CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-560s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 12, 2010
To:	Renata Albrecht, M.D., Director Division of Special Pathogen and Transplant Products (DSPTP)
Through:	Mary Willy PhD, Deputy Director Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	Everolimus Risk Management Team Scientific Lead: Kathryn O'Connell, MD, PhD, Medical Officer (DRISK/OSE) Team Members: ▪ Brian Gordon, MA, Social Science Reviewer (DRISK) ▪ Kate Heinrich, MA, Health Education Reviewer (DRISK) ▪ Kathleen Klemm, PharmD (DDMAC) ▪ Suzanne Robottom, Pharm.D., Team Leader (DRISK)
Subject:	REMS Final Review
Drug Name(s):	Zortress (everolimus)
Submission:	Proposed Zortress REMS submission dated April 7, 2010
Application Type/Number:	NDA 021560
Applicant/sponsor:	Novartis
OSE RCM #:	2010-187

1 INTRODUCTION

This review follows a request from the Division of Special Pathogen and Transplant Products (DSPTP) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for everolimus (original REMS dated January 22, 2010).

Everolimus, an mTOR inhibitor, is under FDA review for the prophylaxis of acute rejection in adult patients receiving a *de novo* kidney transplant, in combination with basiliximab, reduced dose cyclosporine (Neoral®, CsA) and corticosteroids. The sponsor's proposed indication is prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant. Everolimus is to be administered concurrently with reduced doses of Neoral and corticosteroids. Specifically, the proposed dosing is 0.75 mg twice daily administered as soon as possible after transplantation. The sponsor proposes that the dose of Neoral then be reduced to optimize renal function.

An initial NDA submitted to FDA December 19, 2002 demonstrated efficacy for fixed-dose everolimus with standard dose cyclosporine compared to mycophenolate mofetil (MMF; CellCept®) with standard dose CsA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients. However, interpretation of the trial results was complicated by premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the control groups. The NDA was not approved and the applicant was asked to establish a dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy.

The NDA re-submisssion involved 833 *de novo* kidney transplant patients followed for 12 months. Patients were randomized to everolimus starting at either 1.5 and 3.0 mg per day combined with reduced dose CsA or mycophenolic acid (Myfortic®) 1.44 gm per day with standard dose CsA. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice. This application was discussed at the Cardiovascular and Renal Advisory Committee meeting December 7, 2009. In the safety discussion, the AC focused mainly on the potential for poor long-term cardiovascular outcomes and risk factors associated with proteinuria and hyperlipidemia, which include concomitant medications used in this patient population. The advisory committee was also asked to vote on whether they thought a REMS was necessary. The committee voted in the affirmative, but when asked for detailed advice, there was no clear consensus about what the Communication Plan should consist of or who should be targeted for education/communication. A few AC members noted that monitoring needs to be reinforced and one voiced concerns about off-label use. The AC focused almost entirely on post-marketing studies and trials, which are separate from REMS. The committee did note repeatedly that the safety issues identified for everolimus are not significantly different from the risks of other immunosuppressing drugs, particularly sirolimus, used for renal transplant management.

Sirolimus[1], which has the identical mechanism of action and was approved in 1999 for the same patient population as proposed for everolimus, has no risk management program outside of routine labeling and pharmacovigilance (sirolimus has FDA-approved patient instructions for use). In the absence of information that the risks of everolimus are different or more severe than for sirolimus, and considering the 10 years of experience with mTOR inhibitors in solid organ transplantation, DRISK recommended a Medication Guide-only REMS for everolimus. While DRISK did not believe a Communication Plan (CP) necessary to ensure that the benefits of everolimus outweigh the risks, our December 10, 2009 review stated that if DSPTP did believe a CP necessary, we would work with them towards it approval.

The review division sent the sponsor a CR letter (dated December 23, 2009). That letter included a REMS request for a Medication Guide and a Communication Plan 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 cyclosporine. The CR letter also requested a timetable for submission of assessments, but the data needed for assessments was limited to evaluation of patient understanding and Medication Guide (MG) compliance. We recommended in Interim Review #1 that effectiveness of the Communication Plan be included in the Approval letter as follows: 'Healthcare provider understanding of the serious risks associated with Zortress (everolimus) through surveys'.

