CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-560s000

OTHER 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 5, 2010
To:	Renata Albrecht, MD, Director Division of Special Pathogen and Transplant Products
Through:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labels and Labeling Review
Drug Name(s):	Zortress (Everolimus) Tablets 0.25 mg, 0.5 mg, 0.75 mg
Application Type/Number:	NDA 021560
Applicant:	Novartis
OSE RCM #:	2009-1240-1

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Special Pathogens and Transplant Products (DSPTP) for a review of the revised Zortress labels and labeling in response to the Division of Medication Error Prevention and Analysis' (DMEPA's) previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2009-1240 dated December 23, 2009. Since the last review, the Applicant has decided not to market the 1 mg strength.

2 MATERIALS REVIEWED

DMEPA used Failure Mode and Effects Analysis[1] (FMEA) to evaluate the revised blister labels, carton and insert labeling submitted by the Applicant on February 3, 2010 and March 31, 2010. We also evaluated the recommendations in OSE review #2009-1240.

3 RECOMMENDATIONS

Review of the revised labels and labeling shows that the Applicant implemented all of DMEPA's recommendations under OSE review #2009-1240 that pertain to 0.25 mg, 0.5 mg, and 0.75 mg strengths. However, we note one correction is still required.

> Under the Dosage and Administration, Section 2.1, the statement "twice daily" is duplicated in the first sentence. Please remove one of the statements.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Karen Townsend, Project Manager, at 301-796-5413.

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

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/

JUDY J PARK
04/06/2010

CARLOS M MENA-GRILLASCA
04/06/2010

DENISE P TOYER
04/06/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: March 10, 2010

To: Jacquelyn Smith, Regulatory Project Manager
Division of Special Pathogen and Transplant Products (DSPTP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Sharon Watson, Regulatory Review Officer
Marci Kiester, DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager
DDMAC

Subject: NDA 21-560

DDMAC labeling comments for Zortress (everolimus) Tablets for oral administration

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In response to DSPTP's January 27, 2010, consult request, DDMAC has reviewed the draft product labeling (PI) for Zortress (everolimus) Tablets for oral administration (NDA 21-560). DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "Package Insert 1 27 10.doc" that was sent via email to DDMAC on February 26, 2010.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below). DDMAC's comments on the draft Medication Guide will follow under separate cover at a later date.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

31 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/

KATHLEEN KLEMM
03/10/2010

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 23, 2009
To:	Renata Albrecht, MD, Director Division of Special Pathogen and Transplant Products
Through:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labels and Labeling Review
Drug Name(s):	Zortress (Everolimus) Tablets 0.25 mg, 0.5 mg, 0.75 mg, 1 mg
Application Type/Number:	NDA 021560
Applicant:	Novartis
OSE RCM #:	2009-1240

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Special Pathogens and Transplant Products for the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate container labels, and carton and insert labeling for areas that could lead to medication errors. The Applicant submitted the labels and labeling on November 23, 2009.

1.1 REGULATORY HISTORY

The Applicant currently markets Afinitor (NDA 022334) which also contains the active ingredient, everolimus. Table 1 below shows the summary of difference between Zortress and Afninitor.

Table 1: Summary of Product Characteristics of Zortress and Afinitor

	Zortress (NDA 021560)	**Afinitor (NDA 022334)**
Indication	Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogenic renal transplant. It should be used in combination with cyclosporine USP Modified and corticosteroids.	Treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.
Strength	0.25 mg, 0.5 mg, 0.75 mg, 1 mg	2.5 mg*, 5 mg, 10 mg
Dose	1.5 mg/day to 3 mg/day	5 mg to 10 mg
Dosage Form	Oral Tablet	Oral Tablet
Frequency of Administration	Twice daily	Once daily
How Supplied	6 cards with 10 tablets per card	28 tablets/package; 2 blisters of 14 tablets per blister
Tablet Shape	Round	Elongated
Tablet side 1	C, CH, CL, CU	2.5, 5, UHE
Tablet side 2	NVR	NVR
Patient Monitoring	Whole blood trough levels	Not anticipated

2 METHODS AND RESULTS

DMEPA used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the container labels, carton labeling and insert labeling submitted on November 23, 2009 (see Appendices A

* 2.5 mg tablet is not yet marketed but was agreed to be pursued with the Agency to assist in titration needs

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

through D). DMEPA also compared the currently approved labels and labeling for Afinitor with the proposed container labels and carton labeling for Zortress (see Appendices E through G).

Additionally, Afinitor has been approved since March 2009; therefore DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on December 7, 2009, to determine if there are any medication errors associated with the currently marketed product. The MedDRA Higher Level Group Term (HLGT) Medication Error, the Preferred Term (PT) Product Quality Issue, active ingredient "everolimus" and trade name "Afinitor" were used as search criteria. The cases were manually reviewed to determine if medication errors occurred involving the labels or labeling.

We did not identify any cases of medication error related to the container labels, carton, or insert labeling for everolimus.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize medication errors. Section 3.1 *Comments to the Division*, contains our recommendations for the insert labeling. Section 3.2 *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

3.1 COMMENTS TO THE DIVISION

We have the following recommendations for the insert labeling:

3.1.1 Highlights and Full Prescribing Information

1. Delete abbreviations (e.g. b.i.d. or p.o. under *Dosage and Administration* section) throughout the labeling. FDA launched a national campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. As part of this campaign, FDA agreed not to approve such abbreviations in the approved labeling.

3.2 COMMENTS TO THE APPLICANT

We have the following recommendations for the container label and carton labeling:

3.2.1 Blister Labels – Sample and Trade

1. Relocate the dosage form so that it immediately follows the established name. Revise the presentation of the drug name as follows:

   Zortress
   (everolimus) tablet

2. Delete the trailing zero (i.e. 1.0 mg) on 1 mg strength.
3. Black font color is used to differentiate the strength on the 1 mg blister labels. However, on the carton labeling, the 1 mg is highlighted in orange. For consistency purposes, use only one color for the product strength (black or orange) on both the blister label and

carton labeling since all other strengths use the same strength color on the respective blister label and carton labeling.

4. Per 203.38(c), "each unit shall bear a label that clearly denotes its status as a drug sample, e.g., "sample," "not for sale," "professional courtesy package." Revise accordingly if space permits.

3.2.2 Trade Carton Labeling

1. The blue triangular graphic highlights the net quantity statement, takes up more than 1/3 of the principal display panel and distracts from more relevant information. Remove or minimize the graphic so that it does not highlight the net quantity statement and compete in prominence with the proprietary name, established name, and product strength.
2. Relocate the dosage form so that it immediately follows the established name. Revise the presentation of the drug name as follows:

   Zortress
   (everolimus) tablet

3. Delete the trailing zero (i.e. 1.0 mg) on 1 mg strength.
4. Revise the net content statement to more accurately describe the content description (e.g. Carton contains 6 individual blister cards of 10 tablets).

