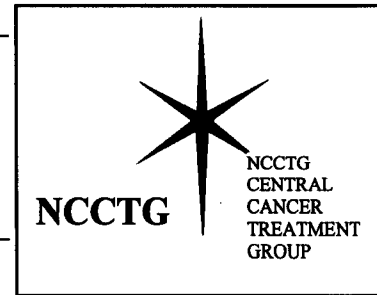


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**Operations Office**

Telephone (507) 266-3853

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**Date:** April 11, 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\_103412\_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



1 DNA Way, MS 59  
South San Francisco, CA 94080  
Fax (650) 225-5862

05 March 3, 2003

PEREZ, Edith, MD  
Mayo Clinic Jacksonville  
Division of Hematology/Oncology  
4500 San Pablo Road  
Jacksonville, FL 32224

RE: Serious Adverse Event from Investigator Sponsored Trial  
Tarceva™ (erlotinib hydrochloride)  
Follow-up report  
MCN 103412

Dear PEREZ, Edith, MD:

A sponsor conducting a study under an investigational new drug application (IND) is required to inform all participating investigators, in writing, of any IND study occurrence of a serious and unexpected adverse drug reaction (ADR). An unexpected ADR is an adverse event that is judged by either an investigator or the sponsor as having a reasonable suspected causal relationship to an investigational product, and that is not already identified as an ADR in the current product Investigator Brochure (IB) or in its amendments.

Attached is a follow-up case summary and analysis of similar events of a serious and unexpected ADR that occurred in a subject exposed to Tarceva while participating in an IND study under IND 61,874. Please review this case report and promptly submit this information to your Institutional Review Board or Independent Ethics Committee. Also, please physically append this follow-up report of hyponatremia to your Tarceva Investigator Brochure.

Although this adverse event has been documented and reported to the appropriate regulatory agencies, this does not reflect a conclusion by Genentech or the regulatory agencies that Tarceva contributed to the adverse event.

Genentech, Inc. intends submission of this IND safety report to also represent a safety amendment to the Tarceva IB.

If questions arise, please contact the undersigned.

Sincerely,

A handwritten signature in black ink, appearing to be "RM", written over a horizontal line.

Robert Mass, MD  
Medical Monitor

Enclosure

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities,  
distributors and manufacturers for  
MANDATORY reporting  
Genentech, Inc.

Relsys International, Inc.  
FDA Facsimile Approval: 11-JUN-1999

Mfr report #	103412
UF/Dist. report #	
FDA Use Only	

Page 1 of 3

A. Patient information			
1. Patient identifier in confidence	2. Age at time of event: <u>74 Years</u> or Date of birth: <u>05/13/1928</u>	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight <u>173.0</u> lbs or <u>78.5</u> 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 (mortality)		<input type="checkbox"/> disability	
<input type="checkbox"/> life-threatening		<input type="checkbox"/> congenital anomaly	
<input checked="" type="checkbox"/> hospitalization - initial or prolonged		<input type="checkbox"/> required intervention to prevent permanent impairment/damage	
<input type="checkbox"/> other:			
3. Date of event (mortality) <u>07/14/2002</u>	4. Date of this report (mortality) <u>03/03/2003</u>		
5. Describe event or problem <b>HYPONATREMIA[HYPONATRAEMIA]</b>  Case Description:  <b>FOLLOW UP IND SAFETY REPORT HYPONATREMIA</b>  This case, manufacturer control number 103412, is a report from the United States referring to a 74-year-old male. An investigator reported this case from study OSI2298g, a Genentech, Inc. sponsored phase III, randomized, double-blind, multinational trial of erlotinib plus paclitaxel and carboplatin versus chemotherapy alone in subjects with advanced (stage IIIb or IV) non-small cell lung cancer (NSCLC) who have not received prior chemotherapy.  Past medical history was significant for hypertension, continued in additional info section...			
6. Relevant tests/laboratory data, including dates #1 07/15/2002 Sodium 115 mEq/L (135 mmol/L to 145 mmol/L) #2 07/19/2002 Sodium 132 mEq/L (135 mmol/L to 145 mmol/L)			
7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) NI			

C. Suspect medication(s)			
1. Name (give labeled strength & mfr/labeler, if known) # 1. <b>ERLOTINIB OR PLACEBO(Erlotinib) (continued)</b> # 2. <b>TAXOL(PACLITAXEL) Solution (continued)</b>			
2. Dose, frequency & route used		3. Therapy dates (if unknown, give duration) <small>(month to (or best estimate))</small>	
# 1. 150 mg, qd, Oral		# 1. 06/17/2002, duration UNK	
# 2. 384 mg, (continued)		# 2. 06/17/2002, duration UNK	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced	
# 1. <b>NON-SMALL CELL (continued)</b>		# 1. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK	
# 2. <b>NON-SMALL CELL (continued)</b>		# 2. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK	
6. Lot # (if known)		7. Exp. date (if known)	
# 1. 110761		# 1. UNK	
# 2. NO(continued)		# 2. UNK	
9. NDC # - for product problems only (if known)			
# 1. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK		# 2. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK	
10. Concomitant medical products and therapy dates (exclude treatment of event) MAXZIDE (HYDROCHLOROTHIAZIDE, TRIAMTERENE) UNK to UNK continued in additional info section...			
G. All Manufacturers			
1. Contact office - name/address (& mfring site for devices) Genentech, Inc. James Nickas Pharm.D. Mailstop: 84, 1 DNA Way South San Francisco, CA 94080 UNITED STATES		2. Phone number	
4. Date received by manufacturer (mortality) <u>02/18/2003</u>		5. (A)NDA # IND # 61,874 PLA # pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes	
6. If IND, protocol # OSI2298G		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:	
7. Type of report (check all that apply) <input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input type="checkbox"/> initial <input checked="" type="checkbox"/> follow-up # 1		8. Adverse event term(s) HYPONATRAEMIA	
9. Mfr. report number 103412			
E. Initial reporter			
1. Name & address		phone #	
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			



