



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_PHRM2007FR01778

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):

Tracheomalacia.
PHRM2007FR01778

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 tracheomalacia.

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 a physician via a sales representative. It refers to a male patient (age not provided) who underwent pancreas transplant 5 years ago. Immunosuppressive regimen included Cellcept (mycophenolate mofetil), Prograf (tacrolimus) and corticosteroids. The transplant was well-tolerated by the patient. However, in May 2007, he experienced allograft nephropathy and Cellcept was replaced by Certican (everolimus) 0.75 mg BID. Fifteen days ago, he was hospitalized for sepulchral cough, sweating, hypoxia (oxygen saturation at 85 %) and fever at 40 °C. An infectious pneumopathy in the right basis area was suspected and he received oxygen therapy 10 L/min. He also experienced pyuria with a suspicion of pyelonephritis. "Antigenuria pneumococcal" was positive and he received Ofloset (ofloxacin) and Clamoxyl (amoxicillin) as antibiotherapy. His condition deteriorated and he was transferred to the intensive care unit. Certican was discontinued. A tracheal scan showed tracheomalacia. His condition improved. It seemed that the "infectious pneumopathy was linked to the tracheomalacia" and not to Certican, but the causality could not be ruled out.


Novartis comment:

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

The reporter mentioned that "infectious pneumopathy was linked to the tracheomalacia" and not to Certican, but the causality could not be ruled out. The "infectious pneumopathy" with the possible use of an endotracheal tube in the intensive care unit could also account for the tracheomalacia.

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

* 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	40 Years	Male	Unk	Day	Month	Year	
			Unk						JUN	2007	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Tracheomalacia [Tracheomalacia] Infectious pneumopathy suspected [Lung infection] ([Cough], [Hyperhidrosis], [Oxygen saturation decreased], [Pyrexia]) Pyelonephritis suspected - antigenuria pneumococcal positive [Bacterial pyelonephritis] ([Pyuria], [Pneumococcal infection]) Case Description: Initial report received on 28 Jun 2007 from a physician via a sales representative. This patient underwent pancreas transplant 5 years ago. Immunosuppressive regimen included Cellcept (mycophenolate mofetil), Prograf (tacrolimus) and corticosteroids. (continue)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1 CERTICAN (RAD) Tablet, 0.75 mg		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 0.75 mg, BID	16. ROUTE(S) OF ADMINISTRATION #1 Oral	
17. INDICATION(S) FOR USE #1 Pancreas transplant		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
18. THERAPY DATES(from/to) #1 MAY-2007 / JUN-2007	19. THERAPY DURATION #1 Unknown	

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 PROGRAF (TACROLIMUS) , ; Unknown #2 CORTICOSTEROID NOS (CORTICOSTEROID NOS) , ; Unknown											
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) <table style="width:100%; border-collapse: collapse;"> <tr> <th style="width: 30%;">From/To Dates</th> <th style="width: 30%;">Type of History / Notes</th> <th style="width: 40%;">Description</th> </tr> <tr> <td>Unknown</td> <td>Current Condition</td> <td>Diabetes mellitus insulin-dependent</td> </tr> <tr> <td>2002 to MAY-2007</td> <td>Historical Drug for pancreas transplant</td> <td>CELLCEPT</td> </tr> </table>			From/To Dates	Type of History / Notes	Description	Unknown	Current Condition	Diabetes mellitus insulin-dependent	2002 to MAY-2007	Historical Drug for pancreas transplant	CELLCEPT
From/To Dates	Type of History / Notes	Description									
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2002 to MAY-2007	Historical Drug for pancreas transplant	CELLCEPT									

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
24b. MFR CONTROL NO. PHRM2007FR01778		25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 28-JUN-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**

The transplant was well-tolerated by the patient. However, in May 2007, he experienced allograft nephropathy and Cellcept was replaced by Certican (everolimus) 0.75 mg BID. Fifteen days ago, he was hospitalized for sepulchral cough, sweating, oxygen saturation at 85 % and fever at 40 °C. An infectious pneumopathy in the right basis area was suspected and the patient received oxygen therapy 10 L/mn. He also experienced pyuria leading to a suspicion of pyelonephritis. Antigenuria pneumococcal was positive and he received Oflozet (ofloxacin) and Clamoxyl (amoxicillin) as antibiotherapy. Patient's condition deteriorated and he was transferred to the intensive care unit. Certican was discontinued. A tracheal scan showed tracheomalacia. Patient's condition improved. It seemed that the infectious pneumopathy was linked to the tracheomalacia and not to Certican, but the causality could not be ruled out.

Novartis Comment: Serious spontaneous report:

Tracheomalacia [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;

Infectious pneumopathy, pyelonephritis [hospitalization], already listed in the Basic Prescribing Information;

All spontaneous reports are considered suspected for reporting purposes.

13. Relevant Tests

(During hospitalization - Jun 2007) O2 saturation: 85 %

(During hospitalization - Jun 2007) Body temperature: 40 °C

(During hospitalization - Jun 2007) Urinary pneumococcal antigen: positive

(During hospitalization - Jun 2007) Tracheal scan: tracheomalacia

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
MAY-2007 to Unknown	Current Condition Allograft nephropathy	Nephropathy