



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_PHBS2007TR02235

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):

Papilloedema.
PHBS2007TR02235

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 papilloedema.

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 an ophthalmologist with follow-up reports received from a nephrologist: It refers to a male patient (year of birth: 1975) who underwent renal transplantation on 22 Sep 2003. Immunosuppressive therapy included Sandimmun Neoral (ciclosporin microemulsion), Cellcept (mycophenolate mofetil) and Deltacortril (prednisolone). The patient was switched from Sandimmun Neoral to Certican (everolimus) on 01 Dec 2006. The dose of Sandimmun Neoral on the day of discontinuation was 25 mg QD. Prograf (tacrolimus) was started on 22 Dec 2006. He complained of weakness and blurred vision in right eye on an unspecified day. He also had epistaxis occasionally. On 19 Jan 2007, ophthalmological consultation was requested by the nephrologic policlinic. The patient was hospitalised in the department of neurology. He was recovering. The physician did not directly suspect a causal relationship between the events and Certican. The side effect was described as optic disc swelling ("papillary" edema).

The ophthalmologist stated that he did not know the reason for the optic disc swelling but that this event commonly occurs as a result of steroid use.


Novartis comment:

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

Papilloedema can occur with arterial hypertension which can be increased by use of steroids as well as immunosuppressants, especially calcineurin inhibitors. In such cases it would be expected to be bilateral. Unilaterally, one might suspect a local ophthalmic disorder or expansive process. Papilloedema has been associated with pseudotumor cerebri (benign intracranial hypertension) which can also occur with corticosteroid therapy and with cyclosporin. However, without additional information a meaningful assessment is not possible.

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.

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

The dose of Sandimmun Neoral on the day of discontinuation was 25 mg QD. Prograf was started on 22 Dec 2006. The patient complaint of weakness and blurred vision in right eye on an unspecified day. He also had epistaxis occasionally. On 19 Jan 2007, ophthalmological consultation was requested by the nephrologic policlinic. The patient was hospitalised in the department of neurology. The patient was recovering. The physician did not directly suspect a causal relationship between the events and Certican. The side effect was described as optic disc swelling ("papillary" edema). The ophthalmologist stated that he did not know the reason of optic disc swelling but that this event commonly occurs as a result of steroid use.

Follow-up information received on 01 May 2007: The patient's year of birth (1975) was provided.

Novartis Comment: The available information was considered inadequate to fully assess the case.

Serious spontaneous report: Papilloedema [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. All spontaneous reports are considered suspected for reporting purposes.

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

#4 DELTACORTRIL (PREDNISOLONE) ; ; Ongoing