

November 16, 2005  
Cardiovascular and Renal Drugs Advisory Committee  
NDA 21-628 Certican® (everolimus)  
FINAL MINUTES

**Food and Drug Administration  
Center for Drug Evaluation and Research**

Advisory Committee Conference Room, Rm. 1066, 5630 Fishers Lane, Rockville, MD.

Final Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting  
November 16, 2005

*The committee discussed new drug application (NDA) 21-628, proposed trade name Certican® (everolimus) Tablets (0.25 mg, 0.50 mg, 0.75 mg, 1.0 mg), Novartis Pharmaceuticals Corporation, for the proposed indication of prophylaxis of rejection in heart transplantation.*

These summary minutes for the November 16, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on November 28, 2005

I certify that I attended the November 16, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

\_\_\_\_\_  
//S//  
Cathy A. Groupe, R.N., B.S.N.  
Executive Secretary

\_\_\_\_\_  
//S//  
William R. Hiatt, M.D.  
(Acting) Chair

Quick Minutes  
Cardiovascular and Renal Drugs Advisory Committee Meeting  
November 16, 2005  
NDA 21-628 Certican® (everolimus)

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 16, 2005 at 5630 Fishers Lane, Advisors and Consultants Staff Conference Room, Rockville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsor (Novartis).

The meeting was called to order by William Hiatt, M.D., (Acting) Chair; the conflict of interest statement was read into the record by Cathy Groupe (Executive Secretary). Opening remarks were made by Renata Albrecht, M.D., Director, Division of Special Pathogen and Transplant Products. There were approximately 65 persons in attendance. There were no speakers for the Open Public Hearing session.

**Attendance:**

**CDER Cardiovascular and Renal Drugs Advisory Committee Members Present (voting)**

William R. Hiatt, M.D. (Acting Chair); David Demets, Ph.D.; Frederick J. Kaskel, M.D.; Thomas Pickering, M.D., D.Phil.; John R. Teerlink, M.D.

**CDER Cardiovascular and Renal Drugs Advisory Committee Consultants (voting):**

Gilbert J. Burckart, Pharm.D.; Susanna L. Cunningham, Ph.D. (Consumer Representative); Steven Nissen, M.D., F.A.C.C.; Paul Oldam (Patient Representative); Darrell R. Abernethy, M.D., Ph.D.; Roslyn Bernstein Mannon, M.D.

**CDER Advisory Committee for Pharmaceutical Science Consultants (voting):**

Raman Venkataramanan, Ph.D.

**CDER Pulmonary-Allergy Drugs Advisory Committee Consultants (voting):**

Michael A. Proschan, Ph.D.

**CDER Cardiovascular and Renal Drugs Advisory Committee Members Absent:**

Ronald J. Portman, M.D.; Lynn L. Warner Stevenson, M.D.; John F. Neylan, M.D. (Industry Representative)

**FDA Participants:**

Mark Goldberger, M.D., M.P.H.; Renata Albrecht, M.D.; Steven Gitterman, M.D.; Marc Cavaille-Coll, M.d., Ph.D.; Karen Higgins, Sc.D.; Arturo Hernandez, M.D.; Lt. LaRee Tracy, M.A.; Joga Gobburu, Ph.D.

**Issue:** New drug application (NDA) 21-628, Certican® (everolimus), Novartis Pharmaceuticals Corporation, for the proposed indication of prophylaxis of rejection in heart transplantation.

The agenda proceeded as follows:

Call to Order and Introductions	<b>William R. Hiatt, M.D.</b> Acting Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	<b>LCDR Cathy Groupe, B.S.N.</b> Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Welcome	<b>Renata Albrecht, M.D.</b> Director Division of Special Pathogen and Transplant Products CDER, FDA

**Novartis Pharmaceutical Corporation Presentation:**

Current Status and Future	<b>Marc L. Barr, M.D.</b>
---------------------------	---------------------------

Quick Minutes  
Cardiovascular and Renal Drugs Advisory Committee Meeting  
November 16, 2005  
NDA 21-628 Certican® (everolimus)

