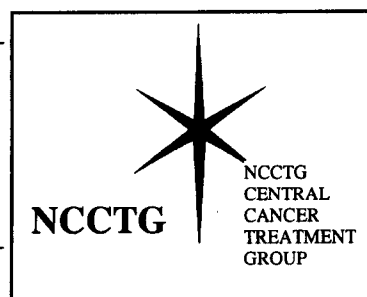

Operations Office

Telephone (507) 266-3853



Date: December 20, 2002
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_1967498_F2

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute

DATE: December 4, 2002
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 IND Safety Report, AE# 1967498
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 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 Adverse Events Assessment that describes the following adverse event is attached:

A 69-year-old male with malignant mesothelioma experienced grade 3 pancreatitis after being treated with OSI-774. The patient was hospitalized for severe abdominal pain. His serum amylase was 581 U/L with a lipase level of 2038 U/L. A computerized tomography scan indicated changes consistent with acute pancreatitis. He was treated with intravenous fluids and pain medications. His lipase and amylase levels improved to 191 U/L and 49 U/L, respectively. The patient recovered and was discharged to home. He will not be retreated with the investigational agent.

There have been no incidences of pancreatitis reported to the NCI as serious adverse events under this IND. There have been a total of 140 patients enrolled in NCI-sponsored clinical trials under this IND.

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NOTIFICATION TO INVESTIGATORS OF EXPEDITED ADVERSE EVENTS REPORTED TO THE FDA

The Food and Drug Administration (FDA) regulations [21 CFR 312.32(c)] require sponsors of clinical studies conducted under an IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. In compliance with these FDA regulations, CTEP will notify its investigators by the following methods:

- **IND Safety Report** - The investigators are sent a copy of the expedited adverse event sent to the FDA by CTEP. The investigators are requested to file a copy with their protocol file and to send a copy to their IRB according to the local IRB's policies and procedures. CTEP does not require a revision to the protocol and/or informed consent document.
- **IND AE Action Letter** - These letters are issued by CTEP for those serious adverse events, which warrant a change in the informed consent form and/or protocol. The investigators are sent a copy of the expedited adverse event sent to the FDA by CTEP with the requirement that the informed consent form and/or protocol be amended to include the new event. The investigators are provided a time frame for which to submit the amendment to the CTEP Protocol and Information Office. The letter will specify if accrual to the protocol is to be suspended until the revision is made and whether patients already on study require reconsenting.

Updates to the ASAEL do not require notification of the investigators. The ASAEL will be available on the CTSU web site, which requires a username and password.

Both the IND Safety Report and IND AE Action Letter will include the number of similar events reported for the agent as well as the number of patients treated to date under the CTEP IND for the agent. Using the following guidelines, the frequency of the event can be categorized: Common event - 20 to 100%, Occasional event - 5 to 20%; and Rare event - < 5%.

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ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774 AE 1967498	ADVERSE EXPERIENCE REPORT NO. 2 IND Safety Report: Event: Gr. 3: Pancreatitis Protocol: S0218
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The patient is a 69-year-old male with malignant mesothelioma of the right thorax who developed pancreatitis while on a phase 2 trial using the investigational agent OSI-774. He began his first course of treatment on September 26, 2002 with oral (PO) doses of OSI-774 150 mg daily. He received 3 weeks of therapy. He developed rash, nausea and water diarrhea after starting OSI-774.

The patient was hospitalized for a one day history of severe abdominal pain on October 21, 2002. His serum amylase was elevated at 581 U/L on admission, a computerized tomography (CT) scan indicated changes consistent with acute pancreatitis, and his lipase level peaked at 2038 U/L on October 23, 2002. He was treated with intravenous fluids and pain medications. His pain resolved, and his condition improved. On October 25, 2002, his lipase level was 191 U/L and amylase level was 49 U/L. Further work-up revealed no hyperlipidemia or gallstones and no abscess developed. He was discharged to home on October 30, 2002 and will not be retreated with the investigational agent.

His past medical history is significant for hypothyroidism, diabetes mellitus, gout, hypertension, degenerative joint disease, hereditary resistance to APC, deep vein thrombosis, and sleep apnea, as well as prostate cancer with no known recurrence. He is a non-smoker and did not drink alcohol. His medications at the time of event included warfarin (Coumadin™), olmesartan (Benicar™), hydrochlorothiazide, rofecoxib (Vioxx™), atorvastatin (Lipitor™), thyroid replacement, metformin HCL (Glucophage™), glyburide, and colchicine/probenecid (ColBenemid™).

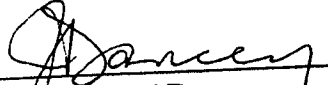
There have been no other incidences of pancreatitis reported to the NCI as serious adverse events under this IND. A possible causal relationship can be attributed to both the agent and the patient's hydrochlorothiazide. There have been 140 patients enrolled in NCI-sponsored clinical trials under this IND.

	Pancreatitis
OSI-774	Possible
Hydrochlorothiazide	Possible

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Date: Dec 4/2002

Signature:


Janet Dancey, M.D.
(IDB Monitor for OSI-774)

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

cc: Christine Boisclair
Brian Watson
OSI Pharmaceuticals, Inc.

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