CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-560

SUMMARY REVIEW

(b) (4)

Division Director Review #2

Applicant:	Novartis
Drug:	everolimus
Trade Name:	Zortress [1]
Date of Submission:	December 19, 2002 (approvable letter October 20, 2003)
Resubmission #1:	February 27, 2004 (approvable letter August 27, 2004)
Resubmission #2:	June 30, 2009 (complete response letter December 23, 2009)
Resubmission #3:	January 22, 2010
PDUFA Goal Date:	June 22, 2010
Division Goal Date:	April 22, 2010
Formulation:	Tablet
Strengths:	0.25 mg, 0.5 mg, and 0.75 mg, (1 mg tablets[2]*)
Indication:	Prevention of rejection in kidney transplant patients at low to moderate immunologic risk
Related NDA:	NDA 21-561 (dispersible tablet)
IND:	IND 52,003

Material Reviewed:

Project Management: Jacquelyn Smith, Diana Willard
Safety Project Manager: Hyun Son
Clinical Review: Ergun Velidedeoglu, Joette Mever, (original submission: Arturo Hernandez, Marc Cavaille Coll)
Pediatric Review: Marc Cavaille Coll
Cross Discipline Team Leader/Safety Deputy Director: Ozlem Belen
Microbiology Review: Simone Shurland, Shukal Bala
CDRH consultation for everolimus assay: Avis Danishefsky, Courtney Harper
Clinical Pharmacology Review: Jang-Ik Lee, Dakshina Chilukuri, Kevin Krudys (pharmacometrics), Pravin Jadhav (pharmacometrics), Phil Colangelo
Statistics Review: Xiao Ding, Karen Higgins, LaRee Tracy, Mohammad Huque, John Stephen Yap, Aloka Chakravarty
Pharmacology/Toxicology Review: Stephen Kunder, William Taylor
Chemistry Manufacturing Controls Review: Mark Seggel, Stephen Miller
Division of Scientific Investigations (DSI): Susan Thompson
Office of Surveillance and Epidemiology (OSE)
OSE/Division of Medication Error and Prevention Analysis (DMEPA): Judy Park, Carlos Mena-Grillasca, Denise Toyer, Kellie Taylor, Nitin Patel, Judy Park, Carol Holquist
OSE/Division of Pharmacovigilence II (DPVII): S. Christopher Jones, Melissa Truffa, Robert Boucher
OSE/Division of Drug Risk Evaluation (DRISK): Kathleen O'Connell, Suzanne Berkman Robottom, Brian Gordon, Kate Heinrich, Claudia Karwoski (REMS); Barbara Fuller, Mary Willy, LaShawn Griffiths (Medication Guide)
Division of Drug Marketing, Advertising, and Communication (DDMAC): Kathleen Klemm
Advisors and Conultants Staff: Elaine Ferguson

[1] previously Certican, rejected by DMEPA as promotional
[2] The 1 mg strength will not be marketed at this time, therefore it will not be included in labeling

Cardiovascular and Renal Drugs Advisory Committee meeting December 7, 2009: quick minutes
Safety Response Team (SRT), SWAT, and Office of Chief Counsel (OCC): review of CR letter and REMS memo

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Table of Contents:

1 RECOMMENDATIONS

Zortress (everolimus) Tablets will be approved for the indication below, based on the submission of acceptable package insert, Medication Guide, carton and container labeling (which includes the statement regarding dispensing of Medguide), and REMS which includes the Medication Guide, communications to physicians, professional societies and pharmacists, as well as a timetable of planned assessments.

The indication and excerpts from the dosage section are summarized below.

1.1 Indication and Usage

Prophylaxis of Organ Rejection in Kidney Transplantation
Zortress (everolimus) is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk[3] receiving a kidney transplant *[see Clinical Studies (14.1)]*. Zortress is to be administered in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids. Therapeutic drug monitoring is recommended for all patients receiving everolimus and cyclosporine *[see Dosage and Administration (2.2 and* (b) (4)

• 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.

• Standard doses of cyclosporine should be avoided with everolimus in order to reduce the risk of nephrotoxicity. [*See Warnings and Precautions (5.8), and Adverse Reactions (6.2)*]

• The safety and efficacy of Zortress has not been established in pediatric patients (<18 years).