3.2.3 Sample Carton Labeling

1. Relocate the dosage form so that it immediately follows the established name. Revise the presentation of the drug name as follows:

   Zortress
   (everolimus) tablet

5 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/

CARLOS M MENA-GRILLASCA
12/23/2009

DENISE P TOYER
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:	November 4, 2009
To:	Ozlem Belen MD, MPH **Deputy Director for Safety** **Division of Special Pathogens and Transplant Products**
Through:	Robert M. Boucher MD, MPH **Director** **Division of Pharmacovigilance II** Melissa M. Truffa RPh **Associate Director** **Division of Pharmacovigilance II**
From:	S. Christopher Jones PharmD, MS **Safety Evaluator** **Division of Pharmacovigilance II**
Subject:	Review of Select Adverse Events Associated with Everolimus
Drug Name(s):	Afinitor® (Everolimus) FDA Approved 3/30/2009 Certican® (Everolimus) NDA under Review
Application Type/Number:	NDA 022334 (Afinitor®) NDA 021560 (Certican®)
Applicant/sponsor:	Novartis
OSE RCM #:	2009-1525

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1 INTRODUCTION

This review summarizes Adverse Event Reporting System (AERS) crude reports of select adverse events associated with everolimus. Adverse events of interest were identified by the Division of Special Pathogens and Transplant Products (DSPTP) medical reviewers and include proteinuria, interstitial lung disease, thromboembolic events, thrombocytopenia, fluid collection or edema, and infections leading to death, hospitalization or prolongation of hospitalization. These events were selected based on known therapeutic class adverse effects of mammalian target of rapamycin (mTOR) inhibitors. Both sirolimus and everolimus are mTOR inhibitors. While the adverse event profile for sirolimus is well documented in the literature and clinical studies, less is known about everolimus.

Everolimus is the subject of two NDAs (21-560 and 22-334). DSPTP issued an approvable letter for NDA 21-560 (Certican®; Novartis, December 2002) in August 2004 citing ongoing safety concerns with dosing regimens of everolimus and cyclosporine in the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients; efficacy was not at issue. Novartis resubmitted the application June 30, 2009 for the prophylaxis of organ rejection in allogeneic renal transplantation only. (NDA 22-334 [priority review] is approved for the treatment of refractory advanced renal cell carcinoma as Afinitor® [Novartis; March 30, 2009]).

Due to remaining safety concerns with Certican® for the proposed indication, DSPTP is convening an advisory committee meeting on December 7, 2009 regarding the approval of the drug. In preparation for that meeting, DSPTP requested that the Division of Pharmacovigilance II conduct an AERS search for select adverse events of concern to DSPTP medical reviewers.

2 METHODS

Six AERS queries were conducted to retrieve reports of interest for Afinitor®, Certican®, and everolimus . All AERS reports were retrieved for review through October 15, 2009 using the criteria outlined in Table 1 below. Data mining scores were reviewed and are summarized in Table 3-Appendix.

Table 1 AERS Search Criteria

Drug Names	AERS Query	DSPTP Adverse Event of Interest	AERS Preferred Term Search
Afinitor Certican Everolimus	1	Proteinuria	1 individual preferred term Proteinuria
	2	Interstitial Lung Disease	29 preferred terms (including alveolar proteinosis) within the SMQ Interstitial Lung Disease (Narrow)
	3	Thromboembolic Events	SMQ Embolic & Thrombotic Events (Broad)
	4	Thrombocytopenia	5 individual preferred terms Thrombocytpenia, platelet count decreased, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, thrombotic microangiopathy
	5	Fluid Collection or edema	13 preferred terms within the "Total Fluid Volume Increased" Higher Level Term (HLT)
	6	Infections leading to death, hospitalization or prolongation of hospitalization	Higher Level Group Terms (HLGT) Bacterial Infectious Disorders, Viral Infectious Disorders and Fungal Infectious Disorders with death or hospitalization (deemed serious) as an outcome

SMQ=Standardized MedDRA Query

3 RESULTS

Table 2 Crude Counts of Reports for Select Adverse Events with Everolimus

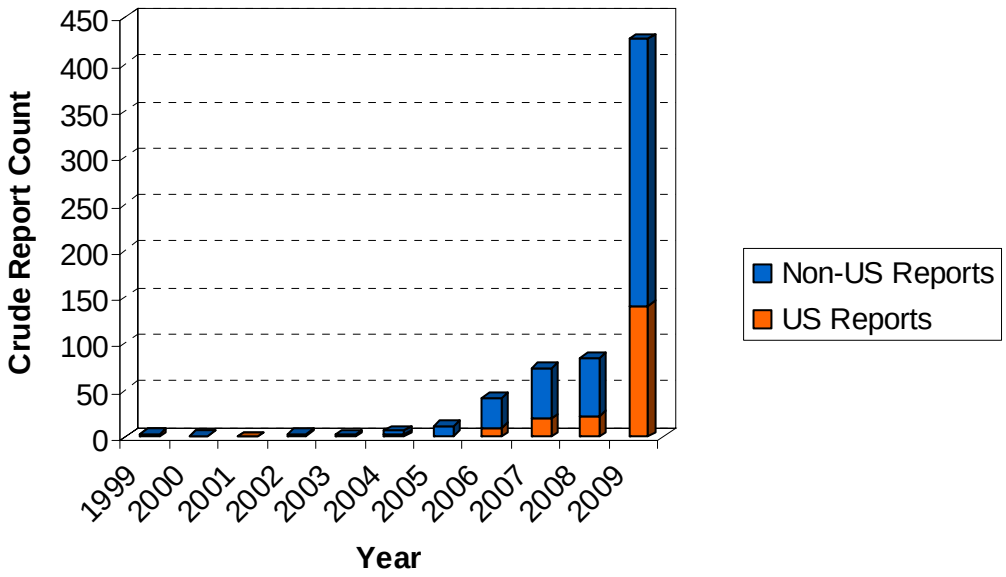
Reports of all Everolimus Adverse Events in AERS (n=653)	
Proteinuria (n=26)	**Interstitial Lung Disease (n=49)**
Age: (Mean±SD): 47±11.3 years	**Age:** (Mean±SD): 59±13.9 years
Gender: Male 20 Female 6	**Gender:** Male 34 Female 13 Unknown 2
Country of origin (reports): Austria 3, Australia 1, Belgium 1, Germany 2, Spain 2, France 3, Greece 1, Italy 7, Poland, 2 United States 4	**Country of origin (reports):** Argentina 1, Austria 1, Australia 2, Canada 2, Germany 8, Denmark 1, Spain 5, Finland 1, France 6, United Kingdom 1, Hungary 1, Italy 1, Japan 1, Korea 4, Norway 1, Taiwan 1, United States 11, Unknown 1
Outcome (reports): Death 1, Hospitalization 13, Other 12	**Outcome (reports):** Death 15, Disability 2, Hospitalization 25, Life threatening 4, Other 3
Everolimus Indication (reports): Renal Transplant 21 Transplant Unspecified 1 Renal Cell Carcinoma 1 Liver Transplant 1 Advanced Solid Tumor 1 Unknown 1	**Everolimus Indication (reports):** Renal Cell Carcinoma 13 Other Cancers 10 Renal Transplant 7 Liver Transplant 4 Heart Transplant 4 Lung Transplant 4 Transplant Unspecified 3 Unknown 3 Cardiac Allograft Vasculopathy 1
Thromboembolic Events (n=75)	**Thrombocytopenia (HUS, TTP, TMA) (n=50)**
Age: (Mean±SD): 59±12.2 years	**Age:** (Mean±SD): 54±13.6 years
Gender: Male 43 Female 19 Unknown 13	**Gender:** Male 27 Female 13 Unknown 10
Country of origin (reports): Australia 4, Belgium 2, Brazil 1, Canada 3, Switzerland 1, China 1, Germany 11, Denmark 1, Spain 1, France 11, United Kingdom 1, India 1, Italy 3, Japan 1, Korea 3, Netherlands 1, Norway 3, United States 24, Unknown 2	**Country of origin (reports):** Australia 3, Belgium 2, Brazil 1, China 1, Germany 10, Spain 1, France 7, Israel 1, India 1, Japan 2, Korea 1, Norway 1, Russia 1, Thailand 1, Turkey 1, United States 15, Unknown 1
Outcome (reports): Death 19, Hospitalization 37, Life threatening 5, Other 14	**Outcome (reports):** Death 13, Hospitalization 23, Life threatening 2, Other 12
Everolimus Indication (reports): Renal Transplant 20 Renal Cell Carcinoma 13 Heart Transplant 12 Other Cancers 7 Stem Cell Transplant 6 Gliobastoma Multiforme 4 Lung Cancer 4 Other 4 Breast Cancer 3 GVHD 2	**Everolimus Indication (reports):** Other Cancers 13 Renal Transplant 12 Stem Cell Transplant 7 Renal Cell Carcinoma 6 Lung Transplant 5 Liver Transplant 3 Cytomegalovirus 1 Graft Versus Host Disease 1 Heart Transplant 1 Unknown 1

