



To: All Investigators in RAD001 Studies\*

Date: Jan 21, 2009

Re: Investigator Notification for RAD001  
Duodenal ulcer /PHHO2009IT00723

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 Duodenal ulcer that occurred in 51-year-old female patient who enrolled in the study enrolled in the study CRAD001C2324, a randomized double-blind phase III study of RAD001 plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET).

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 was performed using MedDRA 11.0 preferred terms of Duodenal ulcer, Gastroduodenal ulcer and Duodenal ulcer haemorrhage. Three cases were identified including the current case. Only the current case is suspected.

For the current case, considering the patient's underlying disease and duodenoscopy showing bleeding in the known ulceration related to the tumor infiltration. It is unlikely that the event was caused by the study drug. The case was also confounded by concomitant use of Paracetamol.

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)	1a. COUNTRY <b>Italy</b>	2. DATE OF BIRTH			2a. AGE <b>51</b> Years	3. SEX <b>Female</b>	3a. WEIGHT <b>70.00</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 THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <b>Duodenal ulcer [Duodenal ulcer] ([Small intestinal haemorrhage], [Haematemesis])</b>  Case Description: Initial report received on 09 Jan 2009: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001C2324, a randomised double-blind phase III study of RAD001 plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET). The patient's medical history was not reported. The patient received her first dose of study medication on 19 Nov 2008.  (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+CMAS) Tablet #2 ) PARACETAMOL (PARACETAMOL) (Continued on Additional Information Page)		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 ) Double blind #2 ) 1 g, TID	16. ROUTE(S) OF ADMINISTRATION #1 ) Oral #2 ) Oral	
17. INDICATION(S) FOR USE #1 ) Pancreatic neuroendocrine tumour (Panc) #2 ) Unknown (Continued on Additional Information Page)		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 ) 19-NOV-2008 / 08-JAN-2009 #2 ) 07-JAN-2009 / 08-JAN-2009	19. THERAPY DURATION #1 ) 51 days #2 ) 2 days	

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

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ) RANITIDINE (RANITIDINE) ; 27-DEC-2008 / Ongoing	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergics, pregnancy with last month of period, etc.) From/To Dates                      Type of History / Notes                      Description Unknown	

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS	
24b. MFR CONTROL NO. <b>PHHO2009IT00723</b>		25b. NAME AND ADDRESS OF REPORTER	
24c. DATE RECEIVED BY MANUFACTURER <b>09-JAN-2009</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>20-JAN-2009</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:		

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

On 09 Jan 2009, the patient presented with hematemesis, which resulted in hospitalisation. A duodenoscopy showed bleeding in the known ulceration related to the tumor infiltration, and the patient was diagnosed with duodenal bleeding. The study medication dosage was adjusted / temporarily interrupted due to the event. The outcome was not reported. The investigator suspected a relationship between this event and the study medication but also stated that "a possible role of paracetamol" could not be excluded, and "the other hypothesis was progression of the tumor".

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

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Endoscopy small intestine		
		Showed bleeding in the known ulceration related to the tumor infiltration.		

**14-19. SUSPECT DRUG(S) continued**

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S): 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to): 19. THERAPY DURATION
#1 ) RAD001 Vs Placebo (RAD 666 RAD+TAB+CMAS) Tablet; Regimen #1	Double blind; Oral	Pancreatic neuroendocrine tumour (Pancreatic neuroendocrine tumour)	19-NOV-2008 / 08-JAN-2009; 51 days