2 MATERIAL REVIEWED

- DSPTP consult dated January 27, 2010
- Everolimus CR letter dated December 23, 2009 (included REMS request)
- Zortress REMS submission dated April 7, 2010 (reviewed 'clean' WORD version REMS and 'tracked' WORD version supporting document)
- DRISK interim REMS reviews dated February 5, 2010 and March 28, 2010 and April 01, 2010

[1] From WARNINGS section sirolimus package insert approved 10/08/2009

3 RESULTS OF REVIEW

3.1 GOALS AND OBJECTIVES

The proposed goals of the REMS are:

- To inform healthcare providers about the following serious risks associated with ZORTRESS: wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine.
- To inform patients about the serious risks associated with ZORTRESS.

Review Comment: These Goals are consistent with the CR letter and our interim comments to sponsor.

3.2 PROPOSED REMS ELEMENTS:

The REMS includes a Medication Guide, Communication Plan, and a timetable for submission of assessments of the REMS. Each element of the REMS is described below.

3.2.1 Medication Guide

The Medication Guide will be attached to the REMS (Attachment A).

Review Comment: The Medication Guide has been reviewed separately (B. Fuller/DRISK completed March 11, 2010). Inclusion of a Medication Guide is consistent with the REMS request.

3.2.2 Communication Plan

A. Audience – the sponsor will target transplant surgeons and nephrologists (with relevant physician extenders), and pharmacists.

B. Distribution plan
   i. Dear Healthcare Professional Letter. The DHCP letter will be distributed within 60 days after product approval and/or in conjunction with product launch, whichever is sooner.
   ii. Dear Pharmacist Letter. This letter will be distributed to members of professional pharmacy associations and societies within 60 days after product approval and/or in conjunction with product launch, whichever is sooner. Pharmacists designated to receive mailings will

be identified through the membership lists of pharmacy organizations, which are delineated in the Supporting Document.

iii. Collaboration with Professional Societies. The sponsor will send the DHCP letter to relevant societies delineated in the REMS document.

iv. REMS website. REMS approved communications materials will be made available via a prominent (single click) link on the homepage of the ZORTRESS product website.

The Dear Healthcare Professional letters are attached to the REMS (Attachment B and C) .

Review Comment: This CP is consistent with the CR letter.

3.2.3 Elements to Assure Safe Use

The REMS does not include Elements to Assure Safe Use.

3.2.4 Implementation System

An implementation system is not a required component of a REMS if there are no elements to assure safe use.

3.2.5 Timetable for Submission of Assessments

The sponsor proposes to assess the REMS at 18 months, 3 and 7 years following approval. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date so that it will be received by the FDA on or before the due date.

Review Comment: This schedule is acceptable.

3.3 REMS ASSESSMENT PLAN

The sponsor will provide the following components as part of their 18 month, 3-year and 7-year assessment reports.

A. An evaluation of prescribers' understanding of the serious risks of wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine.

B. Patients' understanding of the serious risks associated with Zortress.

B. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

C. A report of failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.

D. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Review Comment: This REMS assessment outlined in the Supporting Document is consistent with what FDA has requested.

3.4 Survey Protocols

The sponsor submitted surveys and protocols for HCP and patients. These materials were reviewed by B. Gordon (DRISK) and comments sent to the sponsor in Interim Review #2, dated March 28, 2010. The Supporting Document notes that the protocol, survey instrument, and methodology will be finalized after the product labeling and educational materials are finalized, and will be provided to the FDA at least 90 days before the surveys are administered.

4 RECOMMENDATION

The Sponsor has appropriately responded to all Agency comments. The Division of Risk Management in the Office of Surveillance and Epidemiology finds the proposed REMS for Zortress (everolimus) acceptable as appended here. DRISK recommends approval of the Zortress REMS submitted on April 7, 2010.