HUS= Hemolytic uremic syndrome TTP= Thrombotic thrombocytopenic purpura TMA= Thrombotic microangiopathy

Table 2 Continued. Crude Counts of Reports for Select Adverse Events with Everolimus

Fluid Collection or Edema (n=65)	**Infections (n=101)**
Age: (Mean±SD): 59±14.6 years	**Age:** (Mean±SD): 54±15.5 years
Gender: Male 47 Female 16 Unknown 2	**Gender:** Male 63 Female 34 Unknown 4
Country of origin (reports): Argentina 1, Austria 4, Australia 1, Belgium 2, Brazil 2, Canada 3, Germany 5, Denmark 1, Spain 2, France 8, United Kingdom 3, Greece 1, Israel 1, Japan 2, Korea 1, Norway 1, Sweden 1, United States 22, South Africa 1, Unknown 3.	**Country of origin (reports):** Argentina 1, Australia 3, Brazil 2, Colombia 1, Germany 12, Spain 7, France 17, United Kingdom 3, Hong Kong 1, Italy 2, Japan 5, Korea 5, Netherlands 3, Sweden 2, Thailand 1, Turkey 3, Taiwan 5, United States 25, Unknown 3
Outcome (reports): Death 8, Hospitalization 42, Life threatening 7, Other 8	**Outcome (reports):** Death 23, Hospitalization 71, Life threatening 7
Everolimus Indication (reports): Renal Transplant 21 Heart Transplant 10 Other Cancers 11 Renal Cell Carcinoma 9 Liver Transplant 4 Lung Transplant 2 Pancreatic Cancer 2 Liver Cancer 2 Gliobastoma Multiforme 2 Unknown 2	**Everolimus Indication (reports):** Renal Transplant 38 Hepatic Transplant 10 Renal Cell Carcinoma 10 Heart Transplant 8 Lung Transplant 5 Pancreatic Cancer 5 Other Cancers 15 Other Transplant 5 Other 3 Unknown 2

Figure 1. Reporting Trend for AERS Everolimus Crude Report Counts (n=653) Through 10-15-2009



4 DISCUSSION

This review provides a broad overview rather than a detailed summary of crude AERS reports of adverse events of interest to DSPTP (see Table 1) with everolimus therapy. As these are crude reports, they have not been reviewed in detail to evaluate temporal or causal associations and have not been de-duplicated. Morevoer, since everolimus is usually part of a multidrug regimen, establishing causation using non-controlled AERS data remains difficult even with detailed case review. Many adverse events cited are from Afinitor® controlled trials and are currently labeled events. For example, the Warnings and Precautions section contains a warning for non-infectious pneumonitis, infections, and decreased platelets listed as causally associated with everolimus in the treatment of renal cell carcinoma.

Everolimus is cited in over 650 domestic AERS reports and the drug is commercially available in over 60 countries[1]; with reports originating from a total of 42 countries. The United States is the predominant country of origin for everolimus AERS reports and reporting significantly increased in 2009 (see Figure 1). Nearly all reports evaluated in this review were submitted through the sponsor with <3% direct reports to the FDA.

Reports generally refer to male everolimus users around the fifth decade of life using the drug for prevention of transplant rejection or treatment of cancer. Roughly two-thirds of all everolimus AERS reports are in males and describe DSPTP events of interest. A large percentage of reports indicate an outcome of death or hospitalization. Because many of these patients were given the drug for transplant-related indications or cancer treatment, it is very likely that many of them have indications or co-morbidities, or both, that predispose to hospitalization or death. Given these circumstances, establishing causation would be challenging, if not impossible.

AERS contains cases of proteinuria, a DSPTP adverse event of interest due to everolimus being implicated in post renal transplant proteinuria. As proteinuria is not a labeled event with Afinitor® these reports were reviewed in more detail. The proteinuria case series (n=26) review suggests that everolimus is the probable or possible cause of proteinuria in 18 of 26 cases. Proteinuria reports had a higher percentage of renal allograft rejection indications compared to other adverse events evaluated in this review. Approximately 80% (21/26) of the proteinuria reports indicate everolimus use for renal allograft rejection prevention. Everolimus associated proteinuria is reported in the literature.[2]

Potential adverse event data mining signals for everolimus are summarized in Table 3 of the Appendix. There are several preferred terms identified as signals which are associated with interstitial lung disease, thromboembolic events, thrombocytopenia, fluid collection, serious infections and proteinuria. Some of these event scores are highlighted in the table. Higher scores reflect a disproportionate reporting of the adverse event for everolimus compared to that event for all other drugs in the AERS database. While the data in Table 3 should not be interpreted as suggesting a causal association between the adverse event and the drug, it does represent disproportionate reporting of the event.

