

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-560

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Addendum Review

Date	April 20, 2010
From	Ozlem Belen, MD, MPH Deputy Director for Safety Joette Meyer, Pharm.D. Clinical Team Leader
Subject	Cross-Discipline Team Leader Addendum Review
Division	Division of Special Pathogen and Transplant Products
NDA/BLA # Supplement#	NDA 21-560
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	January 22, 2010
PDUFA Goal Date	June 22, 2010
Date Review Completed	April 20, 2010
Proprietary Name / Established (USAN) names	Zortress (everolimus) Tablets
Dosage forms / Strength	0.25 mg, 0.5 mg, 0.75 mg
Indication	Everolimus is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Everolimus is to be administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids. Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients receiving these products.
Dosing Regimen	An initial everolimus dose of 0.75 mg twice daily is recommended for the general kidney transplant population, administered as soon as possible after transplantation. Administer everolimus consistently approximately 12 hours apart with or without food to minimize variability in absorption and at the same time as cyclosporine. Both cyclosporine doses and the target range for whole blood trough concentrations should be reduced, when given in a regimen with everolimus, in order to minimize the risk of nephrotoxicity.
Recommended:	Approval

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I. Background

Reference is made to the previous CDTL review dated December 23, 2009.

An initial New Drug Application (NDA 21-560) supporting the use of fixed-dose everolimus with standard dose cyclosporine (CsA) compared to mycophenolate mofetil (MMF; CellCept®) with standard dose CsA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients was submitted to the FDA on December 19, 2002 by the applicant, Novartis.

Efficacy of everolimus was demonstrated in two trials (B201 and B251); however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups.

Due to these observed renal toxicities, the NDA was not approved and the applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration-controlled regimens of everolimus and CsA using therapeutic dose monitoring (TDM).

Data from two additional open-label, non-comparative kidney transplant trials (A2306 and A2307), along with some exposure-response analyses, were submitted to the NDA as a Complete Response by the applicant on February 27, 2004. FDA noted these and other limitations in the studies' design, therefore the applicant was asked to provide additional information to establish a safe and effective dosing regimen for everolimus and CsA.

On November 16, 2005 the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) met to discuss the use of everolimus for prophylaxis of rejection in heart transplantation.¹ While the committee agreed that a fixed-dose regimen of everolimus with standard-dose CsA in Trial B253 should not be used in heart transplant due to short-term and long-term loss of renal function, they also commented that additional data were needed to characterize the safety and efficacy of everolimus using TDM regimens to maintain everolimus concentrations while rapidly tapering CsA to minimize renal toxicity.

Subsequently Novartis designed a new trial of concentration-controlled everolimus with low dose CsA both adjusted using TDM in *de novo* kidney transplant recipients, and the protocol was discussed with FDA. Trial RAD001A2309 (also known as A2309) is a 24-month, multicenter, randomized, open-label, three-arm trial that enrolled 833 *de novo* adult renal transplant recipients in Africa, Asia, Australia, Europe, North and South America. Patients were randomized to one of three groups: everolimus starting at either 1.5 or 3.0 mg per day combined with reduced dose CsA, or mycophenolic acid (MPA; Myfortic®) 1.44 gm per day with standard dose CsA.

¹ <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4183M1.pdf>

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In this trial everolimus doses were adjusted to achieve blood trough concentrations of 3 to 8 ng/mL (low dose group, starting at 1.5 mg/day) and 6 to 12 ng/mL (high dose group starting at 3.0 mg/day) combined with reduced exposure to CsA, which was tapered over time. Both drug concentrations were guided by TDM. The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the control group. At Month 2, CsA target concentrations were a maximum of 150 ng/mL in the everolimus groups, while in the control group, the target CsA maximum was 250 ng/mL. The Applicant submitted the data from the first 12-months of the Trial A2309 on December 23, 2009.

During the review of this submission the CDTL and Clinical Team Leader agreed that the results of Trial A2309 demonstrated everolimus has a similar safety profile to other approved immunosuppressants in addition to possessing class toxicities similar to other mTOR Mammalian Target of Rapamycin (mTOR) (also known as mechanistic target of rapamycin) inhibitors in the class, due to its mechanism of action. mTOR inhibitors are known to cause endothelial dysfunction, resulting in thrombotic events, proteinuria, and gastrointestinal mucosal ulcerations. mTOR inhibitors are also known to cause an increased permeability of serosal membranes in the body to proteins and fluids resulting fluid accumulations and alveolar proteinosis and impair wound healing. These class effects of mTOR inhibitors were manifested in Trial A2309 by an increased risk of graft thrombosis, proteinuria, fluid collections, and edema in the everolimus 1.5 mg group compared to the mycophenolic acid (Myfortic) group. However, there was no imbalance in the death rate between treatment arms or thromboembolic events such as MI. SAEs and AEs leading to discontinuation occurred more frequently in the everolimus 1.5 mg group compared to the Myfortic group, but the AE terms (both MedDRA system organ class and preferred terms) were varied and did not clearly indicate a particular toxicity or toxicities that contributed to the higher rates.