5 **Appendix** (REMS and Attachments)

NDA 21-560 ZORTRESS® (everolimus)

Gary S. Friedman, MD

Novartis Pharmaceuticals

One Health Plaza

East Hanover, N.J. 07936-1080

(862) 778-5813

gary.friedman@novartis.com

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

3 GOALS

The goals of the ZORTRESS REMS are:

1) To inform healthcare providers about the following serious risks associated with ZORTRESS: wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine.

2) To inform patients about the serious risks associated with ZORTRESS.

4 REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed as part of the Package Insert with each prescription for ZORTRESS. The product is supplied as 0.25 mg, 0.5 mg, and 0.75 mg tablets. Each strength is available in boxes of 60 (6 blister strips of 10 tablets each), approximately a one-month supply of ZORTRESS per box. One copy of the ZORTRESS Medication Guide will be enclosed in each box of ZORTRESS. The Medication Guide will be available for distribution to patients with each prescription that is dispensed. A reminder to pharmacists to provide the Medication Guide each time ZORTRESS is dispensed will be printed on each box.

In compliance with 21 Code of Federal Regulation (CFR) 208.24, the Sponsor will institute the following measures:

* The Medication Guide will be enclosed in all ZORTRESS packaging.
* Retail pharmacies will be instructed to provide the Medication Guide with each ZORTRESS prescription. Novartis will conduct ongoing surveys to assess distribution and understanding of the Medication Guide by healthcare professionals and patients.

The Medication Guide will also be available from the Novartis ZORTRESS Web Site (www.zortress.com) and by request through the Sponsor's toll-free information phone number 1-888-NOW-NOVA (1-888-669-6682).

See Attachment A.

B. Communication Plan

Novartis will institute a Communication Plan to educate healthcare professionals on the goals of the ZORTRESS REMS. Materials that will be utilized are the US Package Insert, a Dear Healthcare Professional/Professional Association letter (see Attachment B.) and a Dear Pharmacist letter (see Attachment C).

At the time of ZORTRESS launch, Novartis will distribute the letters to key stakeholder healthcare professionals within 60 days of REMS approval and/or in conjunction with product launch, whichever is sooner. The FDA-approved DHCP letters will be available via a prominent (single click) link on the homepage of the ZORTRESS product website.

The following healthcare professionals will be targeted for communication:

1. transplant surgeons
2. transplant medical physicians
3. professionals who act as physician extenders for transplant surgeons and transplant medical physicians
4. pharmacists (in-hospital and community-based)

The following professional associations will be targeted for communication:

1. American Society of Transplantation (AST)
2. American Society of Transplant Surgeons (ASTS)
3. National Foundation for Transplants
4. American Nephrology Nurses Association (ANNA)
5. National Kidney Foundation (NKF)
6. European Society of Organ Transplantation (ESOT)
7. International Transplant Nurses Society
8. The Transplantation Society
9. North American Transplant Coordinators Organization (NATCO)
10. American Society of Health System Pharmacists
11. American College of Clinical Pharmacy
12. American Pharmacists Association

C. Elements To Assure Safe Use

The ZORTRESS REMS can be approved without elements to assure safe use.

D. Implementation System

Because the REMS for ZORTRESS does not include elements to assure safe use, an implementation system is not required.

E. Timetable for Assessments

Novartis will submit REMS Assessments to the FDA by 18 months, by 3 years, and in the 7th year from the date of approval of the REMS. To facilitate inclusion of as much information as

possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

ATTACHMENT A. ZORTRESS Medication Guide

ATTACHMENT B. DEAR HEALTHCARE PROFESSIONAL/ PROFESSIONAL ASSOCIATION LETTER

ZORTRESS Logo & Branding

IMPORTANT DRUG WARNING

Dear [Healthcare Professional/Professional Association]:

This letter informs you of important safety information for ZORTRESS® (everolimus) TABLETS, which have been approved by the US Food and Drug Administration for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

Important Information about the Risks of ZORTRESS

In addition to the Boxed Warning about malignancy, serious infections, and other established risks of immunosuppression, Novartis Pharmaceuticals Corporation (Novartis) is implementing a Risk Evaluation and Mitigation Strategy (REMS) to inform health care providers and patients about the following additional risks of ZORTRESS:

- **Delayed or Impaired Wound Healing**

ZORTRESS delays wound healing and increases the occurrence of wound dehiscence, wound infection, incisional hernia, lymphocele and seroma which may require surgical intervention. Lymphoedema and other types of localized fluid collection, such as pericardial and pleural effusions and ascites have also been reported.