1.2 Dosage and Administration

An initial everolimus dose of 0.75 mg orally twice daily (1.5 mg/day) is recommended for adult kidney transplant patients in combination with reduced dose cyclosporine, administered as soon as possible after transplantation. [*See Therapeutic Drug Monitoring (2.2 and 2.3), Clinical Studies (14.1)*]

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using appropriate assay methodology. The

[3] [3] Low to moderate immunologic risk defined as ABO compatible first organ donor with anti-HLA Class I PRA <20% by complement dependant cytotoxicity assay or <50% by flow cytometry or ELISA-based assay, and with negative T-cell cross match.

recommended everolimus therapeutic range is 3 to 8 ng/mL. [*See Clinical Pharmacology (12.5)*]

The recommended cyclosporine therapeutic range when administered with everolimus are 100 to 200 ng/mL through Month 1 post-transplant, 75 to 150 ng/mL at Months 2 and 3 post-transplant, 50 to 100 ng/mL at Month 4 post-transplant, and 25 to 50 ng/mL from Month 6 through Month 12 post-transplant. The median trough concentrations observed in the clinical trial ranged between 161 to 185 ng/mL through Month 1 post-transplant and between 111 to 140 ng/mL at Months 2 and 3 post-transplant. The median trough concentration was 99 ng/mL at Month 4 post-transplant and ranged between 46 to 75 ng/mL from Months 6 through Month 12 post-transplant. [*See Clinical Pharmacology (12.6) and Clinical Studies (14.1)*]

1.3 Other Requests

Novartis will submit the 24- month study results for A2309 as a postmarketing requirement (PMR) with a due date for the final study report on July 30, 2010.

Work on the evorolimus assay continues in CDRH – the Thermofisher submission is currently on hold [this is analogous to complete response decision in CDER], and the Waters application has not been received.

2 BACKGROUND

The background on everolimus and the studies conducted as part of the development program can be found in the primary reviews for this application, as well as the CDTL reviews of December 23, 2009 and April 20, 2010, and the DD review dated December 23, 2009. The applicant was issued a complete response letter on December 23, 2009, requesting labeling and REMS, and addressed the deficiencies in that letter in the resubmission of January 22, 2010, as amended.

The original NDA 21-560 (tablets) was submitted December 19, 2002 for the indications of heart and kidney transplantation. NDA 21-561 (dispersible tablets) was also submitted and the application remains approvable at this time. The heart transplant indication was administratively assigned different NDA numbers: NDA 21-628 (tablet) and NDA 21-631 dispersible tablet), and a clinical trial in heart transplantation evaluating TDM-monitored everolimus dosing is ongoing at this time.

During the initial development of everolimus for kidney transplantation, Novartis evaluated fixed doses of everolimus and full dose cyclosporine. Two Phase 3 studies (B201 and B251) in kidney transplantation were submitted in the original NDAs in 2002 and reviewed. In these trials, patients were randomized to fixed doses of everolimus – 1.5 mg/day (0.75 mg bid) or 3.0 mg/day (1.5 mg bid) doses, and full dose cyclosporine (CsA) with target trough concentrations of 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12). Patients receive steroids, and no induction. While these trials showed efficacy, glomerular filtration rate calculated by the

Nankivell method, was lower in the everolimus arms compared to the mycophenolate mofetil (MMF) plus CsA arm.

Specifically, the GFR calculated using the Nankivell method was 6 to 8 mL lower in the everolimus 1.5 mg group and 7 to 11 mL lower in the everolimus 3.0 mg group at 12 months (in this 24 month study) compared to the control regimen containing MMF as shown in the table below below:

Table 7: Median Estimated Creatinine Clearance (mL/min) using Nankivell Method by Treatment Group (ITT Group*)

