



To: All Investigators in RAD001 Studies*

Date: February 25, 2009

Re: Investigator Notification for RAD001
Hypophosphatemia /PHHO2009US01705

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 Hypophosphatemia that occurred in 74-year-old female patient who enrolled in a study entitled "Phase I/II evaluation of everolimus (RAD001), radiation and temozolomide (TMZ) followed by adjuvant temozolomide and everolimus in newly diagnosed glioblastoma".

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 Hypophosphataemia and blood phosphorus decreased. Five cases were identified. Only the current case is suspected and the remaining four were considered to be related to the underlying conditions and not suspected to be related to the RAD001.

For the current case, the patient had progression of glioblastoma with seizure. The electrolyte abnormality might be associated with the underlying disease condition. It is difficult to assess the causal relationship with the available information.

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,

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Novartis Pharmaceuticals Corporation
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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.

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

Lethargy [Lethargy]

Anorexic [Anorexia]

Hypocalcemia [Hypocalcaemia]

Glioblastoma multiforme / progression of tumour-pseudoprogression as differential diagnosis [Malignant neoplasm progression] ([Hyperglycaemia], [Hypoalbuminaemia], [Headache], [Brain oedema], [Haemangioma], [Unresponsive to stimuli], [Convulsion])

Case Description: Initial report received on 02 Feb 2009: This patient (patient no. XXX) was enrolled in the phase I/II evaluation of everolimus (RAD001), radiation and temozolomide (TMZ) followed by adjuvant temozolomide and everolimus in newly diagnosed glioblastoma. The patient's medical history was not reported. The patient received the first dose of study medication on 18 Dec 2008. On 27 Jan 2009 she presented with grade 3 fatigue and a grade 4 platelet count of 4, all treatments were held and the patient was transfused one unit of platelets. The next morning (28 Jan 2009) the patient's husband reports that the patient became unresponsive for less than 5 minutes and appeared short of breath. The patient was brought into the ER (emergency room) and further tests were done. The patient's ECG and echo was normal and a CT scan of her head did not show ICH (intracranial hemorrhage). It was felt that the patient had had a seizure and she was started on Kappra and admitted for observation. Later the patient had a carotid doppler ultra sound and a left jugular thrombosis was found. The patient was started on lovenox and coumadin. On the 30 Jan 2009 it was noted that the patient had a low platelet and haemoglobin count and she was transferred 2 units of PRBC (packed red blood cells) and HGB (Haemoglobin). The patient is to start prophylactic antibiotics for neutropenia and Neupogen and is to have transfusions if required. The patient's current condition was not reported. The investigator suspected a relationship between these events and the study medication and temozolomide except for the patient's seizure which the investigator suspected a relationship between the patient's Glioblastoma multiforme which were considered not suspected by the investigator.

Follow-up received on 13 Feb 2009: The patient's phosphorous level was 1.3 on 31 Jan 2009 (hypophosphatemia). HGB remained stable until 05 Feb 2009 when it was 6.7 and 2 units of PRBCs were given. Platelet count fluctuated daily and 2 units of platelets were given on 03 Feb 2009. The patient remained neutropenic with WBC and ANC never recovering and she was given daily Neupogen along with prophylactic antibiotics. On 05 Feb 2009 labs noted calcium 6.7 (hypocalcemia), albumin 1.9 (hypoalbuminemia) and glucose 438 (hypocalcemia). The patient complained of headaches and increasing fatigue and was anorexic. A CT scan of the head was done on 06 Feb 2009 and showed evidence of increased vasogenic edema in the left temporal occipital parietal area without evidence of hemorrhage, which likely represented progression of tumour-pseudoprogression as the differential diagnosis. Also on scan there was present a right inferior frontal subependymal cavernoma with evidence of some interval hemorrhage within the malformation with minimal edema. On 06 Feb 2009 the patient refused any further care and requested a hospice. Labs were noted with HGB 10.2, platelet 27,000, WBC 0.6, ANC 0.3, calcium 7.6, phosphorous 2.8 and albumin 2.5. On 07 Feb 2009 the patient was transferred to an outpatient hospice center. On 10 Feb 2009 she died. It was felt that the death was probably due to underlying disease and possibly related to the study medication. No autopsy was performed. The investigator did not suspect a relationship between the hyperglycemia to RAD001, temozolomide or radiation and felt it was possibly due to glioblastoma multiforme, hypocalcemia was suspected to be related to RAD001 and not suspected temozolomide, radiation or glioblastoma multiforme, anorexia was suspected to RAD001, temozolomide, radiation and to glioblastoma multiforme, hypoalbuminemia was not suspected to RAD001, temozolomide or radiation and was possibly related to glioblastoma multiforme and hypophosphatemia was suspected to RAD001 and not suspected to be related to temozolomide, radiation or glioblastoma multiforme.