- **Hyperlipidemia**

It may not be possible to normalize ZORTRESS-associated hyperlipidemia, despite anti-lipid therapy. Patients on a HMG-CoA reductase inhibitor and/or fibrate should be monitored for rhabdomyolysis and other adverse effects as per labeling for these lipid lowering agents. Due to an interaction with cyclosporine, use of the HMG-CoA reductase inhibitors simvastatin and lovastatin was discouraged in the everolimus clinical trials.

- **Proteinuria**

ZORTRESS is associated with increased proteinuria. This risk increases with higher everolimus whole blood trough concentrations in kidney transplant patients receiving ZORTRESS with cyclosporine.

- **Renal Allograft Thrombosis**

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation.

- **Nephrotoxicity with Standard Dose Cyclosporine**

ZORTRESS with standard dose cyclosporine increases the risk of renal dysfunction which is manifested by lowered glomerular filtration rate. Lower cyclosporine doses are required in combination with everolimus to reduce renal dysfunction.

Additional Information

- ZORTRESS is 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.

- In patients at high immunologic risk, the safety and efficacy of everolimus has not been established.

- Use of everolimus for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

Please review the FDA approved **Medication Guide** with your patients.

Adverse event reporting: Healthcare providers should report all suspected adverse events associated with the use of ZORTRESS. Please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the accompanying complete Prescribing Information. For more information regarding ZORTRESS, please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or visit www.zortress.com.

Sincerely,

Gary S. Friedman, MD

Medical Director

Novartis Pharmaceuticals Corporation

ATTACHMENT C. DEAR PHARMACIST LETTER

ZORTRESS Logo & Branding

IMPORTANT DRUG WARNING

Dear Pharmacist:

This letter informs you of important safety information for ZORTRESS® (everolimus) TABLETS, which have been approved by the US Food and Drug Administration for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

Important Information about the Risks of ZORTRESS

In addition to the Boxed Warning about malignancy, serious infections, and other established risks of immunosuppression, Novartis Pharmaceuticals Corporation (Novartis) is implementing a Risk Evaluation and Mitigation Strategy (REMS) to inform health care providers and patients about the following additional risks of ZORTRESS:

- **Delayed or Impaired Wound Healing**

ZORTRESS delays wound healing and increases the occurrence of wound dehiscence, wound infection, incisional hernia, lymphocele and seroma which may require surgical intervention. Lymphoedema and other types of localized fluid collection, such as pericardial and pleural effusions and ascites have also been reported.

- **Hyperlipidemia**

It may not be possible to normalize ZORTRESS-associated hyperlipidemia despite anti-lipid therapy. Patients on a HMG-CoA reductase inhibitor and/or fibrate should be monitored for rhabdomyolysis and other adverse effects as per labeling for lipid lowering agents. Due to an interaction with cyclosporine, use of the HMG-CoA reductase inhibitors simvastatin and lovastatin was discouraged in the everolimus clinical trials.

- **Proteinuria**

ZORTRESS is associated with increased proteinuria. This risk increases with higher everolimus whole blood trough concentrations in kidney transplant patients receiving ZORTRESS with cyclosporine.

- **Renal Allograft Thrombosis**

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation.

- **Nephrotoxicity with Standard Dose Cyclosporine**

ZORTRESS with standard dose cyclosporine increases the risk of renal dysfunction which is manifested by lowered glomerular filtration rate. Lower cyclosporine doses are required in combination with ZORTRESS to reduce renal dysfunction. Refer to the complete

Prescribing Information for dosing and monitoring, including section *2.3 Therapeutic*

Drug Monitoring- Cyclosporine

Additional Information

- ZORTRESS is 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.
- In patients at high immunologic risk, the safety and efficacy of everolimus has not been established.
- Use of everolimus for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

Dispensing Information

Each carton of ZORTRESS includes the **Medication Guide**. It is important that patients receive the Medication Guide with each new ZORTRESS prescription that you fill and with each refill as there may be new information. For additional copies of the Medication Guide, please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1- 888-669-6682) or visit www.zortress.com.

