

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW  
(REVIEW FOR AMENDMENT OF MARCH 17, 2005)**

NDA	<b>21-628</b>
Submission Date(s)	<b>3/17/05</b>
Brand Name	<b>Certican®</b>
Generic Name	<b>Everolimus (code name; RAD001, SDZ RAD)</b>
Reviewer	<b>Jang-Ik Lee, Pharm.D., Ph.D.</b>
Team Leader	<b>Philip Colangelo, Pharm.D., Ph.D.</b>
OCPB Division	<b>DPE III (HFD-880)</b>
OND Division	<b>ODE IV DSPTP (HFD-590)</b>
Sponsor	<b>Novartis Pharmaceuticals Corp.</b>
Relevant IND(s)	<b>52,003</b>
Submission Type; Code	<b>NDA Amendment; BZ</b>
Formulation; Strength(s)	<b>Tablets; 0.25, 0.5, 0.75, 1.0 mg</b>
Indication	<b>Prophylaxis of organ rejection in allogeneic heart transplants</b>
Dosage and Administration	<b>Oral doses of 0.75 mg b.i.d. or larger to maintain whole blood concentrations <math>\geq</math> 3.0 ng/mL in combination with Neoral and corticosteroids</b>

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## I. EXECUTIVE SUMMARY

Everolimus is a macrolide immunosuppressant derived by chemical modification of the natural product rapamycin. The Sponsor submitted original new drug applications (NDAs) for everolimus on December 19, 2004 and proposed an everolimus-cyclosporine combination regimen for the prophylaxis of organ rejection following allogeneic kidney (N21-560) and heart (N21-628) transplants. The original NDAs were approvable (see the approvable letter of October 20, 2003 in DFS) since the safety of the regimen was not acceptable. The sponsor amended the NDAs first on February 27, 2004. The first amendment was still approvable due to the same reason (see the approvable letter of August 27, 2004 in DFS). The Sponsor also amended N21-568 second on March 17, 2005 and submitted three additional drug-drug interaction study reports. This is the Clinical Pharmacology/Biopharmaceutics (CPB) review of the second amendment.

### A. Recommendation

The three additional drug-drug interaction studies conducted for everolimus by the Sponsor are acceptable from a Clinical Pharmacology and Biopharmaceutics (CPB) standpoint. However, the information on everolimus pharmacokinetics collected by the sponsor thus far is not sufficient to provide clinicians with adequate terminal half-life ( $t_{1/2}$ ) values of everolimus for its clinical use. Detailed recommendations and deficiencies are listed below.

- (1) Ketoconazole co-administration increased the mean area under the everolimus blood concentration-time curve (AUC<sub>b</sub>) 15.3-fold with prolonging  $t_{1/2}$  from 30 hr to 56 hr. Based on such dramatic increase in everolimus exposure due to drug-drug interaction, this reviewer does not recommend a simultaneous use of ketoconazole or a drug that inhibit everolimus elimination in a similar degree as ketoconazole for patients with everolimus administration. Erythromycin and verapamil coadministration increased everolimus exposure in a moderate degree (4.9-fold and 3.6-fold increase in AUC<sub>b</sub>, respectively). If such drug use is necessary at the same time, clinicians should be ready for everolimus dosage reduction based on therapeutic drug monitoring (TDM) to prevent everolimus toxicity. The actual increase in everolimus AUC<sub>b</sub> by erythromycin or verapamil may be much greater in transplant patients receiving cyclosporine in combination due to additional indirect effect through the inhibition of cyclosporine metabolism and transport by those drugs. Alternatively, drugs in the same therapeutic category with minimal effect on everolimus and cyclosporine exposure should be considered.
- (2) In this amendment, the mean  $t_{1/2}$  values of everolimus determined in healthy subjects following a single oral dose of everolimus 2 mg alone (Studies A2408, A2409, and A2410) are 30 hours or slightly longer. The  $t_{1/2}$  values are slightly shorter than previous estimates (see previous CPB reviews in DFS). The Sponsor did not provide updates on the  $t_{1/2}$  values determined in transplant patients: in the previous submission, the mean  $\pm$  SD value estimated in transplant patients receiving cyclosporine coadministration (Study W101) was  $28 \pm 7$  hr. This value appeared to be unreasonably shorter considering the effect of cyclosporine on everolimus disposition. Therefore, in a future submission, the sponsor needs to provide the  $t_{1/2}$  determined adequately at the range of proposed clinical doses or concentrations of

everolimus and cyclosporine following multiple (steady state) administration of a proposed everolimus-cyclosporine combination regimen to transplant patients.