	Study B201			Study B251		
	1.5 RAD (N=194)	3.0 RAD (N=198)	MMF (N=196)	1.5 RAD (N=193)	3.0 RAD (N=194)	MMF (N=196)
Baseline RAD vs. MMF^ 1.5 RAD vs. 3.0 RAD^	18.5 (N=184) p=0.627 p=0.727	18.7 (N=188) p=0.887 NA	18.6 (N=178) NA NA	23.7 (N=187) **p=0.039** p=0.653	24.3 (N=185) p=0.116 NA	26.8 (N=184) NA NA
Month 3 RAD vs. MMF^ 1.5 RAD vs. 3.0 RAD^	57.3 (N=154) p=0.168 p=0.119	54.9 (N=152) **p=0.004** NA	60.0 (N=158) NA NA	61.8 (N=155) p=0.060 p=0.057	58.1 (N=151) **p<0.001** NA	64.0 (N=159) NA NA
Month 6 RAD vs. MMF^ 1.5 RAD vs. 3.0 RAD^	56.7 (N=146) **p=0.003** p=0.197	52.9 (N=135) **p<0.001** NA	61.0 (N=147) NA NA	58.4 (N=150) **p<0.001** p=0.195	54.9 (N=135) **p<0.001** NA	65.6 (N=151) NA NA
Month 12 RAD vs. MMF^ 1.5 RAD vs. 3.0 RAD^	54.3 (N=123) **p=0.002** p=0.389	53.3 (N=119) **p<0.001** NA	60.3 (N=138) NA NA	58.0 (N=140) **p<0.001** p=0.247	55.2 (N=116) **p<0.001** NA	66.6 (N=141) NA NA

This finding was considered a safety issue, and Novartis was issued an approvable letter on October 20, 2003, and asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as a concentration-controlled regimen of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

Initially the applicant submitted results from two open-label non-comparative studies (A2306 and A2307) on February 27, 2004 which suggested that TDM may be a means to minimizing renal toxicity. However, these studies were not designed to evaluate efficacy and did not include a control arm that would allow an assessment whether relative renal toxicity had been minimized, therefore the Division requested a prospective, controlled clinical trial to address whether a TDM regimen would demonstrate efficacy and minimize renal toxicity. In addition, the Division had conducted various exposure-response analyses of available clinical trial data, and proposed target trough levels for everolimus. A second approvable letter was issued August 27, 2004 requesting a comparative study of TDM.

Therefore, Novartis designed study A2309 to evaluate new everolimus regimens in kidney transplantation. Following initial doses of everolimus 1.5 mg/day (0.75 mg bid) and the 3.0 mg/day (1.5 mg bid), subsequent doses were adjusted to target trough concentrations of 3-8 ng/mL and 6-12 ng/mL, respectively. Patients also received basiliximab induction, reduced-dose CsA[4] and steroids. The protocol design was

[4] Protocol specified CsA troughs were 100 to 200 ng/mL through Month 1 post-transplant, 75 to 150 ng/mL at Months 2 and 3 post-transplant, 50 to 100 ng/mL at Month 4 post-transplant, and 25 to 50 ng/mL from Month 6 through Month 12 post-transplant.

discussed with the Division and agreement reached. The results of the study were submitted on June 30, 2009, reviewed, and presented before the Cardiovascular and Renal Advisory Committee on December 7, 2009 for a public discussion of the safety and efficacy.

2.1 Efficacy

The efficacy data from A2309 were presented and are summarized below: The primary efficacy endpoint was efficacy failure at 12 months post transplantation, where efficacy failure is the composite endpoint consisting of treated biopsy-proven acute rejection (BPAR) episode (based on local laboratory assessment), graft loss, death, or loss to follow-up, based on a pre-specified 10% noninferiority (NI) margin. The study is designed to follow patients for a total of 24 months; the 12-month data were submitted June 30, 2009 for review, and the 24-month data will be submitted as a post marketing requirement (PMR) by July 30, 2010.

Table 3: Primary Efficacy Endpoint Analysis by Treatment Group (ITT Population - 12 Month Analysis)

Number of patients (%)	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Efficacy Failure	**70 (25.3)**	**61 (21.9)**	**67 (24.2)**
Treated BPAR	45 (16.3)	37 (13.3)	47 (17.0)
Graft Loss	12 (4.3)	13 (4.7)	9 (3.3)
Death	7 (2.5)	10 (3.6)*	6 (2.2)
Loss to follow-up	12 (4.3)	8 (2.9)**	9 (3.3)
95% CI (everolimus-Myfortic)	**(-6.1, 8.3)**	**(-9.3, 4.7)**	N/A
97.5% CI (everolimus-Myfortic)	(-7.1, 9.3)	(-10.3, 5.7)	N/A