Carton and Container labels for ZORTRESS include the required statement to alert dispenser to provide the Medication Guide.

ZORTRESS is available as 0.25 mg, 0.5 mg, and 0.75 mg tablets

Adverse event reporting: Healthcare providers should report all suspected adverse events associated with the use of ZORTRESS. Please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the accompanying complete Prescribing Information. For more information regarding ZORTRESS, please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or visit www.zortress.com.

Sincerely,

Gary S. Friedman, MD

Medical Director

Novartis Pharmaceuticals Corporation

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

KATHRYN A O Connell
04/12/2010

MARY E WILLY
04/12/2010
I concur

REMS Interim Review Comments

Drug Name:	**BLA / NDA:**	**Date:** 04/01/2010
Zortress (everolimus)	#21-560	**Comment Set # 3**
DRISK Scientific Lead: Kathryn O'Connell, MD, PhD		**Team leader:** Suzanne Robottom, PharmD, (DRISK)
RCM #: 2009-1376		

Materials Reviewed:

- Proposed Zortress REMS re-submission dated March 31, 2010
- Everolimus IR letter dated March 26, 2010

This is DRISK's third interim review of the proposed REMS for Zortress (everolimus).

We provide for the sponsor a revised REMS document in WORD Track Changes. The sponsor should ensure that the re-submitted Supporting Document is revised to be entirely consistent with the REMS document as shown here.

We note that the March 31, 2010 electronic submission includes files under the 'Risk Management' section that are not part of the REMS. Please tell the sponsor that the re-submitted REMS should include only the REMS, DHCP/Association letter, Pharmacist Letter, and the Supporting Document.

10 Page(s) of Draft Labeling have been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

KATHRYN A O Connell
04/02/2010

CLAUDIA B KARWOSKI
04/02/2010
concur

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** 03/28/10
Zortress (everolimus)	#21-560	**Comment Set # 2**
DRISK Scientific Lead: Kathryn O'Connell, MD, PhD		**Reviewers:** ▪ Brian Gordon, MA, Social Science Reviewer (DRISK) ▪ Kate Heinrich, MA, Health Education Reviewer (DRISK) ▪ Kathleen Klemm, PharmD (DDMAC) ▪ Suzanne Robottom, PharmD, Team Leader (DRISK)
RCM #: 2009-1376		

Materials Reviewed:

- Proposed Zortress REMS re-submission dated February 19, 2010
- Everolimus CR letter dated December 23, 2009 (included REMS request)

Background:

The comments below are DRISK's second interim review of the proposed REMS for Zortress (everolimus). We have reviewed DDMAC's comments and changes were incorporated as deemed appropriate within the educational goals of the Communication Plan.

We provide comments for the sponsor, as well as re-written Dear Healthcare Provider Letters. We are not including a re-write of the Dear Professional Association letter, as it should be the same as the Dear HCP letter.

Note to Review Division:

We have removed a large amount of material from the Communication Plan materials because the length and detail level of the submitted documents would likely result in very poor utilization by healthcare professionals. We defer to DSPTP to provide clinical review to determine 1) whether the

12 Page(s) of Draft Labeling have been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

KATHRYN A O Connell
03/29/2010
interim review cleared through team leader, S. Robottom

CLAUDIA B KARWOSKI
03/29/2010
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 11, 2010
To:	Renata Albrecht, M.D., Director **Division of Special Pathogen and Transplant Products (DSPTP)**
Through:	Mary Willy, Ph D, Deputy Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Barbara Fuller, RN, MSN, CWOCN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	Zortress (everolimus)
Application Type/Number:	NDA 21-560
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2010-187

1 INTRODUCTION

On January 22, 2010 the Division of Special Pathogen and Transplant Products (DSPTP) received the resubmission of NDA 21-560, Zortress (everolimus) seeking an indication for the prophylaxis of organ rejection in renal transplantation. The resubmission was in response to the DSPTP complete response (CR) letter dated December 23, 2009. The letter included a request for a REMS with a Medication Guide and a Communication Plan 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 cyclosporine. The CR letter also requested a timetable for submission of assessments, but the data needed for assessments was limited to evaluation of patient understanding and Medication Guide (MG) compliance.

