



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 28, 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_PHHO2008DE11491

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 or 507-538-8226.

SB/kjm
enclosure



To: All Investigators in RAD001 Studies*

Date: Oct 13, 2008

Re: Investigator Notification for RAD001
Vertigo/PHHO2008DE11491

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 event of vertigo that occurred in a 51 year-old female patient being treated with RAD001 during the course of the clinical trial CRAD001C2325 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(s) 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 that contain vertigo. Six cases were identified from the search including the current case. Four cases were not suspected to be related to RAD001 use, and two were suspected. The additional suspected event occurred in association with fatal pneumonitis and aggravated underlying condition.

In this case, inadequate information is available to allow full assessment at this time. 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

* 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.

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	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 THREATENING
		Day	Month	Year	51	Female	59.00	Day	Month	Year	
		13	JUL	1957	Years		kg	22	SEP	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Vertigo [Vertigo] Hypoglycemia [Hypoglycaemia]											
Case Description: Initial report received on 23 Sep 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. The patient's medical history included: reflux oesophagitis, pangastritis, hiatus hernia, hypertension and cardiac disease. The patient received her first dose of study medication on 14 Feb 2008.											
(Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
#1) RAD001 Vs Placebo (RAD 666 RAD+TAB) Tablet #2) SANDOSTATIN LAR (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Unknown		
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
#1) Double blind #2) Double blind	#1) Oral #2) Oral	
17. INDICATION(S) FOR USE		
#1) Carcinoid tumour (Carcinoid tumour) #2) Carcinoid tumour (Carcinoid tumour)		
18. THERAPY DATES(from/to)	19. THERAPY DURATION	
#1) 14-FEB-2008 / 25-SEP-2008 #2) 14-FEB-2008 / Ongoing	#1) 225 days #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)	
#1) BELOC-ZOC FORTE (METOPROLOL SUCCINATE) ; Unknown #2) OMEPRAZOL (OMEPRAZOLE) ; Unknown #3) VALOCORDIN (BROMISOVAL, HUMULUS LUPULUS EXTRACT, PHENOBARBITAL) ; Unknown #4) DIAZEPAM (DIAZEPAM) ; Unknown	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)	
From/To Dates	Description
Unknown	Disorder circulatory system (Cardiovascular disorder)
Unknown	Cardiac disorder (Cardiac disorder)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		26. REMARKS
Investigator's Notification Copy Novartis Pharma Headquarter		
	24b. MFR CONTROL NO.	25b. NAME AND ADDRESS OF REPORTER
	PHHO2008DE11491	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE	
10-OCT-2008	<input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT	25a. REPORT TYPE	
13-OCT-2008	<input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

On 19 Jul 2008, the patient presented with vertigo, which resulted in hospitalisation. The patient made a complete recovery on 23 Sep 2008. The investigator did not suspect a relationship between this event and the study medication.

Follow-up received on 01 Oct 2008: The onset of the vertigo was amended from 19 Jul 2008 to 22 Sep 2008. The patient recovered with sequelae on 27 Sep 2008 (not completely recovered on 23 Sep 2008 as previously reported). Then on 28 Sep 2008 the patient experienced a recurrence of vertigo and hypoglycaemia which involved hospitalisation. The outcome was not reported. The investigator suspected this occurrence of vertigo and hypoglycaemia to be suspected to RAD001 and not suspected to Sandostatin LAR.

Follow up received on 10 Oct 2008: The investigator stated that the patient's additional medical history included circulatory distress since 19 Jul 2008. The patient underwent a glucose test on 24 Sep 2008 and 03 Oct 2008 the results were 2.9mmol/L and 4.5 mmol/L respectively. She also had a glucose tolerance test on 24 Sep 2008 which showed 2.7mmol/L after 4 hours. The patient's condition for both events was reported as "may be in hospital". The patient was treated with "Beloc zok mite" (Beloc-zok forte), Valocardin and Diazepam for the events. Study medication was permanently discontinued on 25 Sep 2008 due to the events. The investigator considered the first onset of vertigo to be not related to either study medication but they suspected the second onset of vertigo and the hypoglycaemia to be caused by RAD001 and not Sandostatin.

Novartis Comment: Serious adverse drug reaction, vertigo (hospitalisation), assessed as unexpected according to the Investigator Brochure (IB) for RAD001. The information provided in this individual case does not warrant a change to the IB text. The topic will be monitored closely. Investigator causality is suspected for RAD001.

Serious adverse drug reaction, hypoglycaemia (hospitalisation), assessed as expected according to the Investigator Brochure (IB) for RAD001. Investigator causality is suspected for RAD001.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	24-SEP-2008	Blood glucose	2.9 mmol/l	
2	03-OCT-2008	Blood glucose	4.5 mmol/l	
3	24-SEP-2008	Glucose tolerance test	2.7 mmol/l	
		After 4 hours		

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Hypertension (Hypertension);
Unknown		Hiatus hernia (Hiatus hernia);
Unknown		Gastritis (Gastritis);
Unknown		Reflux oesophagitis (Reflux oesophagitis);