



To: All Investigators in RAD001 Studies*

Date: Jan 23, 2009

Re: Investigator Notification for RAD001
Cardiogenic shock (fatal) /PHHO2008US14734

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 Cardiogenic shock that occurred in 35-year-old female patient who enrolled in a study “ A Single Arm Phase I/II Study of RAD001 and Sunitinib in Patients with Advanced Solid Tumors”.

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 term of Cardiogenic shock that is associated with fatal outcome. No additional case was identified.

In the index case, the patient presented with acute renal failure in the context of sepsis. Despite supportive care, her condition further deteriorated and she developed ischemic cardiomyopathy and multi-organ failure secondary to septic shock resulting in a fatal outcome. Given the available information, the relationship between the study drug and the fatal cardiogenic/ischemic shock cannot be established.

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 United States	2. DATE OF BIRTH			2a. AGE 35 Years	3. SEX Female	3a. WEIGHT 70.00 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 28	Month SEP	Year 1973			Day 10	Month DEC	Year 2008		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Cardiac shock /ischemic shock [Cardiogenic shock] ([Multi-organ failure], [Renal failure acute], [Ischaemic cardiomyopathy], [Respiratory failure], [Acidosis], [Hypotension]) Severe thrombocytopenia [Thrombocytopenia] Pneumonia [Pneumonia] ([Pyrexia]) Presumed sepsis [Sepsis] ([Diarrhoea]) Case Description: Initial report received on 11 Dec 2008: This patient (patient no. unknown) was enrolled in a Single Arm Phase I/II Study of RAD001 and Sunitinib in Patients with Advanced Solid Tumors. (Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 and Sunitinib (RAD001 and Sunitinib) Tablet #2) SUNITINIB MALATE (SUNITINIB MALATE)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
15. DAILY DOSE(S) #1) 5 mg, QD #2) 37.5 mg x 14 days/7 days off	16. ROUTE(S) OF ADMINISTRATION #1) Unknown #2) Unknown	
17. INDICATION(S) FOR USE #1) solid tumour (Neoplasm) #2) solid tumour (Neoplasm)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
18. THERAPY DATES(from/to) #1) Unknown #2) Unknown	19. THERAPY DURATION #1) Unknown #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) METHADONE (METHADONE) ; Unknown #2) OXYCODONE (OXYCODONE) ; Unknown #3) LYRICA (PREGABALIN) ; Unknown #4) LEXAPRO (ESCITALOPRAM OXALATE) ; Unknown #5) LUTERAN (CHLORMADINONE ACETATE) ; Unknown #6) IRON SULFATE (FERROUS SULFATE) ; Unknown (Continued on Additional Information Page)	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, 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. PHHO2008US14734	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 13-JAN-2009	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 21-JAN-2009	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

(Continued on Additional Information Page)

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

She received the first dose of study medication on an unspecified date. On 10 Dec 2008, the patient presented with a 24 hour history of fever (101 to 103 degrees). She was found to be hypotensive with pneumonia. Her absolute neutrophil count had been 1500 on 08 Dec 2008; however she was afebrile and had no signs of infection on that day. She was hospitalised on 10 Dec 2008 and placed on intravenous antibiotics. The patient's outcome was not reported. The investigator suspected a relationship between this event and the study medication.

Follow-up received on 17 Dec 2008: The patient died on 16 Dec 2008 (the cause was not specified). It was not reported if an autopsy was performed. The investigator did not provide a causality assessment for the death. However, the Novartis medical safety physician provided a provisional causality and did not suspect a relationship between the death and the study medication, based on current available information.

Follow up received on the 13 Jan 2009: On the 10 Dec 2008 the patient went to the local hospital with a 24 hour history of diarrhoea and fever (102 F) and was found to be hypotensive. The patient was supported with intravenous hydration, cardiac pressors and was admitted to the intensive care unit with acute renal failure and presumed sepsis. The patient was found to have right lower lobe infiltrate with grade I neutropenia and she was started on broad spectrum antibiotics. The patient became acidotic and developed respiratory failure and was intubated on the 10 Dec 2008. On the 11 Dec 2008 the patient had haemodialysis for her acute renal failure and on the 12 Dec 2008 it was discovered that the patient had profound ischemic cardiomyopathy with an ejection fraction of 10%. The patient also developed severe thrombocytopenia but did not show signs of disseminated intravascular coagulation (DIC). Despite aggressive supportive measures the patient's multi system organ failure and septic shock did not improve and her condition deteriorated. The family decided to withdraw supportive measures on the 13 Dec 2008 and the patient died on the 16 Dec 2008. The investigator felt that although septic shock is a possible explanation of her sudden multi system organ failure, it is possible her sudden deterioration was brought on by cardiac or ischemic shock secondary to the study medication.

Novartis Comment: Serious adverse drug reaction report, cardiac / ischemic shock, with multiorgan failure (fatal), assessed as unexpected according to the Investigators Brochure. The information provided in this individual case does not warrant a change to the Investigators Brochure text. The topic will be monitored closely. Investigator causality is suspected.

Serious adverse drug reaction report, sepsis (fatal), assessed as expected according to the Investigators Brochure. Investigator causality is suspected.

Serious adverse drug reaction report, pneumonia (hospitalisation), assessed as expected according to the Investigators Brochure. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	08-DEC-2008	Blood creatine	1.0	
2	10-DEC-2008	Blood creatine	4.16	
3	11-DEC-2008	Blood creatine	4.68	
4	12-DEC-2008	Blood creatine	5.21	
5	13-DEC-2008	Blood creatine	1.65	
6	14-DEC-2008	Blood creatine	5.45	
7	12-DEC-2008	Blood creatine phosphokinase MB	131.1	
8	13-DEC-2008	Blood creatine phosphokinase MB	100.6	
9	12-DEC-2008	Blood lactic acid	24.73	
10	10-DEC-2008	Haemoglobin	10.5	
11	08-DEC-2008	Neutrophil count	1500	
12	10-DEC-2008	Neutrophil count	1170	

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
13	11-DEC-2008	Neutrophil count	1449	
14	08-DEC-2008	Platelet count	57,000	
15	10-DEC-2008	Platelet count	79,000	
16	11-DEC-2008	Platelet count	9,000	
17	12-DEC-2008	Platelet count	35,000	
18	13-DEC-2008	Platelet count	27,000	
19	13-DEC-2008	Troponin	69.27	

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) MULTIVITAMINS (ASCORBIC ACID, ERGOCALCIFEROL, FOLIC ACID, NICOTINAMIDE, PANTHENOL, RETINOL, RIBOFLAVIN, THIAMINE HYDROCHLORIDE) ; Unknown

#8) CALCIUM (CALCIUM) ; Unknown

#9) K-PHOS (POTASSIUM PHOSPHATE MONOBASIC) ; Unknown

#10) ATIVAN (LORAZEPAM) ; Unknown

#11) MOTRIN (IBUPROFEN) ; Unknown

#12) SENOKOT-S (DOCUSATE SODIUM, SENNA, SENNA ALEXANDRINA) ; Unknown

#13) MAGIC MOUTHWASH (DIPHENHYDRAMINE HYDROCHLORIDE, HYDROCORTISONE, NYSTATIN) ; Unknown

#14) OXYCONTIN (OXYCODONE HYDROCHLORIDE) ; Unknown

#15) FLEXERIL (CYCLOBENZAPRINE HYDROCHLORIDE) ; Unknown

25b. Name And Address of Reporters continued