### B. Phase IV Commitments

Not applicable.

### C. Summary of CPB Findings

#### Effect of Erythromycin, Ketoconazole, and Verapamil on Everolimus Pharmacokinetics

Table 1 presents the effect of erythromycin (500 mg every 8 hours for 5 days), ketoconazole (200 mg every 12 hours for 5 days), and verapamil (80 mg every 8 hours for 5 days) on everolimus pharmacokinetics following a single oral dose of everolimus 2 mg. Erythromycin coadministration increased the mean maximum blood concentration ( $C_{max,b}$ ) of everolimus 2.1-fold (range, 0.9-fold to 3.5-fold) and the mean area under the blood concentration-time curve ( $AUC_{\infty,b}$ ) 4.9-fold (range, 2.0-fold to 12.6-fold) without affecting median time to  $C_{max,b}$  ( $T_{max}$ ). The mean apparent oral blood clearance ( $CL_{b/F}$ ) of everolimus was decreased from 19.1 L/hr to 4.6 L/hr. The mean terminal half-life ( $t_{1/2}$ ) was prolonged from 32 hr to 44 hr. Ketoconazole co-administration increased the mean everolimus  $C_{max,b}$  4.1-fold (range, 2.6-fold to 7.0-fold) and  $AUC_{\infty,b}$  15.3-fold (range, 11.2-fold to 22.5-fold) with prolonging median  $T_{max}$  by 0.5 hr. The mean  $CL_{b/F}$  was decreased from 23.8 L/hr to 1.6 L/hr. The mean  $t_{1/2}$  was prolonged from 30 hr to 56 hr. Verapamil co-administration increased mean everolimus  $C_{max,b}$  2.4-fold (range, 1.3-fold to 3.8-fold) and  $AUC_{\infty,b}$  3.6-fold (range, 2.2-fold to 6.3-fold) without affecting median  $T_{max}$ . The mean  $CL_{b/F}$  was decreased from 20.1 L/hr to 5.6 L/hr. The mean  $t_{1/2}$  was prolonged from 32 hr to 37 hr.

Table 1: Comparison of everolimus pharmacokinetic parameters (mean  $\pm$  SD) determined following a single oral dose of everolimus 2 mg alone and in combination with an interacting drug.

Interacting Drug	Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Interacting Drug	Mean Ratio (Range)
Erythromycin 500 mg every 8 hr (n = 16)	$C_{max,b}$ (ng/mL)	19.9 $\pm$ 5.0	40.2 $\pm$ 10.4	2.10 (0.90 - 3.48)
	$AUC_{\infty,b}$ (ng-hr/mL)	116 $\pm$ 37	524 $\pm$ 225	4.94 (2.04 - 12.58)
	$t_{1/2}$ (hr)	31.8 $\pm$ 6.0	43.7 $\pm$ 5.8	1.40 (1.09 - 1.72)
Ketoconazole 200 mg every 12 hr (n = 12)	$C_{max,b}$ (ng/mL)	15.3 $\pm$ 4.3	59.4 $\pm$ 13.4	4.14 (2.64- 6.97)
	$AUC_{\infty,b}$ (ng-hr/mL)	90 $\pm$ 23	1324 $\pm$ 232	15.3 (11.2 - 22.5)
	$t_{1/2}$ (hr)	29.7 $\pm$ 4.0	56.0 $\pm$ 4.8	1.91 (1.49 - 2.44)
Verapamil 80 mg every 8 hr (n = 16)	$C_{max,b}$ (ng/mL)	21.0 $\pm$ 8.1	47.1 $\pm$ 18.2	2.42 (1.32 - 3.84)
	$AUC_{\infty,b}$ (ng-hr/mL)	115 $\pm$ 45	392 $\pm$ 142	3.61 (2.21 - 6.30)
	$t_{1/2}$ (hr)	31.7 $\pm$ 6.4	36.9 $\pm$ 6.1	1.18 (0.95 - 1.52)