Challenges in Heart  
Transplantation

Associate Professor of Cardiothoracic Surgery  
Co-Director, Cardiothoracic Transplantation  
University of Southern California and Children's Hospital  
Los Angeles, California

Introduction and Regulatory  
Background

**Mathias Hukkelhoven, Ph.D.**  
Senior Vice President  
Global Head, Drug Regulatory Affairs  
Novartis Pharmaceuticals Corporation

Challenges and Opportunities  
In Cardiac Transplantation

**Howard J. Eisen, M.D.**  
Thomas J. Vischer Professor of Medicine  
Chief, Division of Cardiology  
Drexel University College of Medicine

Efficacy Results of Study B253  
In *De Novo* Heart Transplantation

**Jeffery D. Hosenpud, M.D.**  
Clinical Professor of Medicine  
University of Wisconsin

Intravascular Ultrasound (IVUS)  
Results – Study B253 *De Novo*  
Transplantation

**Jon A. Kobashigawa, M.D.**  
Clinical Professor of Medicine and Cardiology  
Chief, Division of Clinical Faculty Medicine  
The David Geffen School of Medicine at UCLA  
Medical Director, UCLA Heart Transplant Program

Safety of Everolimus

**Kenneth Somberg, M.D.**  
Vice President, Global Head of Clinical Research  
Transplantation and Immunology  
Novartis Pharmaceuticals Corporation

Renal Safety and Efficacy  
Extrapolation, Dose  
Recommendations

**Lawrence G. Hunsicker, M.D.**  
Professor of Medicine and Medical Director of Organ Transplantation  
Carver College of Medicine  
University of Iowa

Benefit/Risk Assessment

**Howard J. Eisen, M.D.**

**Food and Drug Administration Presentation:**

Statistical Overview of Study B253

**LT LaRee Tracy, M.A.**  
Statistician  
Office of Biometrics  
Division of Biometrics 3, CDER

Safety and Efficacy of  
Everolimus

**Arturo Hernandez, M.D.**  
Medical Officer  
Division of Special Pathogen and Transplant Products, CDER

Everolimus and Cyclosporine  
Exposure-Effectiveness and  
-Nephrotoxicity Relationships

**Joga Gobburu, Ph.D.**  
Team Leader, Pharmacometrics,  
Office of Clinical Pharmacology and Biopharmaceutics, CDER

**Committee Questions to the FDA**

**Lunch**

**Open Public Hearing**

**Committee Discussion**

**Break**

**Questions to the Committee**

**Adjournment**

**Questions to the Committee:**

1. Novartis has presented the results and extensively discussed the use of a 'fixed-dose' everolimus regimen with "full-dose" cyclosporine in study B253. Both FDA and Novartis agree that this exact fixed-dose regimen should not be used for the prophylaxis of organ rejection in cardiac transplantation. Do committee members agree with this conclusion?  
**YES: 13      NO: 0**
  
2. Novartis has proposed an alternative 'TDM-based' regimen for the use of everolimus in combination with cyclosporine. The proposed regimen has not been prospectively tested in a cardiac transplantation study. In the absence of a prospective study of this regimen, do committee members believe there is sufficient information available to conclude that the regimen as proposed by Novartis has been demonstrated to be safe and effective for use in heart transplantation?

**YES: 6      NO: 7**

**The committee commented that the one phase 3 study in heart transplant patients was positive on the primary endpoint. However this positive result was driven by a single component of the primary endpoint (biopsy-proven acute rejection) whereas there were no differences between the two regimes for the endpoints of acute rejection associated with hemodynamic compromise, graft loss, death or lost to follow up. In addition, there was an everolimus dose-independent short-term and long-term loss of renal function. Therefore a majority of the committee felt the risk benefit of an everolimus-based regime was not favorable using fixed-dosing.**

- a. In your discussion, please be specific regarding what information supports the proposed TDM-based regimen.