Follow-up received on 25 Feb 2009: The patient's medical history included breast cancer, hysterectomy and bowel resection. Baseline stage for glioblastoma was grade IV. Hypophosphatemia (baseline value 4.7) and hypocalcemia (baseline value 9.0) were considered to be medically significant. Treatment included sodium phosphate and calcium gluconate, "IUPB" and calcium. The patient withdrew from study medication due to weakness, fatigue, anorexia and was tired of requiring repeated venopunctures and transfusions. She then chose hospice care. A CT scan on 06 Feb 2009 showed disease progression. Discontinuation of her supportive medications, for example steroids, likely resulted in increased cerebral edema from tumour progression and death. The investigator did not suspect a relationship between the right inferior frontal subependymal cavernoma with evidence of some internal hemorrhage and the study medication, RAD001 or temozolomide. The investigator did not suspect the patient's death to be related to study medication, RAD001 or temozolomide. The investigator suspected a relationship between hypophosphatemia and hypocalcemia and RAD001, stating that the relationship could not be excluded since there was no other identifiable reason.

Novartis Comment: Serious adverse drug reaction report, Grade 3 Hypophosphatemia (medically significant), assessed as unexpected according to the Investigator's Brochure. The information provided in this individual 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, Grade 4 neutrophils, Grade 4 leukocytes, Grade 4 Haemoglobin, and platelets decreased, Grade 3 Fatigue, Lethargy, Malaise, Asthenia, Grade 3 Thrombosis and Grade 3 anorexia, (Hospitalisation), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

Serious adverse drug reaction report, grade 3 hypocalcemia (medically significant), assessed as expected according to the Investigators Brochure. Investigator causality is suspected.

All remaining reported leading events and associated symptoms were assessed as not suspected by the investigator.

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	05-FEB-2009	Blood albumin	1.9	
2	06-FEB-2009	Blood albumin	2.5	
3		Blood calcium Baseline	9.0	
4	05-FEB-2009	Blood calcium	6.7	
5	06-FEB-2009	Blood calcium	7.6	
6	05-FEB-2009	Blood glucose	438	
7		Blood phosphorus Baseline	4.7	
8	31-JAN-2009	Blood phosphorus	1.3	
9	06-FEB-2009	Blood phosphorus	2.8	
10		Echocardiogram Normal		
11		Electrocardiogram Normal		
12	30-JAN-2009	Haemoglobin at 08.45 : 7.3	6.4	
13	05-FEB-2009	Haemoglobin	6.7	
14	06-FEB-2009	Haemoglobin	10.2	
15	30-JAN-2009	Neutrophil count	0.3	
16	06-FEB-2009	Neutrophil count	0.3	
17	27-JAN-2009	Platelet count	12	
18	30-JAN-2009	Platelet count	36	
19	03-FEB-2009	Platelet count Increased to 129,000, then dropped to 33,000	129,000, 33,000	
20	06-FEB-2009	Platelet count	27000	
21		Scan brain Did not show ICH		

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
22	06-FEB-2009	Scan brain Evidence of increased vasogenic edema in the left temporal occipital parietal area without evidence of hemorrhage, which likely represented progression of tumour-pseudoprogression as the differential diagnosis		
23		Ultrasound Doppler Showed a left jugular thrombosis		
24	30-JAN-2009	White blood cell count	0.5	
25	06-FEB-2009	White blood cell count	0.6	

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

#7) BACTRIM (SULFAMETHOXAZOLE, TRIMETHOPRIM) ; Unknown

#8) PEPCID (FAMOTIDINE) ; Unknown

#9) DEXAMETHASONE (DEXAMETHASONE) ; Unknown

#10) HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Breast cancer (Breast cancer);