#### Basic Everolimus Pharmacokinetic Parameters

In Studies A2408, A2409, and A2410 submitted in this amendment, the mean  $\pm$  SD  $t_{1/2}$  of everolimus were determined to be 31.8  $\pm$  6.0 hr, 29.7  $\pm$  4.0 hr, and 31.7  $\pm$  6.4 hr, respectively, from healthy subjects following a single dose of everolimus 2 mg alone. These values are

slightly shorter than previous estimates from healthy subjects (see previous CPB reviews in DFS). The Sponsor did not provide updates on the  $t_{1/2}$  determined in transplant patients. In the previous submission, the mean  $\pm$  SD value estimated in transplant patients receiving cyclosporine coadministration (Study W101) was  $28 \pm 7$  hr. This value appeared to be unreasonably shorter considering the effect of cyclosporine on everolimus pharmacokinetics.

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## II. QUESTION-BASED REVIEW

### A. *General Attributes*

No update.

### B. *General Clinical Pharmacology*

#### 1. *Were the basic pharmacokinetic parameters for everolimus determined adequately?*

In the previous reviews (see CPB reviews in DFS), this reviewer concluded that everolimus terminal half-life ( $t_{1/2}$ ) was not adequately determined in a targeted patient population. The mean  $\pm$  SD terminal half-life ( $t_{1/2}$ ) of  $28 \pm 7$  hr estimated in transplant patients receiving cyclosporine co-administration (Study W101) was not acceptable: the value was unreasonably shorter than the  $t_{1/2}$  estimated in healthy subjects receiving no cyclosporine coadministration. Based on the Studies A2408, A2409, and A2410 submitted in this amendment, the  $t_{1/2}$  values were determined to be  $31.8 \pm 6.0$  hr,  $29.7 \pm 4.0$  hr, and  $31.7 \pm 6.4$  hr, respectively, from healthy subjects following a single oral dose of everolimus 2 mg without any interacting drug coadministration. These values are slightly shorter than the values determined previously in other healthy subject studies.

Thus, from the reviews of the data provided thus far by the sponsor, this reviewer concludes that the sponsor has not adequately determined the  $t_{1/2}$  of everolimus in the targeted patient population at steady state. Therefore, in a future submission, the sponsor needs to provide the  $t_{1/2}$  of everolimus determined adequately at the range of proposed clinical doses or concentrations of everolimus and cyclosporine following multiple (steady state) administration of the proposed everolimus-cyclosporine combination regimen to transplant patients.

### C. *Intrinsic Factors*

No update.

### D. *Extrinsic Factors*

#### 1. *Are there any in vivo drug-drug interaction studies that indicate the exposure is different when drugs are coadministered?*

##### Effect of Erythromycin on Everolimus Pharmacokinetics

The effect of multiple-dose erythromycin coadministration on single-dose everolimus pharmacokinetics was determined in a fixed sequence drug-drug interaction study conducted in 16 healthy subjects (Study A2408). Table 2 presents a summary and comparison of the everolimus pharmacokinetic parameters determined following a single oral dose of everolimus 2 mg administered alone and in combination with oral erythromycin 500 mg every 8 hours for 5 days. Erythromycin co-administration increased mean everolimus maximum blood concentration ( $C_{max,b}$ ) 2.1-fold (range, 0.9-fold to 3.5-fold) and mean area under the blood concentration-time curve ( $AUC_{0-24,b}$ ) 4.9-fold (range, 2.0-fold to 12.6-fold) without affecting median time to  $C_{max,b}$  ( $T_{max}$ ). The mean apparent oral blood clearance ( $CL_{b/F}$ ) of everolimus

was decreased from 19.1 L/hr to 4.6 L/hr. The mean apparent volume of distribution ( $V_{z,b/F}$ ) was also decreased from 847 L to 287 L. The mean  $t_{1/2}$  was prolonged from 32 hr to 44 hr.