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[1] FDA meeting minutes with Novartis, May 6, 2009 located at \\Cdsesub1\evsprod\NDA021560\0010

[2] Bertoni E, Bruschi M, Candiano G, Boccardi C, Citti L, Mangraviti S, Rosso G, Larti A, Rosati A, Ghiggeri GM, Salvadori M, Posttransplant proteinuria associated with everolimus. Transplantation Proceedings 2009 41: 1216-1217.

5 CONCLUSIONS

The review provides crude descriptive data of AERS reports for interstitial lung disease, thromboembolic events, thrombocytopenias, fluid collection and serious infections, that occurred concurrent with everolimus therapy. While AERS contains everolimus reports for these events, temporal or causal associations should not be implied in a review of crude data only. In aggregate, most reports for adverse events of interest describe events which refer to male users around the fifth decade of life using everolimus to prevent graft rejection or in the treatment of cancer. A large majority experienced an outcome of death or hospitalization, possibly an outcome of the indicated underlying disease or co-existing medical conditions, or both. Data mining scores suggest disproportionate reporting of adverse events of interest. In the majority of AERS cases of proteinuria, the reporter attributed proteinuria to everolimus use. (This association is reported in the literature).

6 APPENDIX-DATA MINING

Table 3. Data Mining Scores with EB05≥2 Sorted by Descending EB05

Preferred Term	N	EBGM	EB05	EB95	PRR
Lymphocele	16	68.23	44.18	101.644	357.199
Nephropathy toxic	37	43.606	32.97	56.791	94.417
Thoracic cavity drainage	6	68.348	32.336	130.867	715.674
Kidney transplant rejection	30	41.495	30.377	55.612	97.163
Pericardial drainage	5	62.293	26.357	129.36	496.996
Concomitant disease progression	17	37.18	24.409	54.745	150.362
Haemolytic uraemic syndrome	13	32.555	20.008	50.648	57.068
Proteinuria	30	21.348	15.616	28.62	36.664
Transplant rejection	19	22.578	15.13	32.622	67.622
Immunosuppressant drug level increased	8	28.946	14.172	52.316	140.328
Pneumonitis	24	16.978	11.669	23.732	27.153
Blood creatinine increased	101	13.209	11.122	15.56	14.864
Lung infiltration	24	14.251	9.15	20.33	19.963
Liver transplant rejection	8	23.476	8.159	44.31	66.004
Kidney fibrosis	7	26.221	7.95	51.92	69.579
C-reactive protein increased	35	11.035	7.602	15.206	21.121
Central venous catheter removal	4	51.893	6.385	132.525	1669.907
Abscess drainage	7	23.504	6.132	48.113	135.293
Malignant neoplasm progression	40	6.913	5.225	9.151	22.91
Wound dehiscence	10	14.251	5.164	28.079	62.59
Renal impairment	39	6.312	4.787	8.271	9.85
Nephrectomy	6	23.609	4.754	54.177	97.088
Glomerular filtration rate decreased	8	15.769	4.612	34.274	83.495
Pyrexia	141	5.141	4.468	5.893	5.415
Thrombotic microangiopathy	10	11.301	4.396	24.343	43.172
Pericardial effusion	18	6.764	4.302	11.226	16.407
Pseudomonas infection	12	8.306	4.135	17.547	27.065
Complications of transplanted kidney	8	12.937	4.037	30.555	70.609
Cytomegalovirus infection	15	6.093	3.773	10.328	24.83
Metastases to liver	13	6.476	3.738	12.49	23.814
Pleural effusion	36	4.91	3.707	6.411	10.724
Productive cough	15	5.891	3.68	9.732	14.181
Hypoxia	21	5.3	3.645	7.58	8.43
Renal failure acute	61	4.244	3.425	5.211	8.324
Lung infection	12	5.826	3.388	10.867	29.126
Haematoma evacuation	4	33.427	3.354	100.838	521.846
Abdominal cavity drainage	4	32.784	3.302	99.748	695.794
Renal tubular atrophy	5	20.054	3.265	58.829	117.269
Lung disorder	19	4.774	3.232	6.886	6.987
Enterococcal infection	9	6.765	3.219	17.181	35.313
Hypokalaemia	21	4.53	3.131	6.4	6.854
Deep vein thrombosis	27	4.292	3.104	5.821	8.208
Ascites	18	4.624	3.099	6.723	10.873
Leukopenia	23	4.407	3.099	6.127	2.851
Lung consolidation	7	9.146	3.097	27.347	42.912
Drug level increased	12	5.125	3.079	8.517	13.714
Haemoptysis	16	4.688	3.061	6.989	11.548
Escherichia infection	9	5.817	2.991	13.723	22.758
Drug level decreased	8	6.174	2.891	16.819	25.111
Heart transplant rejection	5	15.688	2.876	51.707	112.225
Haematuria	16	4.276	2.8	6.332	5.037

Preferred Term	N	EBGM	EB05	EB95	PRR
Pneumocystis jiroveci pneumonia	10	4.895	2.796	8.601	22.788
Sepsis	38	3.616	2.754	4.679	5.818
Urinary tract infection	28	3.714	2.703	5.005	6.674
Anaemia	51	3.406	2.695	4.26	5.55
Renal tubular necrosis	10	4.675	2.693	7.97	11.76
Disease progression	29	3.632	2.659	4.87	10.635
Dyspnoea exertional	13	4.25	2.654	6.569	11.742
Chronic allograft nephropathy	5	12.883	2.65	46.548	168.337
Oedema	19	3.886	2.64	5.565	2.886
Thrombocytopenia	36	3.424	2.589	4.46	3.553
Cough	40	3.336	2.559	4.289	4.364
Pneumothorax	9	4.531	2.533	7.951	15.747
Interstitial lung disease	19	3.656	2.484	5.232	13.3
Rales	7	5.189	2.47	14.133	17.808
Haemoglobin decreased	33	3.25	2.426	4.28	6.46
Blood urea increased	16	3.692	2.422	5.445	3.832
Pneumonia	55	2.997	2.392	3.718	5.165
Blood lactate dehydrogenase increased	14	3.729	2.376	5.643	5.51
Abdominal pain	46	3.04	2.375	3.845	2.462
Diarrhoea	82	2.844	2.365	3.396	3.531
Endotracheal intubation	6	5.804	2.348	20.607	53.182
Oedema peripheral	48	2.974	2.335	3.743	3.659
Hyperglycaemia	18	3.467	2.331	5.006	2.895
Dehydration	39	3.029	2.316	3.906	5.762
Lobar pneumonia	7	4.557	2.297	9.717	25.171
Drug interaction	39	2.973	2.273	3.834	3.532
Aspergillosis	7	4.482	2.272	9.261	30.697
Pulmonary embolism	27	3.122	2.26	4.228	5.423
Lung transplant rejection	4	15.68	2.259	68.055	201.194
Dyspnoea	93	2.629	2.212	3.107	3.142
Hyponatraemia	18	3.217	2.164	4.643	4.561
Hypophagia	13	3.412	2.138	5.231	9.56
Oxygen saturation decreased	12	3.466	2.13	5.401	6.538
Pulmonary oedema	16	3.235	2.123	4.766	4.352
Basal cell carcinoma	8	3.797	2.083	6.557	24.905
Electrolyte imbalance	7	3.991	2.08	7.332	11.865
Haematocrit decreased	13	3.294	2.065	5.048	6.171
General physical health deterioration	22	2.938	2.053	4.101	9.634
Multi-organ failure	18	3.048	2.05	4.398	8.291
Mental status changes	14	3.198	2.039	4.83	10.469