* One patient who died 10 days after withdrew consent was included

** One patient who had graft loss before the randomization was considered as loss to follow-up

The non-inferiority margin justification was provided by the applicant and evaluated independently by the statistical reviewer. In this trial the control regimen consisted of Myfortic, CsA, steroids and basiliximab. Because no studies comparing this regimen to a putative placebo of CsA, steroids and basiliximab were identified, the justification of the margin included a review of 51 studies containing may different regimens using mixed effects modeling, and various additional sensitivity analyses looking at the contribution of the components to the effect in various studies, by examining regimens of MMF, CsA and steroids versus CsA and steroids or studies of MMF, CsA, steroids vs azathiorpine, CsA, steroids. The results yielded a treatment effect of 24.6% with a 95% margin of (18.9%, 30.2%), therefore the conservative M1 at the lower limit of that margin is 18.9% and a margin (M2) of 10% was selected, conserving essentially 50% of the benefit. For the everolimus 1.5 mg arm, the results were within the 10% margin.

2.2 Safety

Everolimus is an mTOR inhibitor, related to sirolimus (Rapamune®). Rapamune was approved as the oral solution for prevention of rejection in kidney transplant patients in

1999, and the tablet formulation was approved in 2000. Initially, the 2 mg dose regimen with CsA was used, but subsequently Wyeth conducted cyclosporine withdrawal studies, and the latter regimen was approved in 2003. As part of the approval it was recommended that sirolimus be dosed to target trough concentrations of 16-24 ng/mL in the first year, and 12-20 ng/mL thereafter.

Everolimus is 40-O-(2-hydroxyethyl)-rapamycin and has a stable 2-hydroxyethyl chain substitution at position 40 on sirolimus. Sirolimus has an oral bioavailability of 14-27%,[5] the bioavailability of everolimus is not provided. The half life for everolimus is 30 hours, compared to 62 hours for sirolimus. Everolimus is a substrate for cytochrome CYP4503A4 and P-glycoprotein. CsA significantly increased levels of everolimus, thus everolimus must be given with reduced CsA to minimize renal toxicity.

Clinical trials excluded use of simvastatin and lovastatin to manage hyperlipidemia because of the interaction with CsA.[6] Cyclosporine labeling includes cautionary language about the use of HMG-CoA reductase inhibitors with CsA and the potential for developing myopathy and rhabdomyolysis. As far as interaction between everolimus and atorvastatin and pravastatin; these HMG-CoA reductase inhibitors show approximately a 10% increase in levels of the HMG-CoA and everolimus levels when the two are given together.

In examining the safety profile of everolimus, it was also kept in mind that since the approval of sirolimus in 1999, the sirolimus labeling had been updated to include new adverse event information, as listed below:

- Boxed warning
  - Hepatic artery thrombosis in liver transplant.
  - Bronchial dehiscence in lung transplant
- Warnings and Precautions
  - Antiproliferative effects
  - Wound healing
  - Renal injury, proteinuria, low GFR
  - Hyperlipidemia
  - Interstitial pneumonitis
  - Edema, fluid collection
  - TMA including HUS and TTP
- Conversion from a CNI-based regimen – safety and efficacy of sirolimus not established

Because many of these events were also seen during the review of everolimus, the decision was made to present NDA 21-560 at the December 7, 2009 Cardiovascular and Renal Drugs Advisory Committee meeting.

[5] Rapamune® product labeling

[6] Lovastatin (Mevacor), simvastatin (Zocor), atorvastatin (Lipitor) and cerivastatin are metabolized via CYP3A4; fluvastatin and pravastatin are not: http://www medscape.com/viewarticle/406700_5

The safety presentation included information on deaths, discontinuations, graft losses, renal function, and adverse events. Events that were seen more frequently see with Myfortic included viral infections, neoplasms, CsA related events such as tremor, gingival hyperplasia, hirsutism, and events seen with MMF including leucopenia, dyspepsia and vomiting. Events that were seen more frequently with everolimus included graft thrombosis, dose-dependent hyperlipidemia and proteinuria, delay in wound healing, increase fluid accumulation (edema, effusions), NODAT, mouth ulcers. A case of alveolar proteinosis, and four cases of thrombotic microangiopathy (TTP/HUS) were seen.