Table 2: Comparison of everolimus pharmacokinetic parameters (mean  $\pm$  SD) determined following a single oral dose of everolimus 2 mg alone and in combination with oral erythromycin 500 mg administered every 8 hours for 5 days to 16 healthy subjects (Study A2408).

Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Erythromycin	Mean Ratio (Range)
T <sub>max</sub> (hr)*	0.5 (0.5 - 1.0)	0.5 (0.5 - 1.5)	0 (-0.5 to 0.5)^
C <sub>max,b</sub> (ng/mL)	19.9 $\pm$ 5.0	40.2 $\pm$ 10.4	2.10 (0.90 - 3.48)
AUC <sub><math>\infty</math>,b</sub> (ng-hr/mL)	116 $\pm$ 37	524 $\pm$ 225	4.94 (2.04 - 12.58)
CL <sub>b/F</sub> (L/hr)	19.1 $\pm$ 6.4	4.6 $\pm$ 2.1	0.26 (0.08 - 0.49)
V <sub>z,b/F</sub> (L)	847 $\pm$ 209	287 $\pm$ 128	0.35 (0.13 - 0.59)
$t_{1/2}$ (hr)	31.8 $\pm$ 6.0	43.7 $\pm$ 5.8	1.40 (1.09 - 1.72)

\* median (range), ^ median difference

#### Effect of Ketoconazole on Everolimus Pharmacokinetics

The effect of multiple-dose ketoconazole co-administration on single-dose everolimus pharmacokinetics was determined in a fixed sequence drug-drug interaction study conducted in 12 healthy subjects (Study A2409). Table 3 presents a summary and comparison of the everolimus pharmacokinetic parameters determined following a single oral dose of everolimus 2 mg (or normalized to 2 mg) administered alone and in combination with oral ketoconazole 200 mg every 12 hours for 5 days. Ketoconazole coadministration increased mean everolimus C<sub>max,b</sub> 4.1-fold (range, 2.6-fold to 7.0-fold) and AUC<sub>b</sub> 15.3-fold (range, 11.2-fold to 22.5-fold) with prolonging median T<sub>max</sub> by 0.5 hr. The mean CL<sub>b/F</sub> was decreased from 23.8 L/hr to 1.6 L/hr. The mean V<sub>z,b/F</sub> was also decreased from 1016 L to 126 L. The  $t_{1/2}$  was prolonged from 30 hr to 56 hr.

Table 3: Comparison of everolimus pharmacokinetic parameters (mean  $\pm$  SD) determined following a single oral dose of everolimus alone (2 mg) and in combination with oral ketoconazole 200 mg (normalized to 2 mg) administered every 12 hours for 5 days to 12 healthy subjects (Study A2409).

Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Ketoconazole	Mean Ratio (Range)
T <sub>max</sub> (hr)*	1.0 (0.5 - 1.0)	0.5 (0.5 - 1.5)	0.5 (-0.5 to 1.0)^
C <sub>max,b</sub> (ng/mL)	15.3 $\pm$ 4.3	59.4 $\pm$ 13.4	4.14 (2.64 - 6.97)
AUC <sub><math>\infty</math>,b</sub> (ng-hr/mL)	90 $\pm$ 23	1324 $\pm$ 232	15.3 (11.2 - 22.5)
CL <sub>b/F</sub> (L/hr)	23.8 $\pm$ 7.4	1.6 $\pm$ 0.3	0.07 (0.04 - 0.09)
V <sub>z,b/F</sub> (L)	1016 $\pm$ 294	126 $\pm$ 25	0.13 (0.09 - 0.19)
$t_{1/2}$ (hr)	29.7 $\pm$ 4.0	56.0 $\pm$ 4.8	1.91 (1.49 - 2.44)

\* median (range), ^ median difference

#### Effect of Verapamil on Everolimus Pharmacokinetics

The effect of multiple-dose verapamil co-administration on single-dose everolimus pharmacokinetics was determined in a fixed sequence drug-drug interaction study conducted in