The reviewer used the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm applied to the AERS database. The MGPS uses a Bayesian model to calculate adjusted observed versus expected ratios of drug-adverse event associations (Empiric Bayes Geometric Mean [EBGM] values). Moreover, a 90% confidence interval is calculated with the lower bound denoted as EB05 and the upper bound EB95. The higher the adjusted reporting ratio, or EBGM value, the greater the strength of the association between a drug and an adverse event. For example, an EBGM of three for a drug-event combination suggests that the event is associated with the drug 3 times more often than would be expected based on that event compared to all other drugs in the AERS database. PRR = proportional reporting ratio.

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

STEVEN C JONES
11/04/2009

MELISSA M TRUFFA
11/04/2009

ROBERT M BOUCHER
11/04/2009

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 30, 2004

TO: Arturo Hernandez, MD, Medical Officer
Division of Special Pathogen and Immunologic Drug Products, HFD-590

FROM: Rita Ouellet-Hellstrom, Ph.D., Epidemiologist
Andrew D. Mosholder, M.D., M.P.H., Epidemiologist

THROUGH: Mark Avigan, MD, CM, Director
Division of Drug Risk Evaluation, HFD-430

DRUG: Certican® (everolimus)
Immunosuppressant, TOR inhibitor

APPLICANT: Novartis

NDA: 21-560
21-628

PID: D040351

SUBJECT: Validity assessment of cross-study comparisons

1 EXECUTIVE SUMMARY[1]

Certican (everolimus) Tablet is a macrolide immunosuppressant proposed for use in the prophylaxis of organ rejection in allogeneic heart (NDA 21-628) and kidney (NDA 21-560) transplantations. Novartis Pharmaceuticals Corporation submitted the original NDAs on December 19, 2002, which received an approvable action on October 17, 2003. The sponsor's re-submission of these NDAs on February 27, 2004, relies heavily on analyses of the efficacy and safety across studies. The Division of Drug Risk Evaluation (DDRE) was consulted on June 6, 2004 by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) to assess the validity of these cross-study comparisons, specifically the comparison of pooled results of studies B201 and B251 with A2306 and the comparison of results of study B156 with A2307.

DDRE concludes that the sponsor has not provided adequate justification for cross study comparisons using historical controls in the analyses of efficacy and safety of studies A2306 and A2307.

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[1] The informa ion contained in this document was discussed with the review division (HFD-590) in a teleconference on August 25, 2004 and summarized in the teleconference minutes.

The sponsor's use of historical controls in this case does not provide adequate comparators to stand on its own. Due to dissimilarities in study design and in the methods used for dosage adjustments with cyclosporine, comparisons of results are difficult to interpret and may be due to patient and/or donor differences. Use of cross-study comparisons are useful mostly for hypotheses generating and the identification of significant risk factors. These, however, may not be sufficient as the basis for regulatory decisions.

Patient and donor characteristics are not comparable (e.g., there were more African American patients enrolled in Study B251 compared to Studies B201 and A2306); therefore, it may be difficult to base safety and efficacy regulatory decisions solely on analyses of the pooled data from these studies.

2 BACKGROUND

This document is in response to a request from the Division of Special Pathogen and Immunologic Drug Products (DPIDP) and the Division of Biometrics III to assist in evaluating the validity of cross-study comparisons to support the Certican® (everolimus, RAD) Tablet NDA application. Certican® was approved in Sweden in July 2004 and it is being reviewed by the other European nations through the European Union mutual recognition process.

On December 19, 2002, New Drug Applications (NDA) Nos. 21-560 and 21-628 were submitted for the use of the Certican® (everolimus, RAD) tablet for the prophylaxis of organ rejection in adult renal and heart transplant patients, respectively. The original submission contained efficacy and safety data from two renal transplants studies (B251 and B201) and one heart transplant study (B253). The original submission also included the Phase 2 supportive studies B156 and B157.

DPIDP completed an initial review of these applications and determined that the NDA was approvable[1] but expressed concern about increased renal toxicity when used with cyclosporine. Before approving these applications, DPIDP requested that the sponsor establish a dosing regimen of RAD and cyclosporine that would be both safe and effective for the prophylaxis of organ rejection in allogeneic renal and cardiac transplant patients. The division requested that the submission include the following:

- Information supporting a safe and effective dosing regimen for RAD and cyclosporine that would minimize renal function and toxicity impairment while maintaining adequate protection against graft rejection, graft loss or death in de novo renal transplantation and also in de novo cardiac transplantation either through
    - A well- controlled study or studies prospectively evaluating concentration-controlled regimens of RAD in combination with concentration- controlled cyclosporine in de novo renal transplant recipients, which would support therapeutic dose monitoring (TDM) schemes for RAD and cyclosporine (renal and cardiac transplantations); or
    - Prospective analyses from completed, controlled studies evaluating lower exposures to cyclosporine in combination with RAD, and dosed according to a prospectively defined therapeutic drug monitoring scheme (TDM) (renal transplantations); or
    - Use of other designs to be discussed with the Division before implementation in studies of patients undergoing renal and cardiac transplantation.

DPIDP emphasized that the data and analyses that determine a therapeutic concentration range in de novo renal transplantation would need to identify a clinically efficacious and safe concentration range of RAD (upper as well as lower limits) when used with the proposed cyclosporine concentration range. In addition, a safe and effective TDM regimen for RAD, used in combination with cyclosporine, would also require a validated assay for RAD blood levels, and need to be supported by experience with a successful

monitoring schedule and dose adjustment scheme, proven capable of maintaining patients within the proposed therapeutic concentration range.