Everolimus was presented on December 7, 2009 at a meeting of CRDAC. The AC voted in favor of approval of this product with a Risk Evaluation and Mitigation Strategy Requirements (REMS) to mitigate these toxicities.

On December 23, 2009, the Agency issued a Complete Response (CR) Letter based on requirement of REMS in accordance with section 505-1 of the FDCA and labeling identified as deficiencies in this letter.

The CR Letter cited that a REMS was necessary for everolimus to ensure that the benefits of the drug outweigh the risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, as well as nephrotoxicity when co-administered with standard doses of CsA. The proposed REMS was required to include a Medication Guide, a Communication Plan and a timetable for assessments. In addition, the Applicant was asked to submit draft labeling that included the revisions proposed in the draft package insert attached to the CR letter.

The Division also listed submission of the final report for Trial A2309 which contains the 24-month follow-up safety and efficacy data on all patients enrolled in the trial as a postmarketing requirement under 505(o), if the submission would be approved.

II. Pediatric Research and Equity Act Waivers

A Pediatric Written Request (PWR), which has now expired, was issued to Novartis on April 25, 2000 for everolimus to obtain information in pediatric transplant patients for the prophylaxis of acute rejection in allogeneic kidney and liver transplantation.

The PWR was issued to obtain needed information on safety, tolerability, and basic pharmacokinetics to select an adequate dosing regimen for pediatric transplant patients. (b)

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Before CR letter was issued in December 2009, a final decision on the pediatric plan has not been made. The division presented the case for a waiving the pediatric assessment requirements from birth to 16 years of age to the Pediatric Research Committee (PeRC). Everolimus was granted a waiver on the basis that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

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III. Recommendation for Postmarketing Risk Management Activities

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

DSPTP reviewers have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses in addition to evaluation of other serious adverse outcomes.

Therefore, the Applicant will be required the full trial report for RAD001A2309; in order to ensure feasibility, the dates for the trial completion and final report submission have been communicated to Novartis prior to approval. The following language will be included in the approval letter.

1624-1 Trial RAD001A2309 “A 24-month, multicenter, randomized, open-label noninferiority study of efficacy and safety comparing concentration-controlled Certican™ in two doses (1.5 and 3.0 mg/day starting doses) with reduced Neoral® versus 1.44 g Myfortic® with standard dose Neoral in de novo renal transplant recipients” which contains the 24-month follow-up safety data on all patients enrolled in the trial.

Final protocol submission	Completed; trial is ongoing
Trial Completion Date:	August 18, 2009
Final Report Submission:	July 30, 2010

Recommendation for other Postmarketing Study Commitments

None.

IV. REMS

The Division consulted DRISK of OSE for the review of the proposed REMS by Novartis and worked very closely with the DRISK review team consisted of Kathryn O’Connell, MD, PhD, (scientific lead) Suzanne Berkman Robottom, Pharm.D (Team Leader).

The applicant submitted a REMS proposal (in the June 30, 2009) submission without request from FDA. The goals they targeted were education about drug level monitoring and the risk of wound healing complications. To achieve these educational goals, they proposed a patient Medication Guide and a Communication Plan (CP) for healthcare professionals (HCP), with a timetable for assessments consistent with FDAAA minimum requirements of 18 months, 3 years, and 7 years post-approval.

On December 7, 2009 the Advisory Committee (AC) voted almost unanimously for approval (with one “no” vote based on lack of demonstration of efficacy). In the safety discussion, the AC focused mainly on the lack of long-term cardiovascular outcomes data. They voiced concern about proteinuria and hyperlipidemia, which are risk factors

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On April 2, 2010, the REMS documents and attachments excluding the Medication Guide were provided to Novartis in track changes format.

On April 8, 2010, the Applicant provided the revised REMS, and REMS supporting documents, and the Medication Guide which were found acceptable by the DRISK review team and DSPTP. Few and final editorial comments were sent to Novartis on April 12, 2010, and the Applicant was asked to submit the final and complete REMS document, attachments to the REMS document (Medication Guide and the Letters) and the Supporting Document to the EDR (See Attachment A).

V. Labeling

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On November 23, 2009 Novartis submitted draft examples of cartons, container labels, and blister foils for all Tablet strengths 0.25mg, 0.5mg, 0.75mg and 1.0mg along with the proposed name of Zortress. In an e-mail dated DMEPA sent notification e-mail to DSPTP email is that the DMEPA has reached the midpoint of their review and determined the proposed proprietary name Zortress is acceptable. Their decision was based upon the information submitted by the Applicant, DDMAC's promotional evaluation, DSPTP's initial comments, and DMEPA's safety evaluation. Their initial review included tables of the names found to look and/or sound similar to Zortress. In addition, DMEPA evaluation did not identify any other factors that render the name unacceptable at this time.