12 healthy subjects (Study A2410). Table 4 presents a summary and comparison of the everolimus pharmacokinetic parameters determined following a single oral dose of everolimus 2 mg administered alone and in combination with oral verapamil 80 mg every 8 hours for 5 days). Verapamil coadministration increased mean everolimus C<sub>max,b</sub> 2.4-fold (range, 1.3-fold to 3.8-fold) and AUC<sub>∞,b</sub> 3.6-fold (range, 2.2-fold 6.3-fold) without affecting median T<sub>max</sub>. The mean CL<sub>b/F</sub> was decreased from 20.1 L/hr to 5.6 L/hr. The mean V<sub>z,b/F</sub> was also decreased from 902 L to 291 L. The t<sub>1/2</sub> was prolonged from 32 hr to 37 hr.

Table 4: Comparison of everolimus pharmacokinetic parameters (mean ± SD) determined following a single oral dose of everolimus 2 mg alone and in combination with oral verapamil 80 mg administered every 8 hours for 5 days to 16 healthy subjects (Study A2410).

Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Erythromycin	Mean Ratio (Range)
T <sub>max</sub> (hr)*	0.5 (0.5 - 1.5)	0.5 (0.5 - 1.5)	0 (-0.5 to 1.0)^
C <sub>max,b</sub> (ng/mL)	21.0 ± 8.1	47.1 ± 18.2	2.42 (1.32 - 3.84)
AUC <sub>∞,b</sub> (ng-hr/mL)	115 ± 45	392 ± 142	3.61 (2.21 - 6.30)
CL <sub>b/F</sub> (L/hr)	20.1 ± 8.1	5.6 ± 1.5	0.30 (0.16 - 0.45)
V <sub>z,b/F</sub> (L)	902 ± 388	291 ± 71	0.35 (0.2 - 0.57)
t <sub>1/2</sub> (hr)	31.7 ± 6.4	36.9 ± 6.1	1.18 (0.95 - 1.52)

\* median (range), ^ median difference

#### Effect of Everolimus on Erythromycin, Ketoconazole, and Verapamil Pharmacokinetics

Studies A2408, A2409, and A2410 were not designed to adequately determine the effect of everolimus coadministration on the pharmacokinetics of erythromycin, ketoconazole, or verapamil. However, geometric mean trough concentrations after compare with before everolimus coadministration were similar for erythromycin (225 ± 500 ng/mL *versus* 190 ± 403 ng/mL), slightly higher for ketoconazole (1.45 - 1.61 µg/mL *versus* 1.26 µg/mL), and much greater for verapamil (32 ± 16 ng/mL *versus* 74 ± 42 ng/mL).

#### **E. General Biopharmaceutics**

No update.

#### **F. Analytical**

##### **1. What bioanalytical methods were used to assess concentrations?**

Everolimus concentrations were determined by a validated reverse phase high performance liquid chromatographic method with mass spectrometric detection using atmospheric pressure chemical ionization (LC-MS). SDZ 233-756 was used as an internal standard. Analytes were prepared by liquid-liquid extraction. The lower limit of quantitation (LOQ) was 0.3 ng/mL and the calibration curves were linear ( $r^2 > 0.988$ ) over the everolimus concentration range of 0.3 ng/mL to 50 ng/mL. The in-process assay performance of the assay determined using quality control samples (0.9, 20, and 40 ng/mL) is summarized in Table 5.

Table 5: Summary of in-process assay performance for everolimus, erythromycin, ketoconazole, and verapamil.

