



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** December 5, 2008

**To:** NCCTG Primary Clinical Research Associates

**From:** Sara Braun  
Protocol Development Coordinator

**Re:** N057K, Phase I/II Evaluation of Everolimus (RAD001), Radiation and Temozolomide (TMZ) Followed by Adjuvant Temozolomide and Everolimus in Newly Diagnosed Glioblastoma

The purpose of this memorandum is to provide investigators with a recent industry report of an adverse event that has occurred in association with RAD-001 at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

**AE\_PHHO2008TW11206\_F1**

Please note that all risks currently cited in the NCCTG consent form cannot 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 Sara Braun at [braun.sara@mayo.edu](mailto:braun.sara@mayo.edu) or 507-538-8226.

SB/kjm  
enclosure



To: All Investigators in RAD001 Studies\*

Date: Nov 18, 2008

Re: Investigator Notification for RAD001  
Hiccups and Urinary incontinence / PHHO2008TW11206 follow-up downgraded to non-serious

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of medically significant information for a serious, unexpected, possibly related adverse events of hiccups and urinary incontinence in a 69-year-old female patient who received RAD001 in the study CRAD001C24108, a phase II study of RAD001 plus cisplatin-HDFL (cisplatin and weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin) chemotherapy for the first-line treatment of non-resectable, recurrent or metastatic gastric cancer.

Follow-up information indicates that hiccups and urinary incontinence were considered as non-serious events with unclear etiology. Approximately one month later, the patient was discontinued from the study due to underlying cancer disease progression and received salvage chemotherapy. Subsequently, the patient expired due to underlying disease. Details of the adverse events as reported to Novartis are provided in the attached CIOMS I form.

We will keep you informed if further medically significant information becomes available. We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an obligation. For clinical trials in the U.S. only, if you are utilizing the services of a central Institutional Review Board (IRB) that has been contracted through Novartis, Novartis will submit the Investigator Notification on your behalf to the central IRB.

Sincerely,

Holly Zhang, MD  
Senior Pharmacovigilance Leader, Integrated Medical Safety  
Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey, 07936-1080

United States

Attachment: CIOMS case report

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\* Novartis Investigator Notification: International Guidelines for Good Clinical Practice as well as specific health authority regulations require that clinical investigators be informed of any adverse drug reaction which is serious (according to specific regulatory criteria), unexpected (i.e. not specifically mentioned in the Investigator's Brochure) and which has a 'reasonable possibility' (in the opinion of the reporter and/or the Company) of being related to the study medication. While Novartis tries to obtain all meaningful information as soon as possible, we are required to communicate all available information within a specified time of its receipt. Since initial data is frequently incomplete, further information must be sent in the form of follow-up reports. Where they have such an obligation, investigators are expected to inform institutional review boards/ethics committees, of each investigator notification. Should Novartis believe that a change in protocol or other action needs to be taken on the basis of clinical reports or other available data, the company will communicate such changes to involved investigators.

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last) <b>XXX</b>	1a. COUNTRY <b>XXX</b>	2. DATE OF BIRTH			2a. AGE <b>69</b> Years	3. SEX <b>Female</b>	3a. WEIGHT <b>67.40</b> kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day <b>02</b>	Month <b>FEB</b>	Year <b>1939</b>			Day <b>16</b>	Month <b>SEP</b>	Year <b>2008</b>		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <b>Dyspnea [Dyspnoea] Septic shock [Septic shock] ([Acinetobacter bacteraemia], [Bacteraemia] Aspiration pneumonia [Pneumonia aspiration] ([Pyrexia], [Sputum purulent], [Lung infiltration]) Hypoxic respiratory failure [Respiratory failure] ([Hypoxia], [Diaphragm muscle weakness]) Lack of drug effect [Drug ineffective] Disease progression [Malignant neoplasm progression] ([Hyperbilirubinaemia]) Thrombocytopenia, suspect disseminated intravascular coagulation related [Disseminated intravascular coagulation] ([Thrombocytopenia])</b>										<input checked="" type="checkbox"/> PATIENT DIED Date: 26-OCT-2008  <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  <input checked="" type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  <input type="checkbox"/> LIFE THREATENING	
<b>(Continued on Additional Information Page)</b>											