The following table from the package insert summarizes the frequency of adverse events occurring at a rate of 10% of greater in study A2309:

Table 1 Incidence Rates of Frequent (≥10% in Any Treatment Group) Adverse Reactions by Primary System Organ Class and Preferred Term

Primary System Organ Class Preferred Term	Zortress (everolimus) 1.5 mg With reduced dose cyclosporine N=274 / n (%)	Myfortic (mycophenolic acid) 1.44 g With standard dose cyclosporine N=273 / n (%)
Any Adverse Events*	271 (99)	270 (99)
Blood lymphatic system disorders	93 (34)	111 (41)
Anemia	70 (26)	68 (25)
Leukopenia	8 (3)	33 (12)
Gastrointestinal disorders	196 (72)	207 (76)
Constipation	105 (38)	117 (43)
Nausea	79 (29)	85 (31)
Diarrhea	51 (19)	54 (20)
Vomiting	40 (15)	60 (22)
Abdominal pain	36 (13)	42 (15)
Dyspepsia	12 (4)	31 (11)
Abdominal pain upper	9 (3)	30 (11)
General disorders and administrative site conditions	181 (66)	160 (59)
Edema peripheral	123 (45)	108 (40)
Pyrexia	51 (19)	40 (15)
Fatigue	25 (9)	28 (10)
Infections and infestations	169 (62)	185 (68)
Urinary tract infection	60 (22)	63 (23)
Upper respiratory tract infection	44 (16)	49 (18)

Injury, poisoning and procedural complications	163 (60)	163 (60)
Incision site pain	45 (16)	47 (17)
Procedural pain	40 (15)	37 (14)
Investigations	137 (50)	133 (49)
Blood creatinine increased	48 (18)	59 (22)
Metabolism and nutrition disorders	222 (81)	199 (73)
Hyperlipidemia	57 (21)	43 (16)
Hyperkalemia	49 (18)	48 (18)
Hypercholesterolemia	47 (17)	34 (13)
Dyslipidemia	41 (15)	24 (9)
Hypomagnesemia	37 (14)	40 (15)
Hypophosphatemia	35 (13)	35 (13)
Hyperglycemia	34 (12)	38 (14)
Hypokalemia	32 (12)	32 (12)
Musculoskeletal and connective tissue disorders	112 (41)	105 (39)
Pain in extremity	32 (12)	29 (11)
Back pain	30 (11)	28 (10)
Nervous system disorders	92 (34)	109 (40)
Headache	49 (18)	40 (15)
Tremor	23 (8)	38 (14)
Psychiatric disorders	90 (33)	72 (26)
Insomnia	47 (17)	43 (16)
Renal and urinary disorders	112 (41)	124 (45)
Hematuria	33 (12)	33 (12)
Dysuria	29 (11)	28 (10)
Respiratory, thoracic and mediastinal disorders	86 (31)	93 (34)
Cough	(b) (4)	30 (11)
Vascular disorders	122 (45)	124 (45)
Hypertension	(b) (4)	30)

* As reported in the safety analysis population defined as all randomized patients who received at least one dose of treatment and had at least one post-baseline safety assessment.

The evidence of renal toxicity that had been seen in B201 and B251 and was the basis for the first approvable letter, was not seen in A2309, specifically the mean GFR at 12 months was 54.6 mL/min in the everolimus 1.5 mg group and 52.2 mL/min in the Myfortic group, showing that in the concentration controlled study renal toxicity associated with fixed dose everolimus and full dose CsA had been minimized.

2.3 Advisory Committee Meeting

Following a presentation of the information by the applicant and Division, discussion, and charge to the committee, the vote was 11 “yes” and 1 “no” that everolimus showed

efficacy for the indication of prophylaxis of acute rejection in *de novo* kidney transplant recipients, although one member considered that the 10% noninferiority margin was not sufficiently conservative (the M1 margin had been estimated at 18.9%, thus in this analysis approximately 50% of the treatment effect had been conserved). The committee then voted that the application could be approved with a REMS (9 yes, 3 no), there were no votes that the application could be approved without a REMS (0 yes). Regarding safety, committee members were interested in long term follow up information, access to TDM, and information directed at health care professionals, and evaluation of whether the safety provisions are working. The final vote recommending approval was 11 "yes" and 1 "no." The member who voted no thought the 10% noninferiority margin should have been even more conservative.

