



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 2, 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_PHRM2007FR01407

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/df
enclosure



To: All Investigators in RAD001 (everolimus) Studies*

07 December 2007

Re: Investigator Notification for "**Limited Distribution**" on a **Spontaneous Report**
RAD001 (everolimus):

Hypogammaglobulinaemia.
PHRM2007FR01407

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of a serious, unexpected, possibly related adverse report of hypogammaglobulinaemia.

This case refers to a **post-marketed spontaneous report**. A special regulatory situation arises for Certican which is marketed outside the US but which is investigational in the US (i.e., there is an open IND but not NDA). In this situation, spontaneous reports from marketed products fulfill the requirement for an IND Safety Report if they are serious and unexpected by the IB used under the open IND.

For the current case, details of the adverse event are provided in the attached CIOMS form, which contains the available information as reported to Novartis.

To summarize briefly:

This initial **spontaneous** report was received from the French Health Authority. It refers to a 55-year-old male patient with a medical history of "primitive" dilated cardiomyopathy (diagnosed at the age of 38 years) leading to two heart transplantations (in 1990, and 2005 - slight initial graft rejection resolved with immunosuppressive treatment), thoracic herpes zoster in 1995 and hypercholesterolemia. The patient was firstly treated with Cellcept (mycophenolate mofetil) from an unspecified date to 09 Jan 2007. One day later, he was switched to Certican (everolimus) and the Prograf (tacrolimus) daily dosage was reduced to 0.5 mg because of renal failure. On 25 Jan 2007, the everolimus blood level was 10.0 ng/mL. On 21 Feb 2007, he presented with fluctuating fever with flu-like syndrome. On 27 Feb 2007, the everolimus blood level was 12.8 ng/mL. In early March 2007, he was hospitalized because of fever and persistence of inflammatory syndrome with increased C-reactive protein (CRP) and sedimentation rate. On 02 Mar 2007, the everolimus blood level was at 10.7 ng/mL. On 05 Mar 2007, Certican was discontinued and Cellcept was resumed. On 06 Mar 2007, an etiological infectious screening (bacteriological, viral, parasitological) proved negative. The urine and blood cultures were negative as well as the viral serologies for CMV, EBV, HHV6, toxoplasmosis, pneumocystis and mycosis. A malignant etiology was ruled out. The everolimus blood level was 7.5 ng/mL. On 08 Mar 2007, a new biological work-up showed hypogammaglobulinemia (19.7 g/L, norm (N): 38-45). A severe renal failure with a creatinine clearance of 15.6 mL/min was revealed with a creatinine blood level at 370 µmol/L (N: 62-115), the urea was at 20.8 mmol/L (N: 2.5-7.5) and the uric acid was increased at 604 µmol/L (N: 200-420). The haptoglobin was increased at 9.23 g/L (N: 1-3). On 14 Mar 2007, the body temperature was normalized and the CRP was at 132.2 mg/L, on 16 Mar 2007 it dropped to 66.5 mg/L with a further decrease to 16 mg/L three days later. On 19 Mar 2007, normocytic normochromic anemia was found with hemoglobin at 8.1 g/dL as well as thrombocytosis (platelets 508,000/mm³, N: 150,000-400,000). The French Health Authority actually only reported fever and CRP increase as events. The final patient's outcome was recovery for these events as soon as

Certican was discontinued; the Authority's causality assessment was possible for fever and CRP increase.

Novartis comment:

A cumulative search for MedDRA term "Hypogammaglobulinaemia" revealed no further reports of hypogammaglobulinaemia in patients on Certican.

The health care professional in fact did not report hypogammaglobulinaemia as a side-effect. Hypogammaglobulinaemia may have been caused by the concurrent onset of severe renal impairment with renal loss of immunoglobulins. Furthermore, a multifactorial process with overall immunosuppression including tacrolimus, mycophenolate mofetil and corticosteroid therapy in this heart transplant patient with possible suppression of lymphocyte lineage (Corales, et al 2000) may also account for the occurrence of hypogammaglobulinaemia.

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,

 Andreas Meyer MD

Pharmacovigilance Leader
Integrated Medical Safety
Novartis Pharma Basel, Switzerland

Attachment: CIOMS case report

Reference: Corales R, Chua J, Mawhorter S, Young JB, et al (2000) Significant post-transplant hypogammaglobulinemia in six heart transplant recipients: an emerging clinical phenomenon? *Transplant Infectious Disease* 2000; 2:133-9.