**II. SUSPECT DRUG(S) INFORMATION**

14. SUSPECT DRUG(S) (include generic name) <b>#1 ) RAD001 + Cisplatin, FU and leucovorin (RAD001 + Cisplatin, FU and leucovorin) Tablet</b>		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <span style="float: right;">Unknown</span>
15. DAILY DOSE(S) <b>#1 ) 10 mg / day</b>	16. ROUTE(S) OF ADMINISTRATION <b>#1 ) Oral</b>	
17. INDICATION(S) FOR USE <b>#1 ) Advanced gastric cancer (Metastatic gastric cancer)</b>		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <span style="float: right;">Unknown</span>
18. THERAPY DATES(from/to) <b>#1 ) 11-MAR-2008 / 13-OCT-2008</b>	19. THERAPY DURATION <b>#1 ) 217 days</b>	

**III. CONCOMITANT DRUG(S) AND HISTORY**

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) <b>#1 ) CISPLATIN (CISPLATIN) ; Ongoing #2 ) 5-FU (FLUOROURACIL) ; Unknown #3 ) LEUCOVORIN (FOLINIC ACID) ; Unknown #4 ) FARLUTAL (MEDROXYPROGESTERONE ACETATE) ; Unknown</b>	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates	Description
Unknown	Liver cirrhosis (Hepatic cirrhosis)
Unknown	HCV (Hepatitis C virus)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. <b>PHHO2008TW11206</b>	
24c. DATE RECEIVED BY MANUFACTURER <b>12-NOV-2008</b>	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER XXX XXX XXX XXX XXX
DATE OF THIS REPORT <b>17-NOV-2008</b>	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP:	

**ADDITIONAL INFORMATION****7+13. DESCRIBE REACTION(S) continued**

Sepsis-related acute renal failure [Renal failure acute]  
Muscle weakness whole body [Muscular weakness]  
Suspected extrapyramidal syndrome [Extrapyramidal disorder] ([Parkinsonism], [Speech disorder], [Mutism], [Disturbance in attention], [Tremor], [Trismus], [Nervous system disorder])  
Anorexia / poor appetite [Anorexia] ([Hyponatraemia], [Hypokalaemia], [Parenteral nutrition])  
Incontinence urinary (non-serious) [Urinary incontinence]  
Hiccoughs (non-serious) [Hiccups]

Case Description: Initial report received on 17 Sep 2008: This patient (patient no. XXX from centre no. XXX) was enrolled in the study CRAD001C24108, a phase II study of RAD001 plus cisplatin-HDFL (cisplatin and weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin) chemotherapy for the first-line treatment of non-resectable, recurrent or metastatic gastric cancer. She received the first dose of study medication on 11 Mar 2008 and had received Farlutal for anorexia since 13 Mar 2008 and received "C6D8" treatment on 09 Sep 2008. On 16 Sep 2008, the patient experienced persistent hiccups and general weakness (left side and right side), poor appetite, incontinence urinary and dyspnea which resulted in hospitalisation and involved persistent or significant disability or incapacity. A diagnosis of anorexia, incontinence urinary, muscle weakness whole body, hiccoughs and dyspnea was made. At the time of this report the patient's condition was still present. The investigator suspected a relationship between this event and the study medication.

Follow-up information received 24 Sep 2008: The investigator confirmed that all of the reported events met the seriousness criterion of hospitalisation. The general weakness and poor appetite were not suspected to be related to RAD001, whereas the hiccoughs and urinary incontinence were suspected to be related to RAD001.