This review is written in response to a request by DSPTP for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Zortress (everolimus). Please let us know if DSPTP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is under review by DRISK and will be provided to DSPTP under separate cover.

2 MATERIAL REVIEWED

- Draft Zortress (everolimus) Prescribing Information (PI) submitted January 22, 2010 and revised by the review division throughout the review cycle. Received by DRISK on February 26, 2010
- Draft Zortress (everolimus) Medication Guide (MG) submitted on January 22, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

BARBARA A FULLER
03/11/2010
DRISK Final Review of ZORTRESS MG

MARY E WILLY
03/11/2010
I concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 22, 2010
To:	Renata Albrecht, M.D., Director
	Division of Special Pathogen and Transplant Products (DSPTP)
Through:	Mary Willy, PhD, Deputy Director
	Division of Risk Management (DRISK)
	LaShawn Griffiths, MSHS-PH, BSN, RN
	Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Barbara Fuller, RN, MSN, CWOCN
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	Zortress (everolimus)
Application Type/Number:	NDA 21-560
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2009-1223

1 INTRODUCTION

The Division of Special Pathogen and Transplant Products (DSPTP) requested that the Division of Risk Management review proposed patient labeling for New Drug Application (NDA) 21-560 Zortress (everolimus) submitted by Novartis Pharmaceuticals Corporation on June 30, 2009.

DSPTP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide until such time as the review division plans to address labeling. Please send us a new consult request at that time. This memo serves to close-out the consult request for Zortress (everolimus) NDA 21-560.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

BARBARA A FULLER
01/22/2010
Zortress MG DRISK 01-10 Deferral Memo

MARY E WILLY
01/25/2010

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Office Antimicrobial Drug Products
Division of Special Pathogen and Transplant Products

NDA/BLA #s: NDA 021560

Products: Zortress (everolimus) Tablets, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg.

APPLICANT: Novartis Pharmaceutical Corporation

FROM: Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products

DATE: December 23, 2009

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Zortress (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 cyclosporine. In reaching this determination, we considered the following:

A. According to the National Health and Nutrition Examination Survey (NHANES) data, approximately 23 million Americans suffer from chronic kidney disease. Of these, around 500,000 receive dialysis and approximately 16,000 patients undergo a kidney transplant each year.

B. Use of immunosuppressive therapy is vital for patients with a solid organ transplant. Without immunosuppressive therapy, transplantation would cause an immune response and result in destruction of the transplanted organ.

C. Zortress (everolimus) is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant. Zortress (everolimus) is to be administered concurrently with reduced doses of Neoral and corticosteroids. An initial Zortress (everolimus) dose of 0.75 mg b.i.d. is recommended for the general transplant population, administered as soon as possible after transplantation. The dose of Neoral can then be reduced to optimize renal function.

D. The treatment with Zortress (everolimus) is chronic/lifelong to ensure there is no organ rejection in transplant patients.

E. The data for the serious known and potential adverse events discussed under this section is derived from the NDA resubmission dated June 30, 2009.
Zortress (everolimus) is an mTOR inhibitor and belongs to the same class of immunosuppressant agents as sirolimus, which is indicated for the prophylaxis of organ rejection in patients (b) (4) receiving renal transplants.

In clinical trials, wound healing complications, including dehischence, hernia, and infection, were more frequent in the Zortress (everolimus) groups as compared to the Myfortic (comparator) groups. In addition, more patients in the Zortress (everolimus) groups required surgical intervention for their wound complications.

