkbox"/> periodic			
<input type="checkbox"/> Initial <input checked="" type="checkbox"/> follow-up # <u>1</u>		8. Adverse event term(s) 1) PULMONARY FIBROSIS (Pulmonary fibrosis)	
9. Mfr. report number 2003000295			

<b>E. Initial reporter</b>			
1. Name & address		phone # 216-445-5368	
Cathy Brewer Taussig Cancer Center 9500 Euclid Avenue Cleveland, OH 44195 USA			

2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation Study Coordinator	4. Initial reporter also sent report to FDA <input checked="" type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk
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Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

**B. Adverse event or product problem**

**B.2 Outcome attributed to adverse event (Cont...)**

Other : Medically significant

**B.5 Describe event or problem (Cont...)**

pneumonitis throughout the right hemithorax and probable early interstitial pneumonitis within the left upper lobe.

On 27-Dec-2002, the subject became more short of breath, necessitating hospitalization. Initial treatment included antibiotics and oxygen. On 30-Dec-2002, the subject was transferred to another hospital for further treatment. The site reported that the subject was evaluated by a pulmonologist who read the chest X-ray as diffuse consolidation, then diagnosed pneumonia. He was intubated the same day. The following day, 31-Dec-2002, bronchoscopy revealed a few mucous plugs in the lower trachea and an otherwise normal bronchoscopic exam with normal mucosa and no endobronchial lesion or foreign body. Bronchial washings for bacterial and fungal culture were sent. Fungal culture showed a light growth of *Candida albicans*. Bacterial culture and pathology results were not reported. A partial hospital record indicated that the pulmonologist assessed the disorder as adult respiratory distress syndrome (ARDS) that this condition improved, and he was extubated on 12-Jan-2003. Complete records were not available. Date of discharge was not provided.

On 23-Jan-2003, a follow-up chest CT at an outside hospital revealed extensive bilateral pulmonary fibrosis with a possible confluent area of pulmonary fibrosis involving the left lung base, as well as mediastinal lipomatosis.

On 12-Feb-2003, the subject was asymptomatic. A follow-up chest CT at the study center revealed signs of improvement but still clear-cut pulmonary fibrosis and multiple pulmonary emboli. The investigator noted that pulmonary emboli are relatively common in patients with brain tumors. The subject was admitted for IV anticoagulation. The investigator was considering restarting erlotinib at a later date as the subject had exhibited an initial response to erlotinib.

The investigator and the consulting pulmonologist assessed the pulmonary fibrosis as possibly related to erlotinib.

Follow-up Received 25-Feb-2003: Follow-up included identification of the protocol number, additional chest x-ray and CT results, culture results and that the patient became asymptomatic on 12-Feb-2003 with a follow-up chest CT showing "signs of improvement but still clear-cut pulmonary fibrosis" and multiple pulmonary emboli. The patient received IV anticoagulation.

**B.6 Relevant tests/laboratory data, including dates (Cont...)**

31-Dec-2002, bronchoscopy revealed a few mucous plugs in the lower trachea and an otherwise normal bronchoscopic exam with normal mucosa and no endobronchial lesion or foreign body. Fungal culture showed a light growth of *Candida albicans*.

23-Jan-2003, follow-up chest CT revealed extensive bilateral pulmonary fibrosis with a possible confluent area of pulmonary fibrosis involving the left lung base, as well as mediastinal lipomatosis.

Follow-up chest CT at the study center revealed signs of improvement but still clear-cut pulmonary fibrosis and multiple pulmonary emboli.

**C. Suspect medication (Cont...)**

Seq No. : 1  
C.1 Suspect medication : Erlotinib HCl (Tablets)

**C10. Concomitant medical products**

Seq No. : 4  
Concomitant Medical Product : ACETYLSALICYLIC ACID  
Seq No. : 5  
Concomitant Medical Product : DEXAMETHASONE

OSI Pharmaceuticals  
Boulder Safety  
2860 Wilderness Place  
Boulder, CO 80301  
USA

**Continuation Sheet for FDA-3500A Form**

Page 3 of 3

**Mfr. report # : 2003000295**

**Date of this report : 03/07/03**

Seq No.	: 6
Concomitant Medical Product	: GABAPENTIN
Seq No.	: 7
Concomitant Medical Product	: FAMOTIDINE
Seq No.	: 8
Concomitant Medical Product	: ALPRAZOLAM
Seq No.	: 9
Concomitant Medical Product	: MINOCYCLINE
Seq No.	: 10
Concomitant Medical Product	: CEFALEXIN
Seq No.	: 11
Concomitant Medical Product	: CHERACOL



## **Drug Safety Department**

**Tarceva™ (erlotinib HCl, OSI-774)**

**Serious Adverse Event Report – 15 Day Investigator Notification**  
**Report # 2003000295 (Follow-up) Preferred Term: Pulmonary Fibrosis**

12-March-2003

Re: **OSI2510s**, a phase II study of erlotinib in subjects with recurrent/progressive glioblastoma multiforme.

Dear Investigator:

This letter is to advise you that we have submitted a follow-up report to local regulatory authorities regarding a patient who was hospitalized with pulmonary fibrosis while participating in an Investigator-sponsored trial, OSI2510s. This report of pulmonary fibrosis was originally received by OSI Pharmaceuticals on 07-Feb-2003 from the USA with follow-up information received on 25-Feb-2003. Please include a copy of this letter as a supplement to the Investigator's Brochure for Tarceva™ (erlotinib HCl, OSI-774), and forward a copy to your Institutional Review Board/Ethics Committee as required by local regulations.