During the current review cycle, Novartis withdrew the 1 mg Tablet strength from the pending everolimus NDA without prejudice to refilling. Per Novartis, this action was based solely on an administrative decision for business reasons.

2. Package Insert

The Applicant responded to FDA comments/revisions to the package insert (PI) and provided the final version on April 8, 2010. DSPTP received DDMAC labeling review on March 10, 2010 and took DDMAC reviewers' (Kathleen Klemm, Lisa Hubbard, and Sharon Watson) comments into consideration for the PI. Reference is made e-mail communication on March 16, 2010 from the CDTL reviewer to Kathleen Klemm of DDMAC explaining the Review Division's rationale in approaching DDMAC's comments for the PI.

The following is a summary of the final version of the PI, including revisions from the DSPTP review team and DDMAC, as it compares to the original version proposed by Novartis in the June 30, 2009 resubmission.

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3. Carton and Container Labels

DMEPA's (Division of Medication Error Prevention and Analysis) recommendations for the carton container labels were communicated to Novartis on February 1, 2010 and the Applicant responded to these requests on February 3, 2010.

In addition, Novartis withdrew the 1 mg Tablet strength from the pending the Zortress® (everolimus) NDA 21-560 without prejudice to refilling. Per Novartis, this action was based solely on an administrative decision for business reasons.

4. Medication Guide

Patient Labeling reviewers of DRISK (Barbara Fuller, RN, MSN, CWOCN and LaShawn Griffiths, MSHS-PH, BSN, RN) were involved with the review of the proposed Medication Guide and finalized their review when the Physician Labeling was near complete on March 11, 2010. The DSPTP review team, including the CDTL and Clinical Team Leader, met with LaShawn Griffiths of DRISK on March 15, 2010 to discuss in detail the proposed revisions to the Medication Guide and comments were sent to Novartis upon reaching internal agreement between the two groups.

Novartis agreed to the FDA's revisions; the final Medication Guide including minor editorial changes was submitted to the Agency April 8, 2010 (See Appendix).

VI. Other Issues Included in the CR Letter

Other issues that are not deficiencies were included in the December 23, 2009 CR letter and are included below followed by updated information on their status.

- *Provide the results from any pre-testing of the proposed communication materials for the required REMS. This should include explanation of how the materials were modified based on the results.*

There was no new information that was provided during this review cycle pertaining to the proposed communication materials for the required REMS. The approved REMS will include a survey of the healthcare providers' and patients' understanding of the

serious risks of Zortress and will be submitted according to the timetable for submission of assessment of the REMS.

- *Voluntarily submit the proposed advertising and launch material that you propose to use with Zortress (everolimus).*

As required under 21 CFR 314.81(b)(3)(i), the Applicant must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253 for Division of Drug Marketing, Advertising, and Communications (DDMAC) review of these materials. There were no advertising or promotional materials submitted during this review cycle.

- *We encourage you to work with diagnostic companies developing everolimus assays*

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VII. Recommendations/Risk Benefit Assessment

As noted in the previous CDTL review, the CDTL and the Clinical Reviewer agree that the efficacy results from Trial A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. Additionally, the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and Myfortic, although numerically these events were more frequent in the everolimus groups compared to the Myfortic group.

The CDTL and Clinical Team Leader agree that the results of Trial A2309 demonstrate that everolimus has a similar safety profile to other approved immunosuppressants (i.e., risk of infection, malignancy, NODM, proteinuria, hyperlipidemia, etc.) and also appears to possess class toxicities similar to the mTOR inhibitor class due to its mechanism of action. mTOR inhibitors are known to cause endothelial dysfunction, resulting in thrombotic events, proteinuria, and gastrointestinal mucosal ulcerations. mTOR inhibitors are also known to cause an increased permeability of serosal membranes in the body to proteins and fluids resulting in fluid accumulations and alveolar proteinosis and impair wound healing. These class effects of mTOR inhibitors were manifested in Trial A2309 by an increased risk of graft thrombosis, proteinuria, fluid collections, and edema in the everolimus 1.5 mg group compared to the Myfortic group. However, there was no imbalance in the death rate between treatment arms or thromboembolic events such as MI.

Of note, the Clinical Reviewer recommends non-approval of everolimus due to safety concerns compared to the control regimen and does not think that the risks can be mitigated by REMS. In addition, the Clinical Reviewer believes the Applicant did not demonstrate an efficacy benefit with the everolimus regimen over the control regimen.

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The CDTL and Clinical Reviewer agree that everolimus appears to possess toxicities related to its mechanism of mTOR inhibition and that the toxicities can be addressed through product labeling and a REMS.

The Applicant has responded to the CR letter adequately and this resubmission can be approved with the REMS consisting of a Medication Guide and a Communication Plan to mitigate the risks associated with mTOR inhibitors summarized above including wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when everolimus is co-administered with standard doses of cyclosporine and to inform patients about the serious risks associated with everolimus.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Zortress (EVEROLIMUS) TABLETS

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/s/

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04/20/2010

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04/20/2010