Study	Analyte	Limit of Quantitation (ng/mL)	Calibration Range (ng/mL)	Accuracy (% deviation)	Precision (% CV)
A2408	Whole Blood Everolimus	0.3	0.3 - 50	-4.1 to 6.6	4.9 to 7.9
	Plasma Erythromycin	20	20 - 2000	-1.2 to 3.5	3.4 to 6.9
A2409	Whole Blood Sirolimus	0.3	0.3 - 50	5.3 to 9.5	4.4 to 9.9
	Plasma Ketoconazole	20	20 - 15,000	-9.8 to 0.8	not determined
A2410	Whole Blood Sirolimus	0.3	0.3 - 50	1.3 to 9.5	6.9 to 9.3
	Plasma Verapamil	1.99	1.99 - 498	3.3 to 13.9	not determined

Erythromycin concentrations were determined by a validated reverse phase high performance liquid chromatographic method with tandem mass spectrometric detection using electrospray ionization (LC-MS/MS). Oleandomycin was used as an internal standard. Analytes were prepared by protein precipitation of plasma samples. The LOQ was 20 ng/mL and the calibration curves were linear ( $r^2 > 0.997$ ) over the everolimus concentration range of 20 ng/mL to 2000 ng/mL. The in-process assay performance of the assay determined using quality control samples (60, 800, and 1700 ng/mL) is summarized in Table 5.

Ketoconazole concentrations were determined by a validated LC-MS/MS method. Bifonazole was used as an internal standard. Analytes were prepared using a cohesive on-line extraction procedure from plasma samples. The LOQ was 20 ng/mL and the calibration curves were linear ( $r^2 > 0.996$ ) over the everolimus concentration range of 20 ng/mL to 15,000 ng/mL. The in-process assay performance of the assay determined using quality control samples (60.4, 1,810, and 12,100 ng/mL) is summarized in Table 5.

Verapamil concentrations were determined by a high resolution gas chromatographic method with mass spectrometric detection (GC-MS). Methoxyverapamil was used as an internal standard. Analytes were prepared using a liquid-liquid extraction procedure from plasma samples. The LOQ was 1.99 ng/mL and the calibration curves were linear ( $r^2 > 0.995$ ) over the everolimus concentration range of 1.99 ng/mL to 498 ng/mL. The in-process assay performance of the assay determined using quality control samples (4.95, 198, and 396 ng/mL) is summarized in Table 5.

**III. DETAILED LABELING RECOMMENDATIONS**

Detailed labeling recommendations are deferred until the approval action to this amendment is decisive.

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**IV. APPENDICES**

***A. Package Insert (Proposed and Annotated)***

Please refer to [\\Cdsesub1\n21083\S\\_017\2004-01-19\0000\m1\us\final-annotated.pdf](\\Cdsesub1\n21083\S_017\2004-01-19\0000\m1\us\final-annotated.pdf)

*B. Summary of Individual Studies*

Study	Objectives	Design	Subject No. (M/F), Age, Race	Dosage Form, Dose, Route, Duration
A2408	To evaluate the single-dose pharmacokinetics of everolimus when administered alone and during multiple-dose erythromycin.	open-label, 2-period, single-sequence study	healthy subjects 16 (11/5) 23 - 37 years 6 blacks, 5 whites, 1 Asian, 4 other	<u>Everolimus</u> : 2 mg (2 x 1 mg tablets) orally without (Day 1) and with erythromycin (Day 14) <u>Erythromycin</u> : 500 mg (1 x 500 mg immediate release tablet) every 8 hr on Days 10 through 18
A2409	To evaluate the single-dose pharmacokinetics of everolimus when administered alone and during multiple-dose ketoconazole.	open-label, 2-period, single-sequence study	healthy subjects 12 (10/2) 19 - 45 years 6 blacks, 2 whites, 4 other	<u>Everolimus</u> : 2 mg (2 x 1 mg tablets) orally without (Day 1) and 1 mg with ketoconazole (Day 13) <u>Ketoconazole</u> : 200 mg (1 x 200 mg tablet) every 12 hr on Days 10 through 17
A2410	To evaluate the single-dose pharmacokinetics of everolimus when administered alone and during multiple-dose verapamil.	open-label, 2-period, single-sequence study	healthy subjects 16 (10/6) 18 - 55 years 3 whites, 13 other	<u>Everolimus</u> : 2 mg (2 x 1 mg tablets) orally without (Day 1) and with verapamil (Day 11) <u>Verapamil</u> : 80 mg (1 x 80 mg immediate release tablet) every 8 hr on Days 10 through 15