Follow-up received on 06 Nov 2008: The patient was admitted to oncology ward on 18 Sep 2008. TPN (total parenteral nutrition) was given due to poor oral feeding. Hyponatremia and hypokalemia were also corrected. Platelet transfusion was also given. However, gradual verbal output decrease, progressive to total mutism occurred on 19 Sep 2008, and failure to follow simple orders and tremors over 4 limbs were noted. Trismus and poor cough power were also noted. Consultant neurologist depicted the scenario as Parkinsonism feature and suggested MRI and EEG workup. On 24 Sep 2008, MRI showed mild brain atrophy. On 25 Sep 2008, sudden onset fever and dyspnea developed. Purulent sputum was also noted. Septic workup was done and Tazosin was given for suspected nosocomial pneumonia. Oxygen demand was increased gradually (room air to 60% 10L O2 mask). Due to poor cough power and impending hypoxic respiratory failure, intubation was performed and the patient was transferred to ICU (intensive care unit) on 25 Sep 2008. After ICU admission, trihexyphenidyl was administered. Levophed was discontinued on 25 Sep 2008. The consciousness improved gradually. Blood culture yielded MSSA (methicillin-sensitive Staphylococcus aureus) and Acinetobacter Iwoffii in three sets. EEG showed moderate to severe diffuse cortical dysfunction. On 27 Sep 2008, lumbar puncture showed WBC (white blood count) 0, RBC (red blood count) 1, TP (total protein) 45.4, LDH (lactate dehydrogenase) 62, Glu (glucose) 81 and negative India ink. On 28 Sep 2008, extubation was performed after spontaneous breathing trial. On 30 Sep 2008, shock (SBP - systemic blood pressure 75 mmHg) was noted, after port-A usage. After intravenous (IV) hydration, the BP (blood pressure) recovered gradually. On 30 Sep 2008, the preliminary blood culture showed GNB (Gram-negative bacilli) (II/II) and Stenotrophomonas x II from peripheral and port-A. CVS (cardiovascular) doctor was consulted to remove port-A as soon as possible, but medical treatment, to achieve stable hemodynamics, was suggested first. On 01 Oct 2008, the inotropic agent was tapered off. On 02 Oct 2008, the patient was transferred to general ward for further care. On 03 Oct 2008, antibiotics were shifted to Ciproxin. Fever subsided gradually. On 06 Oct 2008, portal A was removed. On 07 Oct 2008, central venous catheter (CVC) was removed due to blood culture showing S-M/infection (Stenotrophomonas maltophilia). Progressive hyperbilirubinemia was noted, abdominal CT (computed tomography) was performed and showed progressive liver metastasis. On 13 Oct 2008, the patient was discontinued from the study due to progressive disease. The fever subsided and follow-up blood culture showed no bacteria growth. Ciproxin was discontinued after a 14-day course. On 13 Oct 2008, salvage chemotherapy, with HDFL-48, was given. On 16 Oct 2008, progressive hyperbilirubinemia, up to 13.52, was noted. Abdominal echo revealed progressive liver metastasis and no IHD (intrahepatic duct)/CBD (common bile duct) dilation. On 22 Oct 2008, Maxipime was given after septic work-up. On 23 Oct 2008, high fever, up to 39.6 C, was noted. Chest x-ray (CXR) showed multiple pneumonic patch, especially right lower lobe (RLL). Sepsis-related acute renal failure was noted. Renal function improved a little after Maxipime and metronidazole. The patient suffered from hypotension and expired on 26 Oct 2008. Final diagnoses were hyperbilirubinemia, hospital-acquired pneumonia with septic shock, Acinetobacter Iwoffii and Stenotrophomonas bacteremia, suspect aspiration pneumonia with impending hypoxic respiratory failure, Parkinsonism feature, suspected extrapyramidal syndrome and thrombocytopenia, suspect disseminated intravascular coagulation related. The investigator did not suspect a relationship between these events and the study medication, but indicated they were due to lack of efficacy and progression of underlying illness.

Follow-up received on 12 Nov 2008: The investigator confirmed that the hiccups and urinary incontinence were non-serious events. The cause of these events was unknown.

Novartis Comment: Serious adverse drug reaction report, dyspnea, resulting in hospitalisation, assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

New information received on 12 Nov 2008, reported that the hiccoughs and urinary incontinence have been reassessed as non-serious by the investigator.

**ADDITIONAL INFORMATION****13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	16-SEP-2008	Alanine aminotransferase U/l	56	
2	16-SEP-2008	Aspartate aminotransferase U/l	58	
3	16-SEP-2008	Blood alkaline phosphatase U/l	289	
4	16-SEP-2008	Blood bilirubin mg/dl	1.45	
5	16-SEP-2008	Blood calcium mmole/l	1.95	
6	16-SEP-2008	Blood creatinine mg/dl	1.5	
7	25-SEP-2008	Blood culture Yielded MSSA and Acinetobacter Iwoffii		
8	30-SEP-2008	Blood culture Showed GNB (II/II) and Stenotrophomonas x II from peripheral and port-A.		
9	13-OCT-2008	Blood culture Follow-up, no bacteria growth		
10	23-OCT-2008	Body temperature	39.6 °C	
11	23-OCT-2008	Chest X-ray Showed multiple pneumonic patch, especially RLL (right lower lobe)		
12	OCT-2008	Computerised tomogram abdomen Showed progressive liver metastasis		
13	25-SEP-2008	Electroencephalogram Showed moderate to severe diffuse cortical dysfunction.		
14	16-SEP-2008	Haemoglobin g/dl	8.5	
15	27-SEP-2008	Lumbar puncture WBC 0, RBC 1, TP 45.4, LDH 62, Glu 81 and negative India ink		

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**ADDITIONAL INFORMATION****13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
16	24-SEP-2008	Nuclear magnetic resonance imaging  Showed mild brain atrophy		
17	16-SEP-2008	Platelet count  K/ul	43	
18	16-OCT-2008	Ultrasound scan  Revealed progressive liver metastasis and no IHD(intrahepatic duct)/CBD (common bile duct) dilation		