* 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 <small>(first, last)</small>	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	55 Years	Male	75.00 kg	Day	Month	Year	
			Unk					21	FEB	2007	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Flu like syndrome [Influenza like illness] ([Pyrexia], [Inflammation], [Normochromic normocytic anaemia], [Red blood cell sedimentation rate increased], [C-reactive protein increased], [Haptoglobin increased], [Haemoglobin decreased]) Thrombocytosis [Thrombocythaemia] Hypogammaglobulinemia [Hypogammaglobulinaemia] Severe renal failure [Renal failure] ([Blood urea increased], [Blood uric acid increased], [Creatinine renal clearance decreased], [Blood creatinine increased]) (continue)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1 CERTICAN (RAD) Tablet		20. DID REACTION ABATE AFTER STOPPING DRUG? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1 2 DF daily	16. ROUTE(S) OF ADMINISTRATION #1 Oral	
17. INDICATION(S) FOR USE #1 Heart transplant		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
18. THERAPY DATES(from/to) #1 10-JAN-2007 00:00 / 05-MAR-2007 00:00	19. THERAPY DURATION #1 55 days	

III. CONCOMITANT DRUG(S) AND HISTORY (Continued on Additional Information Page)

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ISOPTINE (VERAPAMIL HYDROCHLORIDE) , ; Ongoing #2 SOLUPRED (PREDNISOLONE SODIUM SULFOBENZOATE) , ; Ongoing #3 EUPRESSYL (URAPIDIL) , ; Ongoing														
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) <table style="width:100%; border-collapse: collapse;"> <tr> <td style="width:30%;"><small>From/To Dates</small></td> <td style="width:30%;"><small>Type of History / Notes</small></td> <td style="width:40%;"><small>Description</small></td> </tr> <tr> <td>Unknown</td> <td>Historical Condition</td> <td>Congestive cardiomyopathy</td> </tr> <tr> <td>1990 to Unknown</td> <td>Historical Condition</td> <td>Heart transplant</td> </tr> <tr> <td colspan="3">1st heart transplantation performed in 1990 and 2nd in 2005.</td> </tr> </table>			<small>From/To Dates</small>	<small>Type of History / Notes</small>	<small>Description</small>	Unknown	Historical Condition	Congestive cardiomyopathy	1990 to Unknown	Historical Condition	Heart transplant	1st heart transplantation performed in 1990 and 2nd in 2005.		
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Unknown	Historical Condition	Congestive cardiomyopathy												
1990 to Unknown	Historical Condition	Heart transplant												
1st heart transplantation performed in 1990 and 2nd in 2005.														

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHRM2007FR01407	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 09-MAY-2007	24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input checked="" type="checkbox"/> OTHER: Spontaneous Report	
DATE OF THIS REPORT 07-DEC-2007	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

Case Description: Initial report received on 09 May 2007 from the French Health Authority (RS0700039). It refers to a patient with a medical history of primitive dilated cardiomyopathy (diagnosed at the age of 38 years old) leading to two heart transplantations (in 1990, and 2005 - slight initial graft rejection resolved with immunosuppressive treatment), thoracic herpes zoster in 1995 and hypercholesterolaemia. The patient was firstly treated with Cellcept (mycophenolate mofetil) from unspecified date to 09 Jan 2007. On 10 Jan 2007, the patient was switched to Certican (everolimus) so that Prograf (tacrolimus) daily dosage was reduced to 0.5 mg because of renal failure. On 25 Jan 2007, the everolimus blood level was 10.0 ng/mL. On 21 Feb 2007, the patient presented fever fluctuating between 38 and 39 degrees C with flu like syndrome. On 27 Feb 2007, the everolimus blood level was 12.8 ng/mL. Early in Mar 2007, the patient was hospitalized because of fever and inflammatory syndrome persistence (C-reactive protein and sedimentation rate increased). On 02 Mar 2007, the everolimus blood level was at 10.7 ng/mL. On 05 Mar 2007, Certican was discontinued and Cellcept was resumed. On 06 Mar 2007, an etiological infectious screening (bacteriological, viral, parasitological) was found negative. The urine and blood cultures were negative as well as the viral serologies CMV, EBV, HHV6, toxoplasmosis, pneumocystis and mycosis. A malignant etiology was ruled out. The everolimus blood level was 7.5 ng/mL. On 08 Mar 2007, a new biological work-up was performed and showed hypogammaglobulinemia (19.7 g/L, norm (N): 38-45). It existed a renal failure rather severe with a creatinine clearance at 15.6 mL/min and creatinine blood level increased at 370 µmol/L (N: 62-115), the urea was at 20.8 mmol/L (N: 2.5-7.5) and the uric acid was increased at 604 µmol/L (N: 200-420). The haptoglobin was increased at 9.23 g/L (N: 1-3). On 14 Mar 2007, the body temperature was normalized and the C-reactive protein was at 132.2 mg/L. On 16 Mar 2007, it was at 66.5 mg/L and on 19 Mar 2007, it was at 16 mg/L. On 19 Mar 2007, normocytic normochromic anaemia was found with hemoglobin at 8.1 g/dL as well as thrombocytosis (platelets 508,000/mm³, N: 150,000-400,000). The FHA only reported fever and C-reactive protein increased as events. The final patient's outcome was recovery for these events as soon as Certican was discontinued. Authority's causality assessment was possible.