The dose to be approved is the 1.5 mg/day starting dose, adjusted to 3-8 ng/mL whole blood trough concentration. The higher dose (3.0 mg/day starting, adjusted to 6-12 ng/mL) was also shown to be effective but had more adverse events, including dose related adverse events of proteinuria and hyperlipidemia, and is not being requested for approval.

2.4 Other Information

On a related note, the use of everolimus for prophylaxis of rejection in heart transplantation was discussed at the November 16, 2005 the Cardiovascular and Renal Drugs Advisory Committee.[7] At that meeting, the committee noted that a fixed-dose regimen of everolimus with standard-dose CsA as evaluated in Study B253 showed short-term and long-term loss of renal function and alternative regimen be evaluated. A study in heart transplantation evaluating a TDM regimen is currently ongoing.

As summarized by Novartis, everolimus is currently approved in over 70 countries for the prophylaxis of organ rejection in adults receiving a renal or cardiac transplant, and approximately 4,000 kidney, 500 liver, and 250 heart transplant patients have been treated. The drug is approved for transplant patients in the European Union, but has not been approved in Canada, United Kingdom, Ireland. Everolimus is known by several other names. During development it was named SDZ RAD or RAD001. It is marketed worldwide under the trade name Certican which was rejected by DMEPA, and in the US will be marketed under the trade name, Zortress. Everolimus under the trade name Afinitor® was approved in March 2009 for use in renal cell carcinoma patients. Novartis states that everolimus has not been withdrawn from marketing for safety or efficacy reasons in any country.

3 REVIEW

3.1 Complete Response Letter

All review issues had been addressed during the previous cycles. The complete response letter requested that the package insert and REMS be submitted, and this was done by the applicant in the January 22, 2010 submission.

[7] http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4183M1.pdf

3.2 Labeling – Package Insert, Medication Guide, Carton and Container

The text of the package insert is in the Physician Labeling Rule (PLR) Format per 21 CFR 201.57; it was reviewed by all disciplines and consulting groups, and recommended revisions were incorporated by the applicant. The package insert includes a boxed warning summarizing the risk of lymphomas, malignancies, graft thrombosis, and reduced doses of cyclosporine to reduce nephrotoxicity. The Warnings and Precautions section summarizes information on these events as well as angioedema, wound healing and fluid accumulation, hyperlipidemia, proteinuria, polyoma virus, interaction with CYP3A4, noninfectious pneumonitis, thrombotic microangiopathy, new onset diabetes, male infertility, immunizations, interactions with grapefruit juice, use in hereditary deficiency. The Adverse Reactions provides a summary of data from study A2309, including a table of adverse events seen in 10% or more of patients in the everolimus 1.5 mg arm and the control arm. A summary of the efficacy of Study A2309 is included in the Clinical Studies section.

The Medication Guide is written consistent with 21 CFR 208.20 and provides a summary of the serious side effects, as well as adverse effects, and discusses other important information of which patients who receive Zortress should be aware.

Carton and container labeling includes the statement, "Dispense with medication guide enclosed or provided separately" as required under 21 CFR 208.24(d) and is otherwise consistent with 21 CFR 201.15.

3.3 REMS

A proposed REMS was included in the June 30, 2009 submission, and revisions were proposed by the Division and consulting groups in OSE. The final REMS was submitted by Novartis, and includes the items summarized below:

The goals of the Zortress 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.

The REMS elements are:

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).

FDA link for the Zortress REMS:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

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 and a Dear Pharmacist letter.

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:

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

The following professional associations will be targeted for communication:

- American Society of Transplantation (AST)
- (b) (4)

(b) (4)

(ESOT)

- International Transplant Nurses Society
- The Transplantation Society
- North American Transplant Coordinators Organization (NATCO)
- American Society of Health System Pharmacists
- American College of Clinical Pharmacy
- American Pharmacists Association

The REMS program is approved without elements to assure safe use.

Timetable for Assessments

Novartis will submit REMS assessments to FDA by month 18, by 3 years and in the 7th year from the date of approval of the REMS.