In response to DPIDP's request for additional efficacy and safety data, the sponsor submitted, on February 10, 2004, two new phase 3b studies for *de novo* renal patients, A2306 and A2307. The new clinical information is provided to support the safety and effective use of Certican® (RAD) in renal and heart transplantation including the completed 12 month results of two controlled studies in de novo renal transplantation, studies A2306 and A2307**.** The submission is considered a complete response to DPIDP's request for additional information.

In these studies, therapeutic drug monitoring (TDM) was prospectively evaluated and the sponsor considers that the feasibility and utility in monitoring patients prior to cyclosporine dose reduction has been demonstrated. The sponsor considers the results from the open-label studies A2306 and A2307 demonstrate an improvement in the safety while maintaining efficacy.

Because the analysis includes comparing data obtained in the new open-label studies with data from the randomized phase 3 renal studies B201, B251, and B156 (B157) effectively relying on cross-study comparisons, DPIDP requested assistance from the Office of Drug Safety (ODS) to determine the validity of such comparisons. The problems with interpreting externally controlled trials are well known and are discussed in the ICH E10 Guidance[2].

3 STUDY DESIGN

The original registration trials (B251 and B201) were randomized, double blind, double dummy, active controlled trials with 2 grams of mycphenolate mofetil (MMF), multicenter studies designed to test efficacy, safety, and pharmacokinetics in *de novo* renal transplant patients, and B253 was double blind, double dummy, active controlled with azathioprine[2] 1.0 mg or 3.0 mg per kilogram of body weight, multicenter studies designed to test efficacy, safety, and pharmacokinetics in *de novo* heart transplant patients. In addition to RAD or the comparator drug, the treatment regimen included cyclosporine, corticosteroids, and statins. The primary efficacy end point was a composite of death, graft loss or re-transplantation, loss-to-follow-up, biopsy-proved acute rejection of grade 3A, or rejection with hemodynamic compromise. All three studies were initially designed to be a one-year study, but all were extended an additional two years as open-label to provide long-term safety data. The sponsor's Table 1.1-1 summarizes the study designs in the submission.

[2] AZASAN™ (azathioprine) is an immunosuppressive antimetabolite available in tablet form for oral administration. Each scored tablet contains 25 mg, 50 mg, 75 mg or 100 mg azathioprine and the inactive ingredients lactose monohydrate, pregelatinized starch, povidone, corn starch, magnesium stearate, and stearic acid.

Table 1.1-1 Summary of key and supportive studies

Study no.	Design	Duration	No. of patients/study drug
	Key renal safety population		
B251	R, DB, DD, AC, MC, MD, E, S, PK, *de novo*	3 years (1 year DB/2 years OL by amendment)	Total – 583 RAD 1.5 mg – 193 RAD 3 mg – 194 MMF 2 g – 196
B201	R, DB, DD, AC, MC, MD, E, S, PK, *de novo*	3 years (1 year DB/2 years OL by amendment)	Total - 588 RAD 1.5 mg – 194 RAD 3 mg – 198 MMF 2 g – 196
	Supportive renal safety population		
B156	R, OL, MC, MD, E, S, *de novo*, w/Simulect	3 years	RAD 3 mg – 111 (full dose Neoral – 53 & reduced dose Neoral – 58)
B157	R, DB, MC, MD, S, T, PK, *de novo*	3 years (1 year DB/2 years OL ext.)	Total - 103 RAD 1 mg – 34 RAD 2 mg – 34 RAD 4 mg – 35
	Key heart safety population		
B253	R, DB, DD, AC, MC, MD, E, S, PK, *de novo*	3 years (1-year DB/1 year OL by amendment) + 1-year OL ext	Total – 634 RAD 1.5 mg – 209 RAD 3 mg – 211 AZA 1-3 mg/kg/day – 214

AC = active controlled, DB = double blind, DD = double dummy, E = efficacy, MC = multicenter, MD = multiple dose, OL = open label, PK = pharmacokinetics, R = randomized, S = safety, and T = tolerability.
Note: Includes all data as reported in the 12-month CSRs for all studies.

Studies B156 and B157 were Phase 2 dose evaluation studies and have been submitted originally to support the proposed doses (1.5 mg. and 3.0 mg) in the pivotal studies.

To address the DPIDP's concern about renal function and toxicity impairment with RAD requesting either prospective or retrospective well controlled analyses of studies that used therapeutic drug monitoring schemes, the sponsor submitted study A2306 and A2307. Table 1.1-2 summarizes the design of these two studies.

Table 1.1-2 Renal studies A2306 and A2307

Study no.	Study design	Duration	No. of subjects
2306	R, OL, MC, MD, E, S, T, *de novo*, with reduced Neoral by C_2 monitoring	1 year	Total – 237 RAD 1.5 mg – 112 RAD 3 mg – 125
2307	R, OL, MC, MD, E, S, T, *de novo*, with Simulect and with reduced Neoral by C_2 monitoring	1 year	Total – 256 RAD 1.5 mg – 117 RAD 3 mg – 139

E = efficacy, MC = multicenter, MD = multiple dose, OL = open label, R = randomized S = safety, and T = tolerability.
Note: All black patients were assigned to the RAD 3 mg group in both studies.

In study A2307, low- dose Neoral®[3] was used from Day 1 in combination with Simulect[4]®, while in study A2306, Neoral® exposure more representative of the pivotal trials was used for the first month post-transplantation followed by Neoral reduction based on total dose monitoring (TDM).

[3] Cyclosporine (CSA), the active principle in Neoral ®, is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nivea* .

The new analysis compared the pooled results of studies B201 and B251 with A2306 and the comparison of results of study B156 with A2307.

Revised analysis of Certican (everolimus) Safety; Summary of Comparisons Groups	
B201 and B251: key renal safety population	A2306: follow-up renal dosing study
B156: supportive renal safety study	A2307: follow-up renal dosing study

4 COMMENTS - Division of Drug Risk Evaluation (DDRE)

4.1 Inadequate justification

The sponsor's submittal included analyses that combined B201 and B251 mycophenolate mofetil (MMF) comparator populations as the reference population for the additional studies, the sponsor has not adequately provided documentation on the reasons for doing so. It can be assumed that the combination was done because both MMF populations were treated with the same immunosuppressant at the same dose. Patient and donor characteristics differ in both B201 and B251 studies and it is assumed that the sponsor wanted to combine the two populations to make the pooled data more similar to A2306. At various sections of the analyses, the sponsor presents analyses with and without African Americans included, attempts to adjust for donor age, but overall, there is no systematic analysis or justification for doing this.