Hyperlipidemia and proteinemia were reported as adverse events (AEs) at higher rates in the Zortress (everolimus) groups than in the comparator groups in the clinical trials. One case of hyperlipidemia was reported as a serious adverse event. Proteinuria is not only a manifestation of renal disease, but is also a predictor of survival in most renal diseases.

Due to observed renal toxicities, this NDA was previously not approved (original NDA submission dated December 19, 2002) and the applicant was asked to establish a safe and effective dosing regimen for Zortress (everolimus) and cyclosporine that minimizes renal function impairment while maintaining efficacy. Therefore, use of reduced dose cyclosporine is necessary to reduce/minimize nephrotoxicity in renal transplant patients as will be specifically summarized the product labeling. Thrombogenicity is a well known class effect of mTOR inhibitors. In the clinical trials, 10 patients in the Zortress (everolimus) groups developed graft thrombosis (artery and vein) and consequently lost their grafts. One of these patients later died from complications related to their renal vein thrombosis.

F. Zortress (everolimus) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Zortress (everolimus). FDA has determined that Zortress (everolimus) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zortress (everolimus). FDA has determined that Zortress (everolimus) is a product for which for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Zortress (everolimus).

The elements of the REMS will be a Medication Guide, a communication plan and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

HYUN J SON
12/23/2009

RENATA ALBRECHT
12/23/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 10, 2009
To:	Renata Albrecht, M.D., Director Division of Special Pathogen and Transplant Products (DSPTP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	Everolimus Risk Management Team Scientific Lead: Kathryn O'Connell, MD, PhD, Medical Officer (DRISK/OSE) Team Members: Mary Dempsey, Risk Management Coordinator (DRISK/OSE) Suzanne Berkman Robottom, Pharm.D., Senior Drug Risk Management Analyst, Team Leader (DRISK/OSE)
Subject:	Review of Risk Management Options
Drug Name(s):	Everolimus
Submission Number:	CR Amendment dated June 30, 2009
Application Type/Number:	NDA 021560
Applicant/sponsor:	Novartis
OSE RCM #:	2009-1223

1 INTRODUCTION

This review follows a request from the Division of Special Pathogen and Transplant Products (DSPTP) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for everolimus dated June 30, 2009.

Everolimus, an mTOR inhibitor, is being developed for the prophylaxis of acute rejection in adult patients receiving a *de novo* kidney transplant, in combination with basiliximab, reduced dose cyclosporine (Neoral®, CsA) and corticosteroids. The sponsor's proposed indication is prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant. Everolimus is to be administered concurrently with reduced doses of Neoral and corticosteroids. Specifically, the proposed dosing is 0.75 mg twice daily administered as soon as possible after transplantation. The sponsor proposes that the dose of Neoral then be reduced to optimize renal function.

An initial NDA submitted to FDA December 19, 2002 demonstrated efficacy for fixed-dose everolimus with standard dose cyclosporine compared to mycophenolate mofetil (MMF; CellCept®) with standard dose CsA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients. However, interpretation of the trial results was complicated by premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the control groups. Due to 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.

The current submission involves 833 *de novo* kidney transplant patients followed for 12 months. Patients were randomized to everolimus starting at either 1.5 and 3.0 mg per day combined with reduced dose CsA or mycophenolic acid (Myfortic®) 1.44 gm per day with standard dose CsA. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice.

2 MATERIAL REVIEWED

The following materials were reviewed:

- Sponsor's proposed REMS dated June 30, 2009
- DSPTP draft advisory committee briefing package dated October 22, 2009
- Notes from Advisory Committee attendance December 7, 2009
- Labeling for Rapamune (sirolimus, an approved mTOR for renal transplant with similar risks and indication as everolimus)

3 RESULTS OF REVIEW

The sponsor submitted a REMS 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. They did not submit any of the Communication Plan materials. During the NDA review, the sponsor was offered interim advice about the goals in the event that FDA did request a REMS. Specifically, they were advised of the 3 safety issues noted above (proteinuria, wound healing, lipid abnormalities) that the REMS should address, and that *if* a CP became necessary, mock-ups of all materials and the specifics of distribution would need to be submitted for review.