4 CONSULTATIVE REVIEWS

4.1 Compliance

No new issues - Inspections of manufacturing sites were found acceptable.

4.2 Division of Scientific Investigations (DSI)

No new issues - DSI indicated the further inspections were not needed for the application to be approved.

4.3 OSE/Division of Medication Error and Prevention Analysis (DMEPA)

The trade name "Zortress" was found acceptable by DMEPA, and was communicated in the letter from Dr. Holquist on January 15, 2010.

4.4 OSE/Division of Drug Risk Evaluation (DRISK)

The Medication Guide and REMS were reviewed by DRISK and recommendations incorporated in the final documents.

4.5 Division of Drug Marketing, Advertising, and Communication (DDMAC):

Labeling recommendations were discussed and incorporated as applicable.

4.6 Center for Devices and Radiological Health (CDRH)

The Division has been in contact with CDRH regarding the everolimus assay given that therapeutic drug monitoring (TDM) to target trough concentrations of 3 to 8 ng/mL is part of the management of patients. Thermofisher submitted their everolimus assay to CDRH and CDRH consulted DSPTP regarding cross-reactivity of everolimus and

metabolites, and regarding labeling. At this time, the Thermofisher application is on hold in CDRH, pending questions to the company. Waters is expected to submit an LCMS assay but CDRH has not received that application.

4.7 Pediatric and Maternal Health Staff (PMHS)

The pediatric development plan, specifically whether pediatric studies would be required under the Pediatric Research Equity Act (PREA), was discussed with the Pediatric and Maternal Health Staff, and presented before the Pediatric Review Committee (PeRC) on January 27, 2010. Based on consideration of the available therapies and patient populations, the recommendation was made that pediatric studies be waived because everolimus is not likely to offer a meaningful therapeutic benefit (it is related to sirolimus, another mTOR inibitor) and is not likely to be used in a substantial number of patients (less than 1000 pediatric kidney transplant patients).

Everolimus is related to sirolimus, an mTOR inhibitor first approved in 1999 for use with cyclosporine and in 2003 in a regimen that included sirolimus therapeutic drug monitoring (TDM) and cyclosporine withdrawal to minimize renal toxicity in patients at low to moderate immunologic risk. The latter is analogous to the everolimus regimen. Everolimus was compared to a regimen of Myfortic and CsA, and no particular advantages were noted. It is also expected that everolimus is likely to be similar to sirolimus, the other currently approved mTOR inhibitor.

In 2009, according to the Health Resources and Services Administration (HRSA), Organ Procurement and Transplantation Network (OTPN) there were 16,830 kidney transplants in the United States (all ages), approximately 870 of these were in pediatric patients 17 years in age and younger.[8]

5. DISCUSSION AND CONCLUSIONS

The Zortress (everolimus) Tablet application will be approved given that all deficiencies have been resolved and the applicant has submitted an acceptable package insert, Medication Guide, carton and container labeling, and REMS. DMEPA has reviewed the Zortress trade name and found it acceptable.

Although most reviewers considered the information submitted for study A2309 as providing evidence that the product is effective and can be used in patients as long as a REMS program is in place, the primary Medical Officer and one member of the Advisory Committee (AC) recommended against approval; the medical officer had major concerns about safety and the AC member was concerned that the NI margin was not convervative enough. Other reviewers and AC members recommended that the application be approved.

Regarding the efficacy of everolimus, the efficacy failure was reported as 25.3% for everolimus and 24.2% for the control; the prespecified noninferiority margin was met.

[8] HRSA/OPTN http://optn.transplant.hrsa.gov/latestData/rptData.asp

There was a 2.2% difference in death, graft loss and loss to follow up. The glomerular filtration rate at 12 months post transplant was 54.6 mL/min/1.73m^2 in the everolimus arm and 52.3 mL/min/1.73m^2 in the control arm. These numeric differences do not reach statistical significance. Additional information will be provided from the 24-month results to show whether the outcomes continue to be similar or whether they diverge.