4.2 Design and Method Dissimilarities

B201, B251, and B253 were all randomized, double blind, double dummy, active controlled trials designed to test efficacy, safety, and pharmacokinetics in *de novo* renal transplant patients. B156 and B157 were Phase 2 open-label, dose evaluation studies. A 2306 and A2307 are open-label, supposedly randomized (although African Americans were all treated with RAD 3 mg) trials with reduced cyclosporine by monitoring and no prospective active controls. Historical controls differ in demographic and donor characteristics (Section 4.3).

Patients for B201 were from Austria, Australia, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Norway, Russia, South Africa, Spain, Switzerland, and the United Kingdom (UK).

Patients for B251 were from Argentina, Brazil, Canada, and the United States (US).

Patients for B253 were from the US.

Patients for B156 were from the US, France, Germany, and Italy.

Patients for B157 were from the US, Canada, UK, and Germany.

[4] Simulect ® (basiliximab) is a chimeric (murine/human) monoclonal an ibody (IgG $_{1[kgr]}$), produced by recombinant DNA technology, that functions as an immunosuppressive agent, specifically binding to and blocking the interleukin-2 receptor (alpha)-chain (IL-2R(alpha), also known as CD25 antigen) on the surface of activated T-lymphocytes.

Patients for A2306 were from the US, Canada, Brazil, Italy, Belgium, Poland, Spain, and Venezuela.

Patients for A2307 were from the US, Argentina, Australia, Columbia, Chile, Czech Republic, France, Germany, Switzerland, and Norway.

4.3 Patient and Donor Characteristics

Patient and donor characteristic of the **mycophenolate mofetil (MMF) treated groups are relatively balanced with their respective randomized study groups but** differ between themselves (Table A).

Table A. Patient and Donor Differences in Mycophenolate mofetil (MMF Studies

MMF		B201	B251	Combined	Ratio (IND-MMF/Combined)	
N		%	%	%	B201 MMF	B251 MMF
Age	Mean	46.1	43.4	44.8	1.0	1.0
Sex	Male	70.9	67.3	69.1	1.0	1.0
Race	Caucasian	87.2	65.8	76.5	1.1	0.9
	Black	5.6	16.8	11.2	0.5	1.5
Weight (kg)		71.2	78.7	75.0	0.9	1.0
Height (cm)		171	171	171	1.0	1.0
Diabetes		6.1	24.5	15.3	0.4	1.6
ESRD	Glomerular	40.3	21.9	31.1	1.3	0.7
	Polycystic	17.3	15.3	16.3	1.1	0.9
	Hypertension	12.8	17.3	15.1	0.8	1.2
	Diabetes	3.1	21.9	12.5	0.2	1.8
Donor	Cadaveric	90.8	45.9	68.4	1.3	0.7
	Living	9.2	54.1	31.6	0.3	1.7
DGF		19.9	5.6	12.8	1.6	0.4

The two MMF comparator groups differ on race (B201 has fewer African Americans), presence of diabetes at the time of transplant, cadarveric versus living donor organ, and delayed graft function (DGF) characteristics, all factors that influence graft outcome. According to the sponsor when evaluating patient and donor characteristics using a multivariate analysis, donor age appeared to be an important predictive variable. Donor age, however, is not presented with the demographic and other donor characteristics.

Table B compares the population characteristics of the combined MMF population used as a comparator with A2306. It must be kept in mind, however, that all African Americans were treated with 3 mg of RAD in A2306. Consequently, differences observed when comparing 1.5 mg RAD with the combined population are not easily interpretable since differences could all be attributed to the racial differences. African Americans, if they receive transplants at all, are at increased risk of allograft loss as a result of possible immunologic and non-immunologic factors[3,4]. Comparing a RAD study group containing no African Americans with the combined MMF population that has an 11% African Americans population would artificially skew the results in favor of the RAD 1.5 mg group. In addition to race, the compared populations differ in the proportion of diabetics, donor organ types, cause of their end stage renal disease (ESRD) and delayed graft function, all of which has an effect on outcome. Such differences make interpretation of outcome differences difficult at best.

Table B. Patient and Donor Characteristic for A2306 Study Compared to the Combined MMF

B251		1.5 mg Mean	3.0 mg Mean	Combined MMF Mean	Ratio (RAD/MMF) 1.5 mg	Ratio (RAD/MMF) 3.0 mg
Age		42.5	42.8	44.8	0.9	1.0
Weight (kg)		68.9	70.1	75.0	0.9	0.9
Height (cm)		168	167	171	1.0	1.0
B251		**1.5 mg %**	**3.0 mg %**	**Combined MMF %**	**Ratio (RAD/MMF) 1.5 mg**	**Ratio (RAD/MMF) 3.0 mg**
Sex	Male	62.5	53.6	69.1	0.9	0.8
Race	Caucasian	78.6	66.4	76.5	1.0	0.9
	Black	0.0	12.0	11.2	0.0	1.1
Weight (kg)	Mean	68.9	70.1	75.0	0.9	0.9
Height (cm)	Mean	168	167	171	1.0	1.0
Diabetes		8.9	7.2	15.3	0.6	0.5
ESRD	Glomerular	26.8	30.4	31.1	0.9	1.0
	Polycystic	14.3	12.0	16.3	0.9	0.7
	Hypertension	10.7	16.8	15.1	0.7	1.1
	Diabetes	5.4	5.6	12.5	0.4	0.4
Donor	Cadaveric	26.8	30.4	31.1	0.9	1.0
	Living	40.2	34.4	31.6	1.3	1.1
DGF		13.4	16.8	12.8	1.1	1.3

The demographic donor differences may explain differences in outcome. As an example, Table C compares the 6-month and 12-month outcome between the B201 MMF and the B251 MMF comparison groups. Both groups received the same treatment with **mycophenolate mofetil (MMF) 2 grams. However, the groups differ in demographic and donor characteristics. Table C shows that MMF B201 has twice as many graft losses and deaths at 6 months compared to MMFB251. Tables D to F summarize patient characteristics for all studies.**

Table C. Six- and twelve-month outcome measurements for MMF 251 and MMF 201 patients.