During internal discussions, the review division considered a number of safety issues that might require a Communication Plan, including wound healing, hyperlipidemia, proteinuria, nephrotoxicity with use of standard dose of cyclosporine, and graft thromboses. None of these potential problems is unique to everolimus. For example, the Warnings section of the Rapamune package insert includes (approved label dated 10/08/2009)[1]: Hypersensitivity Reactions, Angioedema, Fluid Accumulation and Wound Healing, Hyperlipidemia, Renal Function/Proteinuria, Latent Viral Infection, Interstitial Lung Disease, *De Novo* Use Without Cyclosporine, and Increased Risk of Calcineurin Inhibitor-induced HUS/TTP/TMA.

The December 7 advisory committee voted almost unanimously for approval (1 no vote based on efficacy). In the safety discussion, the AC focused mainly on the potential for poor long-term cardiovascular outcomes and risk factors associated with proteinuria and hyperlipidemia, which include concomitant medications used in this patient population. The advisory committee was also asked to vote on whether they thought a REMS was necessary. The committee voted in the affirmative, but when asked for detailed advice, there was no clear consensus about what the Communication Plan should consist of or who should be targeted for education/communication. A few AC members noted that monitoring needs to be reinforced and one voiced concerns about off-label use. The AC focused almost entirely on post-marketing studies and trials, which are separate from REMS. The committee did note repeatedly that the safety issues identified for everolimus are not significantly different from the risks of other immunosuppressing drugs, particularly sirolimus, used for renal transplant management.

[1] Rapamune was initially approved August 25, 2000.

4 DISCUSSION

Management of organ transplant recipients involves teams of highly experienced healthcare practitioners well versed in therapeutic drug monitoring and the plethora of potentially serious side effects of currently available drugs for rejection prevention. Sirolimus[2], which has the identical mechanism of action and was approved in 1999 for the same patient population as everolimus,has no risk management program outside of routine labeling and pharmacovigilance (sirolimus FDA-approved patient labeling consists only of patient instructions for use). We are unaware of postmarketing information that suggests that sirolimus patients are inadequately monitored. The risks identified during the course of the everolimus application review are recognized mTOR class effects and are not specific to this moiety. In the absence of information that the risks of everolimus are different or more severe than for sirolimus, additional measures beyond labeling and pharmacovigilance do not appear necessary to ensure that the benefits of the drug outweigh the risks.

For these reasons, we do not recommend a Communication Plan or Elements to Assure Safe Use if everolimus is approved. A Medication Guide is a consideration, since the product does have serious risks that could affect a patient's decision to use or continue to use the drug, and patient adherence to directions is crucial to the product's clinical benefit (for example, (comply with blood testing schedules, don't discontinue concomitant CsA without prescriber input). There is potential for harm in this patient population if risk is presented outside the context of benefit. Consideration can be given to including a risk-benefit context and the importance of discussion with the healthcare team. This would, however, require careful attention to void promotional messages or suggestions that this product is better than other drugs for the indication. Furthermore, if a Medication Guide is required or any other additional measures for everolimus, it appears it should be required for sirolimus, as well.

A REMS for everolimus would logically obligate the same REMS for sirolimus. This requires additional considerations. First, whether "new safety information" specific to sirolimus would be needed to require a REMS for sirolimus or if citing class effects would suffice. If new safety information is needed, it is not clear if such information is available. Further, the introduction and timing of generic sirolimus is a factor if a Communication Plan is required. Under FDAAA, when generic products enter the market, FDA becomes responsible for the Communication Plan for the generics and the innovator product.

[2] From WARNINGS section sirolimus package insert approved 10/08/2009

5 RECOMMENDATION

Based on the information available at this time, and considering the 10 years of experience with mTOR inhibitors in solid organ transplantation, we recommend a Medication Guide-only REMS for everolimus. While DRISK does not believe a Communication Plan is necessary to ensure that the benefits of everolimus outweigh the risks, if the review division does believe one is necessary, DRISK will work with the review division towards it approval.

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/s/

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01/19/2010

CLAUDIA B KARWOSKI
01/19/2010
copy sent to DSPTP on December 8, 2009

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