There are a number of adverse events that are now recognized as being mTOR-related events, due to the recognized anti-proliferative activity of everolimus as well as sirolimus, activity which is also responsible for the immunosuppressive effect by blocking progression of T-cells from G1 to S phase. A number of these adverse events, such as proteinuria and hyperlipidemia show an exposure-response relationship. Some patients tolerate everolimus, while others develop adverse events, including serious events that lead to discontinuation of everolimus. Some events such as wound healing, fluid collection, edema, and graft thrombosis did not show an exposure-response pattern but were more frequent in everolimus patients, although not statistically significant. As noted above, adjustment of doses to target trough concentrations, or discontinuation of everolimus were two of the measures used to manage patients. In A2309, a higher dose of everolimus (3.0 mg/day, target trough 6-12 ng/mL) was also evaluated and shown to have higher adverse event rates, including serious events. Therefore, the higher dose was not selected for labeling, and suggests toxicity may be related to exposure, even though such a relationship was only shown for proteinuria and hyperlipidemia. By comparison, there were more adjustments in doses in the Myfortic arm for leucopenia and for viral infections, particularly CMV infection. Gastrointestinal adverse events were higher only in female patients, but not male patients.

Although the adverse events and rates associated with everolimus should not be underestimated, they should also be taken in context. All immunosuppressant agents used (b) (4) eloped. Corticosteroids and azathioprine were used initially but were insufficiently effective and had safety findings. In A2309, the overall rate of adverse events exceeded 98% in the everolimus arm and in the control arm.

Cyclosporine was the first calcineurin inhibitor approved, and has a range of toxicities, most notably renal toxicity, which is paradoxical considering that it is used for prevention of rejection in kidney transplant, yet causes nephrotoxicity especially with chronic use. In A2309, the measure of renal function as GFR was comparable in the everolimus and Myfortic arms, while proteinuria was higher in the everolimus arm. This could be explained by the mechanisms of action of cyclosporine, constricting afferent arterioles, reducing GFR and reducing the amount of protein that can pass into the nephron and urine. Other CsA toxicities include hypertension, and less frequently hyperlipidemia. Cosmetic changes include gingival hyperplasia and hirsutism which are not serious but apparently cause great concern especially to female patients.

Tacrolimus when approved was associated with various neurotoxicities and new onset diabetes mellitus was a noteworthy toxicity. Examination of the Prograf package insert shows that a fair number of adverse events occur in greater frequency that the CsA control regimen.

Mycophenolate mofetil and mycopheloic acid are associated with leucopenias, often more gastrointestinal toxicity and viral infections, particularly CMV. Induction agents, such as the monoclonals and polyclonal have hypersensitivity reactions or immunotoxicity and may require pretreatment.

Other products have abandoned development for failing to demonstrate efficacy or for being associated with immediately life threatening toxicity (bradycardia, asystole, and potential sudden death).

Everolimus can be used effectively in a reduced cyclosporine regimen. While most transplant patients do develop adverse reactions on treatment (over 98% for all three arms of A2309), many are mild, and the severe or serious events need to be monitored and decisions can be made whether to continue treatment or switch to alternative therapy. It has been stated that sirolimus use is lower than the use of tacrolimus or cyclosporine, and some have expressed the opinion that tacrolimus is better than cyclosporine as its use has increased. To communicate some of the serious adverse events associated with everolimus, a REMS program has been submitted by Novartis and revised based on input from reviewers in the Division and OSE to include a Medication Guide and a Communication Plan. Given that there will now be a REMS for use with everolimus, postmarketing adverse event data on sirolimus will be examined to determine whether there is new safety information, as defined under FDAAA, to warrant use of a REMS and Medication Guide for the safe use of sirolimus.

The pediatric developed of everolimus has been waived, as summarized above.

There is no CDRH cleared device to measure everolimus concentrations for TDM at this time, although an application has been submitted to CDRH by Thermofisher and is currently on hold. Given there is no written Agency policy that a TDM device needs to be available at the time of approval, this is not considered a deficiency precluding approval. Novartis indicated that the LCMS assay used during clinical trials will continue to be available for monitoring of everolimus levels.

6. SUMMARY

An approval letter will be issued, which includes a REMS and a PMR for the 24-month data from study A2309.

The final labeling in PLR format, including the Medication Guide, as well as the approved REMS including the elements, goals, the Medication Guide, Communication Plan, and Timeline for Assessment will be appended to the approval letter.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
04/20/2010