	MMF (251)		MMF (201)	
N	**196**		**196**	
6 Months	**N**	**%**	**N**	**%**
Failure	51	26.4	58	29.9
Rejection	46	23.8	46	23.7
Graft loss/death	9	4.7	18	9.3
Graft loss	7	3.6	15	7.7
Death	2	1.0	3	1.5
Lost to Follow-up	0	0.0	0	0.0
	MMF (251)		**MMF (201)**	
N	**196**		**196**	
12 Months	**N**	**%**	**N**	**%**
Failure	54	28.0	61	31.4
Rejection	47	24.4	47	24.2
Graft loss/death	12	6.2	21	10.8
Graft loss	10	5.2	18	9.3
Death	4	2.1	5	2.6
Lost to Follow-up	1	0.5	1	0.5

5 CONCLUSIONS

- The sponsor has not provided adequate justification for their approach to rely on efficacy and safety analyses from studies A2306 and A2307 based on cross study comparisons using historical controls.
- The sponsor's use of historical controls in this case is not justified. Due to dissimilarities in study design and in the methods used for dosage adjustments with cyclosporine, comparisons of results are difficult to interpret and may be due to patient and/or donor differences. Use of cross-study comparisons are useful mostly for hypotheses generating and the identification of significant risk factors. These, however, may not be sufficient as the basis for regulatory decisions.
- Patient and donor characteristics are not comparable (e.g., there were more African American patients enrolled in Study B251 compared to Studies B201 and A2306); therefore, it may be difficult to base safety and efficacy regulatory decisions solely on analyses of the pooled data from these studies.

Table D Baseline demographics by treatment group (12-months ITT population)

		Mycophenolate mofetil ((MMF) 2 g)						A2306				A2307			
		B201		B251		Combined MMF		1.5 mg		3 mg		RAD 1.5		RAD 3 mg	
N		**196**	**%**	**196**	**%**	**392**	**%**	**112**	**%**	**125**	**%**	**117**		**139**	
Age	Mean	46.1		43.4		44.8		42.5		42.8		43.9		46.3	
	<50	112	57.1	126.0	64.3	238	60.7	76	67.9	82	65.6	73	62.4	72	51.8
	≥50	84	42.9	70.0	35.7	154	39.3	36	32.1	43	34.4	44	37.6	67	48.2
Sex	Male	139	70.9	132	67.3	271	69.1	70	62.5	67	53.6	81	69.2	87	62.6
	Female	57	29.1	64	32.7	121	30.9	42	37.5	58	46.4	36	30.8	52	37.4
Race	Caucasian	171	87.2	129	65.8	300	76.5	88	78.6	83	66.4	106	90.6	116	83.5
	Black	11	5.6	33	16.8	44	11.2	0	0.0	15	12.0	0	0.0	13	9.4
	Oriental	6	3.1	2	1.0	8	2.0	0	0.0	5	4.0	4	3.4	3	2.2
	Hispanic	0	0.0	24	12.2	24	6.1	13	11.6	14	11.2	4	3.4	4	2.9
	Other	8	4.1	8	4.1	16	4.1	11	9.8	8	6.4	3	2.6	3	2.2
Weight (kg)		71.2		78.7		75.0		68.9		70.1		73.6		74.6	
Height (cm)		170.8		171.0		170.9		168.3		166.9		170.5		170.4	
Diabetes		12	6.1	48	24.5	60	15.3	10	8.9	9	7.2	13	11.1	19	13.7
ESRD	Glomerular	79	40.3	43	21.9	122	31.1	30	26.8	38	30.4	32	27.4	41	29.5
	Polycystic	34	17.3	30	15.3	64	16.3	16	14.3	15	12.0	14	12.0	23	16.5
	Hypertensic	25	12.8	34	17.3	59	15.1	12	10.7	21	16.8	4	3.4	12	8.6
	Diabetes	6	3.1	43	21.9	49	12.5	6	5.4	7	5.6	10	8.5	15	10.8
Donor	Cadaveric	178	90.8	90	45.9	268	68.4	67	59.8	82	65.6	79	67.5	107	77.0
	Living	18	9.2	106	54.1	124	31.6	45	40.2	43	34.4	38	32.5	32	23.0
DGF		39	19.9	11	5.6	50	12.8	16	14.3	21	16.8	23	19.7	29	20.9
Donor Age	<50 years														
	≥ 50 years														

DGF - delayed graft function (exclusion criteria for B251 only)

MMF - mycophenolate mofetil (2g)

Table E Baseline demographics by treatment group, Phase 2

		B156 (RAD 3 mg)			
		Neoral Full Dose		Neoral Reduced Dose	
N		**53**	**%**	**58**	**%**
Age	Mean	45.9		43.9	
	<50	30	56.6	39	67.2
	≥50	23	43.4	19	32.8
Sex	Male	30	56.6	38	65.5
	Female	23	43.4	20	34.5
Race	Caucasian	36	67.9	47	81.0
	Black	13	24.5	10	17.2
	Oriental	2	3.8	1	1.7
	Hispanic		0.0		0.0
	Other	2	3.8	0	0.0
Weight (kg)		70.8		76.4	
Height (cm)		169.0		173.4	
ESRD	Glomerular	13	24.5	17	29.3
	Polycystic	7	13.2	9	15.5
	Hypertension/nephrosclerosis	13	24.5	7	12.1
	Diabetes	5	9.4	3	5.2
Diabetes		11	20.8	4	6.9
Donor	Cadaveric	41	77.4	48	82.8
	Living	12	22.6	10	17.2
DGF		8	15.1	4	6.9
Donor Age	<50 years				
	≥ 50 years				

Table F Baseline demographics by treatment group - B157

RAD		RAD 1mg/day		RAD 2mg/day		RAD 4 mg/day	
N		**34**	**%**	**34**	**%**	**35**	**%**
Age	Mean	43.6		44.2		46.1	
	<50	24	70.6	20	58.8	19	54.3
	=50	10	29.4	14	41.2	16	45.7
Sex	Male	22	64.7	19	55.9	25	71.4
	Female	12	35.3	15	44.1	10	28.6
Race	Caucasian	28	82.4	25	73.5	31	88.6
	Black	3	8.8	5	14.7	1	2.9
	Oriental	1	2.9	0	0.0	0	0.0
	Hispanic		0.0		0.0		0.0
	Other	2	5.9	4	11.8	3	8.6
Weight (kg)		73.6		76.1		78.8	
Height (cm)		168.4		170.0		172.5	
ESRD	Glomerular						
	Polycystic						
	Hypertension/nephrosclerosis						
	Diabetes						
	Obstructive/reflux						
Diabetes		13	38.2	4	11.8	7	20.0
Donor	Cadaveric	21	61.8	23	67.6	24	68.6
	Living	13	38.2	11	32.4	11	31.4
DGF							
Donor Age	<50 years						
	= 50 years						

6 REFERENCES

[1] Approvable letter for NDA 21-560 and NDA 21-628, October 20, 2003.

[2] USDHHS. Guidance for Industry E10 Choice of Control Group and Related Issues in Clinical Trials. May 2001 ICH.

[3] Gaston RS. Factors affecting renal allograft survival in African Americans. Blood Purif 1996; 327-333.

[4] Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, and Merion RM. Chronic renal failure after transplantation of a nonrenal organ. 2003; NEJM 349(10):931-940.

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/s/

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11/8/04 03:06:50 PM
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11/10/04 03:58:53 PM
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