### **Follow-up Information:**

**Complete medical history and more detailed description of index case and similar events have been provided. A follow-up chest CT showed "signs of improvement but still clear-cut pulmonary fibrosis" and multiple pulmonary emboli. The patient received IV anticoagulation.**

### **Event Narrative**

This 55-year-old male was enrolled in OSI2510s, a phase II study of erlotinib in subjects with recurrent/progressive glioblastoma multiforme. The subject was diagnosed with glioblastoma multiforme of the right parietal lobe. From June 2002 through August 2002, he was treated with whole brain radiation therapy. Other significant history includes stable angina, tobacco use (primarily second-hand smoke) and hypertension. Protocol therapy consisted of erlotinib 150 mg PO, QD commencing on 27-Sep-2002. Protocol therapy was held on 27-Dec-2002.

On 19-Dec-2002, the subject was diagnosed with an upper respiratory infection and treated with cephalexin. On 25-Dec-2002, the subject developed a fever of 101 degrees Fahrenheit. He was evaluated by his primary physician and started on co-trimoxazole. The following day, 26-Dec-2002, he was re-evaluated because his condition had not improved. A chest x-ray showed mild cardiomegaly, evidence of interstitial pneumonitis throughout the right hemithorax and probable early interstitial pneumonitis within the left upper lobe.

On 27-Dec-2002, the subject became more short of breath, necessitating hospitalization. Initial treatment included antibiotics and oxygen. On 30-Dec-2002, the subject was transferred to another hospital for further treatment. The site reported that the subject was



## **Drug Safety Department**

evaluated by a pulmonologist who read the chest X-ray as diffuse consolidation, then diagnosed pneumonia. He was intubated the same day. The following day, 31-Dec-2002, bronchoscopy revealed a few mucous plugs in the lower trachea and an otherwise normal bronchoscopic exam with normal mucosa and no endobronchial lesion or foreign body. Bronchial washings for bacterial and fungal culture were sent. Fungal culture showed a light growth of *Candida albicans*. Bacterial culture and pathology results were not reported. A partial hospital record indicated that the pulmonologist assessed the disorder as adult respiratory distress syndrome (ARDS) that this condition improved, and he was extubated on 12-Jan-2003. Complete records were not available. Date of discharge was not provided.

On 23-Jan-2003, a follow-up chest CT at an outside hospital revealed extensive bilateral pulmonary fibrosis with a possible confluent area of pulmonary fibrosis involving the left lung base, as well as mediastinal lipomatosis.

On 12-Feb-2003, the subject was asymptomatic. A follow-up chest CT at the study center revealed signs of improvement but still clear-cut pulmonary fibrosis and multiple pulmonary emboli. The investigator noted that pulmonary emboli are relatively common in patients with brain tumors. The subject was admitted for IV anticoagulation. The investigator was considering restarting erlotinib at a later date as the subject had exhibited an initial response to erlotinib.

The investigator and the consulting pulmonologist assessed the pulmonary fibrosis as possibly related to erlotinib.

### **Company Medical Assessment**

The patient developed CT-signs of extensive pulmonary fibrosis following a pneumonia after being treated with erlotinib for approximately 3 month. Concomitant medication included agents previously associated with ILD (e.g. minocycline, NSAID). A causal relationship to erlotinib cannot be excluded.

### **Similar Events:**

The global drug safety database for erlotinib was searched and no similar events of pulmonary fibrosis were found. In order to capture events indicative of possible drug-induced interstitial lung disease, the search was expanded to include all serious events of pneumonitis, interstitial pneumonia, bronchiolitis obliterans with organizing pneumonitis (BOOP), and ARDS.

Of the 10 identified cases (Table 1), 5 received erlotinib and 5 received blinded treatment with erlotinib/placebo.

There were 8 previously reported serious adverse events (SAEs) of pneumonitis / interstitial pneumonia, 5 of which were fatal. Investigators assessed 4 of the 8 events as related to erlotinib and concomitant chemotherapy, if applicable. There was 1 previous report of fatal ARDS, which the investigator assessed as related to erlotinib and gemcitabine. There was 1



## Drug Safety Department

previous report of fatal BOOP, which the investigator assessed as related to erlotinib, paclitaxel and carboplatin.

The total safety database is estimated to include more than 4,000 subjects treated with erlotinib or placebo.

### Conclusion

The 10 reports of possible interstitial lung disease received to date have included one or more confounding factors such as progression of pulmonary metastatic disease, previous radiation therapy, previous parenchymal lung disease, sepsis or concomitant medications that may cause interstitial lung disease. The index case occurred in the setting of glioblastoma multiforme and thus has fewer confounders than previously reported cases; however, the patient did receive concomitant agents known to be associated with interstitial lung disease (e.g. minocycline and NSAID).

Based on the review of available data, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of erlotinib and the occurrence of pulmonary fibrosis. Ongoing randomized controlled trials will allow a comparison of the rates of such events in erlotinib treatment arms to those in chemotherapy alone treatment arms.

After review of the clinical details and investigators' comments pertaining to this adverse event and based upon the experience of erlotinib to date, the sponsor does not believe that changes to the conduct of this clinical trial are warranted. However, OSI intends the submission of this IND Safety Report of PULMONARY FIBROSIS to represent a safety amendment to the Tarceva™ (erlotinib HCl; OSI-774) Investigator Brochure.

Please feel free to contact the OSI Drug Safety Department or your local clinical contact with any questions or concerns you may have in this regard. We appreciate your continuing efforts and cooperation in the conduct of our clinical trials.

Sincerely,

A handwritten signature in black ink, appearing to read "Karsten Witt".

Karsten Witt, M.D.  
Sr. Medical Director  
Drug Safety and Clinical Development

" A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the drug caused or contributed to an adverse experience." [CFR 312.32]