**The Committee commented that the single phase 3 study in heart transplant patients was primarily based on fixed doses of study drugs and therefore did not directly support the concept of therapeutic drug monitoring (TDM). However, the sponsor's proposed studies (one in Europe and one in the United States) should provide the means to support many of the reasonable extrapolations of the data, for the proposed TDM-based regimen. Additionally, members commented that therapeutic drug monitoring is quite appropriate for this patient population to minimize drug toxicity and maintain efficacy, as opposed to a fixed-dose regimen, and TDM is an established component of any transplant program. The committee cited, as supporting evidence for approval, the results from the German heart experience, the kidney transplant data and the post-hoc analysis of trial B253.**

***(See transcripts for detailed discussion)***

- b. Please discuss in your answer whether you believe that everolimus has been shown safe and effective for all cardiac transplant recipients.

**The committee felt that while everolimus was shown to be effective on the primary endpoint the safety of a fixed-dose regime was not yet established. Therefore additional data was necessary using TDM regimes to maintain everolimus in a therapeutic concentration and with rapid tapering of cyclosporin to minimize renal toxicity. The committee additionally commented that the everolimus heart transplantation study did suggest a potential benefit on post-transplant vasculopathy, providing a prospect for long-term benefits. However other committee members found significant methodologic problems with the intra-vascular ultrasound data that limited interpretation.**

***(See transcripts for detailed discussion)***

- c. Alternatively, please discuss whether you believe there are certain subgroups where use should be specifically indicated or specifically restricted

**The committee identified subgroup restrictions for everolimus therapy, specifically those patients with severe stage four kidney disease at baseline. There was insufficient information in women and Afro-Americans to know if changes should be made in dosing. Other subgroups identified by the committee include those with an increased risk of GI bleeds, for which risks may need to be considered. However there were no strong signals in the data presented to suggest that there were any subgroups that should be excluded or subgroups that were particularly responsive. Comments from the committee included the need for additional information about special patient populations such as African Americans, as there are pharmacogenic differences in this subgroup that need to be addressed.**

**Some of the committee caution against a subgroup approach given a limited amount of supporting data and that once TDM is established, decisions regarding subgroup restrictions should be left up to the expertise of the clinicians caring for these patients. Additional comments from the committee supported that, with the additional information provided through the sponsor's proposed studies, it will be possible to further analyze certain subgroup restrictions and/or specific indications. (See transcripts for detailed discussion)**

3. If your answer to question #2 is yes, that the proposed TDM-regimen is safe and effective, please comment on what additional information should be obtained regarding everolimus post-approval. Additionally, do you have any recommendations regarding labeling (package insert).

**The committee recommends more aggressive follow-up on the renal and lipid profiles be done, to better understand the mechanisms of action, as well as to obtain needed safety data. The committee also provided strong recommendations for using more accurate methods to measure renal function in future trials (See transcripts for detailed discussion)**

4. If your answer to question #2 is no, please comment what additional information would be necessary for approval. For example, please comment whether the currently-ongoing European study and/or the planned US cardiac transplantation study would be adequate to demonstrate safety and efficacy. Also comment whether additional data or studies would be necessary.

**The committee commented that modeling for proposed TDM-based regimen has many caveats and there are still unanswered questions to whether it is safe and effective. Definitive answers to these questions lie in the proposed studies. Some of the committee felt that efficacy had been established and that additional studies need to specifically address safety concerns. The consumer perspective was represented in comments citing that the drug has not yet been demonstrated to be safe and effective, and that the consumer needs to be assured that a drug will be safe and effective before they take it.**

**Committee members appreciate that the current data is extremely hypothesis generating. They agree that, with the information that the sponsor's proposed studies offer, it is hopeful that additional safety and efficacy data will yield the approval of everolimus. Additionally, the committee commented that, while appreciating the challenging nature of this patient population, approved drug therapy is currently available (mycophenolate) for this indication and there is lacking information that everolimus provides added benefit compared to currently approved regimens. Other committee members expressed concern, with regard to Intravascular Ultrasound [IVUS] results, and the high percentage of missing data from the study population.**

**The patient representative also had safety concerns, citing his first-hand experience with kidney failure. Qualifying comment, however, included that hopeful results from the proposed trials will bring future approval of everolimus, given the potential to show the reduction or elimination of safety risks. (See transcripts for detailed discussion)**

The committee adjourned at approximately 4:30 P.M.

Please see transcripts for detailed discussion.