



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** October 3, 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**

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: Sep 29, 2008

Re: Investigator Notification for RAD001  
Hiccups and Urinary incontinence / PHHO2008TW11206

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of 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.

Details of the adverse events as reported to Novartis are provided in the attached CIOMS I form.

A search of the Novartis Clinical Safety Database for RAD001 for similar cases was performed using MedDRA 11.0 Preferred Terms of Hiccups, Stress urinary incontinence and Urinary incontinence. One additional case of hiccups and two additional cases of urinary incontinence were identified. These cases were considered to be related to patients' underlying conditions and they were not suspected to be related to RAD001.

In the current case, the patient had advanced gastric cancer. Given the available information in the current case, a causal relationship between study drug and event occurrences cannot be established or excluded. Additional information has been requested.

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>X</b>	1a. COUNTRY <b>X</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  <input type="checkbox"/> PATIENT DIED <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
		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>Incontinence urinary [Urinary incontinence]</b> <b>Hiccoughs [Hiccups]</b> <b>Dyspnea [Dyspnoea]</b> <b>Anorexia / poor appetite [Anorexia]</b> <b>Muscle weakness whole body [Muscular weakness]</b>  Case Description: Initial report received on 17 Sep 2008: This patient (patient no. x from centre no.)  <p style="text-align: right;">(Continued on Additional Information Page)</p>											

**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 ) UNK</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 / Unknown</b>	19. THERAPY DURATION <b>#1 ) Unknown</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</b> <b>#2 ) 5-FU (FLUOROURACIL) ; Unknown</b> <b>#3 ) LEUCOVORIN (FOLINIC ACID) ; Unknown</b> <b>#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>17-SEP-2008</b>	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT <b>24-SEP-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

x) 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.

Novartis Comment: Serious adverse drug reaction report, hiccoughs and urinary incontinence resulting in hospitalisation, assessed as unexpected according to the Investigator's Brochure. However, other alternative causes (gastric cancer, chemotherapy) provide a possible explanation for the reported adverse event. Investigator causality is suspected.

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

**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	16-SEP-2008	Haemoglobin g/dl	8.5	
8	16-SEP-2008	Platelet count K/ul	43	