3500A - Facsimile

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

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

**Medication and Device  
Experience Report  
(continued)**

Mfr report #	103412
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<b>1. Name (give labeled strength &amp; mfr/labeler, if known)</b>	
# 3. CARBOPLATIN Solu (continued)	
# 4.	
<b>2. Dose, frequency &amp; route used</b>	<b>3. Therapy dates (if unknown, give duration)</b> <small>months (or less, continue)</small>
# 3. 690 mg, (continued)	# 3. 06/17/2002, duration UNK
# 4.	# 4.
<b>4. Diagnosis for use (indication)</b>	<b>5. Event abated after use stopped or dose reduced</b>
# 3. NON-SMALL CELL (continued)	# 3. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK
# 4.	# 4. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
<b>6. Lot # (if known)</b> <b>7. Exp. date (if known)</b>	<b>8. Event reappeared after reintroduction</b>
# 3. NO(continued) # 3. UNK	# 3. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK
# 4.                              # 4.	# 4. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
<b>9. NDC # - for product problems only (if known)</b>	
NA	
<b>10. Concomitant medical products and therapy dates (exclude treatment of event)</b>	
NA	

Mfr report #	103412
UF/Dist. report #	
	FDA Use Only

**Medication and Device  
Experience Report**  
(continued)

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## Additional Information

**B5. EVENT DESCRIPTION (cont.)**

emphysema and 50+ pack-years of cigarette smoking. On 20 May 2002, he was diagnosed with poorly differentiated large cell carcinoma by fine needle aspiration to a left supraclavicular lymph node. Concomitant medications included triamterene/hydrochlorothiazide and verapamil.

On 17 Jun 2002, the subject received erlotinib (150 mg by mouth QD), paclitaxel (384 mg IV Q3W) and carboplatin (690 mg IV Q3W).

On 8 Jul 2002, the second cycle of paclitaxel/carboplatin was held due to neutropenia with absolute neutrophil count (ANC) 1.36 K/mcL; at this time, serum sodium was 127 mEq/L and serum osmolality was 269 mOsm (278-305). On 14 Jul 2002, ANC was 0.904 and chemotherapy was again held. Serum sodium had decreased to 119 mEq/L. A 2-week history of fatigue was reported; no other symptoms. Performance status was 1. The following day, on 15 Jul 2002, repeat serum sodium was 115 mEq/L and he was hospitalized. Treatment included hypertonic normal saline and demeclocycline. On 17 Jul 2002, serum sodium was 120 mEq/L, white blood cell count was 2.2 K/mcL with 41% neutrophils. Erlotinib was held during the hospitalization. At the time of this report, the event remains ongoing.

The investigator assessed the event of hyponatremia as related to erlotinib, concurrent medication and protocol-specified chemotherapy.

Additional information has been requested.

Additional information received on 18 Feb 2003, indicated on 19 Jul 2002, the subject's serum sodium was reported to be 132 mEq/L, his condition had stabilized and was discharged home and continued on demeclocyclin (300 mg PO BID). On 24 Jul 2002, carboplatin and paclitaxel were re-started at 50% of the original dose. Study drug was also resumed at 150 mg PO QD on 24 Jul 2002. The investigator re-assessed the event of hyponatremia as related to erlotinib and the disease under study. No further information is expected.

**C1. Name (cont.)**

Suspect Medication #1: ERLOTINIB OR PLACEBO(ERLOTINIB OR PLACEBO) Tablet

Suspect Medication #2: TAXOL(PACLITAXEL) Solution for injection

Suspect Medication #3: CARBOPLATIN(CARBOPLATIN) Solution for injection

**C2. Dose, frequency & route used (cont.)**

Suspect Medication #2: 384 mg, Q3W, Intravenous

Suspect Medication #3: 690 mg, Q3W, Intravenous

**C4. Diagnosis for use (cont.)**

#1: NON-SMALL CELL LUNG CANCER

#2: NON-SMALL CELL LUNG CANCER

#3: NON-SMALL CELL LUNG CANCER

**C6. lot#(if known) (cont.)**

Suspect Medication #2: NOT REPORTED

Suspect Medication #3: NOT REPORTE

**C10. CONCOMITANT MEDICAL PRODUCTS**

CALAN (VERAPAMIL HYDROCHLORIDE) UNK to UNK

Genentech, Inc.

