



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** June 20, 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\_PHHO2008DE05923**

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/df  
enclosure



To: All Investigators in RAD001 Studies\*

Date: June 9, 2008

Re: Investigator Notification for RAD001  
Bladder tamponade with bloody urine /PHHO2008DE05923

Dear Doctors,

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 event of bladder tamponade with bloody urine that occurred in a 61-year-old male patient being treated with RAD001 during the course of the clinical trial entitled “A randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo”.

Details of the adverse event 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 10.1 Preferred Terms of Bladder tamponade, Blood urine, Blood urine present and Haematuria. A total of 19 cases were identified including 18 cases of hematuria and one case of bladder tamponade. Of the 19 cases, five were reported as suspected, four cases of hematuria and the current case of bladder tamponade with bloody urine. Of the four suspected cases of hematuria, two were reported in association with renal tumor bleeding and one was reported in the context of urinary tract infection and one reported intermittent hematuria with advanced pancreatic neuroendocrine tumor.

Based on the review of available data, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of RAD001 and the event. 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>XXX</b>	1a. COUNTRY <b>Germany</b>	2. DATE OF BIRTH			2a. AGE <b>XX</b> Years	3. SEX <b>Male</b>	3a. WEIGHT <b>64.50</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 type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  <input type="checkbox"/> LIFE THREATENINGX
		Day <b>XX</b>	Month <b>XXX</b>	Year <b>XXX</b>				Day <b>08</b>	Month <b>MAY</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>Tamponade of the urine bladder with blood [Bladder tamponade] ([Urinary bladder haemorrhage], [Blood urine present], [Postrenal failure], [Bladder irrigation])                  Nausea [Nausea]</b>  Case Description: Initial report received on 08 May 2008: This patient (centre no. XXX, patient no. XX was enrolled in the study CRAD001C2325, a randomised, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumour receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo.  (Continued on Additional Information Page)											

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

14. SUSPECT DRUG(S) (include generic name) #1 ) RAD001 Vs Placebo (RAD 666 RAD+TAB) Tablet #2 ) SANDOSTATIN LAR (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Unknown		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
15. DAILY DOSE(S) #1 ) 10 mg #2 ) Code not broken	16. ROUTE(S) OF ADMINISTRATION #1 ) Oral #2 ) Oral	
17. INDICATION(S) FOR USE #1 ) carcinoid tumour (Carcinoid tumour) #2 ) Carcinoid tumour (Carcinoid tumour)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
18. THERAPY DATES(from/to) #1 ) 10-APR-2008 / 09-MAY-2008 #2 ) 10-APR-2008 / 09-MAY-2008	19. THERAPY DURATION #1 ) 30 days #2 ) 30 days	

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

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ) AMARYL (GLIMEPIRIDE) ; JUN-2003 / Ongoing #2 ) NEXIUM (ESOMEPRAZOLE MAGNESIUM) ; APR-2006 / Ongoing #3 ) OPIUM TINCTURE (PAPAVER SOMNIFERUM TINCTURE) ; JUN-2006 / Ongoing		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
1988 to Unknown	Current Condition	Pollinosis (Seasonal allergy)
APR-2008 to Unknown	Current Condition	Hoarseness of voice (Dysphonia)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
24b. MFR CONTROL NO. <b>PHHO2008DE05923</b>		
24c. DATE RECEIVED BY MANUFACTURER <b>28-MAY-2008</b>		25b. NAME AND ADDRESS OF REPORTER XXX XXX  XXXX
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>09-JUN-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The patient's medical history was not reported. The patient received his first dose of study medication on 10 Apr 2008. On an unknown date, the patient presented with bloody urine, followed by acute postrenal/postbladder failure. The patient was diagnosed with tamponade of the urine bladder with blood. The outcome was not reported. In the absence of an investigator causality, a Novartis medical safety physician provisionally assessed that this event was not suspected to be related to study medication, based on current available information.

Follow-up received on 28 May 2008: The onset date of the event was 08 May 2008, and resulted in hospitalization. On 09 May 2008, the study medication was permanently discontinued. On 16 May 2008, the patient was discharged, recovered, without sequelae. The investigator suspected a relationship between the event and RAD001 but did not suspect a relationship between the event and Sandostatin LAR.

Follow-up received on 28 May 2008: The patient's medical history included type II diabetes mellitus, thyroid nodule, gastritis, diarrhea, dry skin, hoarseness of voice and pollinosis. Treatment for "tamponade of the urine bladder with blood, bloody urine" included bladder irrigation. On 08 May 2008, the patient also presented with nausea. Treatment, for nausea, included MCP (metoclopramide hydrochloride). The outcome was not reported. The investigator stated that there was no definitive relationship of RAD001 and the SAE however it could not be excluded. In the absence of an investigator's causality assessment the Novartis medical safety physician provided a provisional causality assessment and suspected the nausea to be related to study medication, based on the available information.

Novartis Comment: Serious adverse drug reaction, tamponade of urinary bladder with blood, (hospitalisation), assessed as unexpected according to the Investigator's Brochure.

The information provided in this case does not warrant a change to the Investigator's Brochure. The topic will be monitored closely. Investigator causality is suspected.

Serious adverse drug reaction report, nausea (hospitalisation), assessed as expected for RAD001 according to the Investigators Brochure and listed for Sandostatin LAR according to the Core Data Sheet.

In the absence of an investigator causality the Novartis medical safety physician has provisionally assessed the event as suspected for RAD001 and Sandostatin LAR based on the current available information.

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
APR-2008 to Unknown	Current Condition	Dry skin (Dry skin);
JAN-2008 to Unknown	Current Condition	Diarrhea (Diarrhoea);
APR-2006 to Unknown	Current Condition	Gastritis (Gastritis);
APR-2006 to Unknown	Current Condition	Thyroid nodule (Thyroid neoplasm);
JUN-2003 to Unknown	Current Condition	Type II diabetes mellitus (Type 2 diabetes mellitus);