Novartis Comment: Serious spontaneous report

Flu like syndrome, thrombocytosis, hypogammaglobulinemia [hospitalization], assessed as unlisted according to the Basic Prescribing Information.

The information provided in this individual case does not warrant a change to the Basic Prescribing Information text. The topic will be monitored closely;

Severe renal failure [hospitalization], already listed in the Basic Prescribing Information.

All spontaneous reports are considered suspected for reporting purposes.

13. Relevant Tests

(21 Feb 2007) Body temperature: between 38 and 39 degrees C

(25 Jan 2007) Everolimus blood level 10.0 ng/mL

(27 Jan 2007) Everolimus blood level 12.8 ng/mL

(02 Mar 2007) Everolimus blood level 10.7 ng/mL

(06 Mar 2007) Everolimus blood level 7.5 ng/mL

(Early Mar 2007) C-reactive protein: increased (unspecified)

(14 Mar 2007) C-reactive protein 132.2 mg/L

(16 Mar 2007) C-reactive protein 66.5 mg/L

(19 Mar 2007) C-reactive protein 16 mg/L

(Early Mar 2007) Sedimentation rate: increased (unspecified)

(Early Mar 2007) Blood cells count: normal

(19 Mar 2007) Hb 8.1 g/dL

(19 Mar 2007) Platelets 508,000/mm³ (N: 150,000-400,000/mm³)

(08 Mar 2007) Gammaglobulin blood level 19.7 g/L (N: 38-45 g/L)

(08 Mar 2007) Creatinine clearance 15.6 mL/min

(08 Mar 2007) Creatinine blood level 370 µmol/l (N : 62-115)

(08 Mar 2007) Urea : 20.8 mmol/L (N: 2.5-7.5 mmol/L)

(08 Mar 2007) Uric acid : 604 µmol/L (N: 200-420 µmol/L)

(08 Mar 2007) Haptoglobin 9.23 g/L (N: 1-3 g/L)

ADDITIONAL INFORMATION**13. Relevant Tests**

(06 Mar 2007) Bacteriological infectious screening: negative
 (06 Mar 2007) Viral infectious screening: negative
 (06 Mar 2007) Parasitological infectious screening: negative
 (06 Mar 2007) Mycobacteriological infectious screening: negative
 (06 Mar 2007) Urine cultures: negative
 (06 Mar 2007) Blood cultures: negative
 (06 Mar 2007) Viral serologies - CMV, EBV, HHV6: negative
 (06 Mar 2007) Toxoplasmosis: negative
 (06 Mar 2007) Pneumocystis: negative
 (06 Mar 2007) Mycosis: negative

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

#4 PROGRAF (TACROLIMUS) , ; Ongoing

#5 TAHOR (ATORVASTATIN CALCIUM) , ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1995 to Unknown	Historical Condition Thoracic herpes zoster	Herpes zoster disseminated
Unknown	Current Condition	Hypercholesterolaemia
Unknown to 09-JAN-2007	Historical Drug mycophenolate mofetil	CELLCEPT
Unknown	Current Condition renal failure under Cellcept and Prograf	Renal failure
Unknown	Historical Condition Slight graft rejection episode resolved thanks to immunosuppressive treatment.	Transplant rejection