<b>MED WATCH</b>	A.1. Patient Identifier	G.9. Mfr. report number 103412	Addendum
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**FOLLOW-UP IND SAFETY REPORT  
CASE SUMMARY MCN 103412:**

This IND safety report from the USA of HYPONATREMIA refers to a 74-year-old male enrolled in OSI2298g, a phase III, randomized, double-blind trial of erlotinib plus paclitaxel and carboplatin versus chemotherapy alone in subjects with advanced non-small cell lung cancer (NSCLC). Past medical history was significant for hypertension, emphysema and smoking. Concomitant medications included triamterene/hydrochlorothiazide and verapamil. Trial medication consisted of erlotinib (150 mg PO QD) with paclitaxel (384 mg IV Q3W) and carboplatin (690 mg IV q3W). On a scheduled office visit one month into the study, serum sodium of 119 mEq/L was observed. Repeat serum sodium on the following day was 115 mEq/L. The patient was hospitalized for treatment, which included hypertonic normal saline and demeclocycline. The event remained ongoing.

**Follow-up report:** Additional information, received on 18 Feb 2002, indicated that the event resolved on 19 Jul 2002. The investigator changed the causality assessment for the event of hyponatremia from related to Tarceva, concomitant medications, and protocol specified chemotherapy to related to Tarceva and the disease under study.

**ANALYSIS OF SIMILAR EVENTS**

The Roche, OSI-P, and Genentech Safety Databases for erlotinib were searched for all serious events with the primary or linking preferred term of hyponatremia.

**Previous Reports of Hyponatremia:**

There were 5 previously reported serious adverse events (SAEs) of hyponatremia (Table 1). All 5 cases were assessed as not related to erlotinib.

**MCN 312305:**

A 19-year-old female with glioblastoma was enrolled in OSI2367s, an investigator sponsored open label study of erlotinib and temozolomide for treatment of glioma. The subject was hospitalized with dehydration, hyponatremia, hyperkalemia and increased white blood count, then died due to progressive glioblastoma. The investigator assessed hyperkalemia and hyponatremia as not related to erlotinib, but related to frequent paracenteses and dehydration.

**MCN 310183:**

A 52-year-old male with non-small cell lung cancer was enrolled in study BR.21, a randomized placebo-controlled study of erlotinib in patients with advanced NSCLC. The subject was hospitalized for pain management, and on admission was dehydrated with acute renal insufficiency, hyponatremia, elevated creatinine and lactic acidosis. The subject died due to

disease progression with liver metastases. The investigator assessed hyponatremia, elevated creatinine and lactic acidosis as not related to erlotinib/placebo, but related to dehydration.

**MCN 302332:** A 54-year-old male with rectal cancer was enrolled in an open label, dose escalation, phase I study of erlotinib for patients with advanced solid tumors. The subject was hospitalized with confusion, dehydration and hyponatremia. The events resolved and the subject discontinued the study due to progression of rectal cancer. The investigator assessed dehydration and hyponatremia as not related to erlotinib, but related to furosemide and progression of cancer.

**MCN 300458:** A 30-year-old female with breast cancer was enrolled in study OSI2288g, a phase II open label trial of erlotinib in subjects with metastatic breast cancer. The subject was hospitalized for a concussion following a motor vehicle accident. The concussion resolved and the subject was discharged. One week later, she was re-hospitalized for nausea, vomiting, ataxia, headache, diarrhea and hyponatremia. The investigator assessed the hyponatremia as not related to erlotinib, but related to nausea and vomiting; the nausea and vomiting were assessed as related to the concussion.

**MCN 268836:** A 47-year-old female with ovarian cancer was enrolled in a phase II open label study of erlotinib in patients with advanced ovarian cancer. The subject was hospitalized with pericardial and pleural effusions and hyponatremia. The investigator assessed events as not related to erlotinib, but related to disease under study.

#### **ASSESSMENT OF RELATIONSHIP**

This OSI2298g IND safety report describes a serious, unexpected event of HYPONATREMIA in a 74-year-old male with NSCLC on erlotinib, paclitaxel and carboplatin, as well as concomitant hydrochlorothiazide/triamterene for hypertension. Of the five similar events of hyponatremia identified in subjects receiving erlotinib, etiologies other than erlotinib/placebo were more plausible, eg, dehydration, head trauma, brain tumor—all of these cases were assessed as unrelated to study drug by the investigators. For the current case of hyponatremia, MCN 103412, diuretic therapy and lung cancer provide plausible explanations for the event.

Based on review of the available data, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of erlotinib and the occurrence of hyponatremia. Ongoing randomized controlled trials, such as the current Phase III trial OSI2298g, 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, Genentech, Inc., intends the submission of this IND Safety Report to represent a safety amendment to the OSI-774 (erlotinib; Tarceva) Investigator Brochure.

**Follow-up report:** There is no change to the assessment of this IND safety report subsequent to the additional information received.