

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203985Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 203985

Supporting document/s: 0 (new NDA) and subsequent amendments (#1-13)  
EDR: <\\CDSESUB1\EVSPROD\NDA203985\203985.enx>

Applicant's letter date: February 29, 2012

CDER stamp date: February 29, 2012

Product: Everolimus tablets for oral suspension (Afinitor Disperz®)

Indication: children and adults with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC) that requires therapeutic intervention but cannot be curatively resected

Applicant: Novartis Pharmaceuticals Corporation

Review Division: Division of Hematology Oncology Toxicology (DHOT) in support of Division of Oncology Products 2 (DOP2), Office of Hematology and Oncology Products (OHOP), CDER

Reviewer: Andrew J. McDougal, Ph.D., D.A.B.T., DHOT-DOP2

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## 1 Executive Summary

- Novartis Pharmaceuticals Corporation (Novartis) submitted NDA 203985 under 505(b)1 of the Federal Food, Drug and Cosmetic Act and 21 CFR314.50.
- As the sponsor noted in the cover letter of the original NDA submission (February 29, 2012), the purpose of this NDA for everolimus is to support “a new pediatric-appropriate formulation of Afinitor <sup>(b) (4)</sup> (Afinitor® DISPERZ™) for the treatment of patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) and require therapeutic intervention but are not likely to be cured by surgery. The purpose of this NDA is to provide the Agency with all outstanding components outlined in the Written Request (WR) issued for everolimus and to request a pediatric exclusivity determination.”
- Nonclinical information was incorporated by cross-reference to Novartis’s IND 66279, NDA 22334, and NDA 21560. One new nonclinical study was submitted, and has been reviewed (below).

### 1.1 Recommendations

#### 1.1.1 Approvability

From a nonclinical Pharmacology/Toxicology perspective, this reviewer recommends approval of NDA 203985 for the proposed indications:

-  <sup>(b) (4)</sup>
- 
- 
- 
- Children and adults with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but is unlikely to be curatively resected.

#### 1.1.2 Additional Non Clinical Recommendations

No nonclinical recommendations, postmarketing commitments, or postmarketing requirements are warranted to support the NDA.

### 1.1.3 Labeling

No labeling revisions are recommended based on the nonclinical information submitted to NDA 203985; however, nonclinical revisions are recommended for concordance across indications and pending supplements as shown in the table below.

Applicant Proposed	Recommended Changes for Consistency across Divisions/Indications
<p>Highlights, Warnings and Precautions</p> <p>(b) (4)</p>	<p>Highlights, Warnings and Precautions</p> <p>Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.10, 8.1)</p>
<p>(b) (4)</p>	<p><b>5.10 Embryo-fetal Toxicity</b>                      There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to use a highly effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment [see <i>Use in Specific Populations (8.1)</i>].</p>
<p><b>8.1 Pregnancy</b></p> <p>(b) (4)</p>	<p><b>8.1 Pregnancy</b></p> <p>Pregnancy Category D [see <i>Warnings and Precautions (5.10)</i>].                      There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman.</p>

(b) (4)	<p>Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use a highly effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.</p> <p>In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses <math>\geq 0.1</math> mg/kg (<math>0.6</math> mg/m<sup>2</sup>) with resulting exposures of approximately 4% of the exposure (AUC<sub>0-24h</sub>) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (<math>9.6</math> mg/m<sup>2</sup>), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.</p> <p>In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (<math>0.6</math> mg/m<sup>2</sup>), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the</p>
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<p>(b) (4)</p>	<p>developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.</p>
<p><b>12.1 Mechanism of Action</b></p> <p>(b) (4)</p>	<p><b>12.1 Mechanism of Action</b></p> <p>Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus</p>

<p>(b) (4)</p>	<p>has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in <i>in vitro</i> and/or <i>in vivo</i> studies. Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. <i>In vitro</i> studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.</p> <p>Two regulators of mTORC1 signaling are the oncogene suppressors tuberinsclerotic complexes 1 and 2 (<i>TSC1</i>, <i>TSC2</i>). Loss or inactivation of either <i>TSC1</i> or <i>TSC2</i> leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the <i>TSC1</i> or the <i>TSC2</i> gene lead to hamartoma formation throughout the body.</p>
<p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p>(b) (4)</p>	<p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p>Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure (<math>AUC_{0-24h}</math>) at the 10 mg daily human dose.</p> <p>Everolimus was not genotoxic in a battery of <i>in vitro</i> assays (Ames mutation test in <i>Salmonella</i>, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an <i>in vivo</i> mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m<sup>2</sup>/day, approximately 255-fold either</p>

(b) (4)	<p>the 10 mg daily dose or the median dose administered to patients with SEGA and TSC, based on the body surface area), administered as two doses, 24 hours apart.</p> <p>Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in male rats treated with 5 mg/kg. These doses result in exposures which are within the range of therapeutic exposure (52 ng.hr/mL and 414 ng.hr/mL respectively compared to 560 ng.hr/mL human exposure at 10 mg/day), and resulted in infertility in rats at 5 mg/kg. Effects on male fertility occurred at the AUC<sub>0-24h</sub> values below that of therapeutic exposure (approximately 10%-81% of the AUC<sub>0-24h</sub> in patients receiving the 10 mg daily dose). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).</p> <p>Oral doses of everolimus in female rats at <math>\geq 0.1</math> mg/kg (approximately 4% the AUC<sub>0-24h</sub> in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus [see <i>Use in Specific Populations</i> (8.1)].</p>

<p><b>13.2 Animal Toxicology and/or Pharmacology</b></p>  <p>(b) (4)</p>	<p><b>13.2 Animal Toxicology and/or Pharmacology</b></p> <p>In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day, which is equivalent to 15% of the median dose administered to patients with TSC who have SEGA, based on body surface area.</p>
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## 1.2 Brief Discussion of Nonclinical Findings

- Novartis Pharmaceuticals Corporation (Novartis) submitted NDA 203985 under 505(b)1 of the Federal Food, Drug and Cosmetic Act and 21 CFR314.50.
- Nonclinical information was incorporated by cross-reference to Novartis's IND 66279, NDA 22334, and NDA 21560
- Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTORC1 and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.
- Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.
- The applicant provided one new nonclinical study report to NDA 203985, a brain distribution study in rats (report # 1000720). Pre-treatment with cyclosporine (to inhibit P-gp efflux pumps in the blood-brain barrier) resulted in higher concentrations of everolimus in the brain following oral dosing in rats. No toxicity endpoints were measured.

- This reviewer searched the cross-referenced IND and NDAs for nonclinical information potentially relevant to the change in formulation, and identified a rat two week oral toxicity study designed to compare two solid dispersions of everolimus (report # 634678, submitted to NDA 22334). This study was re-reviewed and is not particularly relevant; the additional context provided by this NDA submission raise no new safety concerns from the results of this study.
- The applicant asserted, and this reviewer verified, that no new impurities and no increased exposures to unqualified impurities will result from this formulation because the drug substance specifications are the same as previously approved specifications; this finding was confirmed by the Quality reviewer (personal communication, McDougal/Lin).

## 2 Drug Information

### 2.1 Drug

#### 2.1.1 CAS Registry Number

159351-69-6

#### 2.1.2 Generic Name

Everolimus

#### 2.1.3 Code Names

- 42-O-(2-hydroxyethyl)-rapamycin (9CI)
- 40-O-(2-hydroxyethyl)-rapamycin
- 4"-O-(2-hydroxyethyl)-rapamycin
- (b) (4)
- SDZ RAD
- RAD 666
- (b) (4)
- RAD (b) (4)

#### 2.1.4 Chemical Name

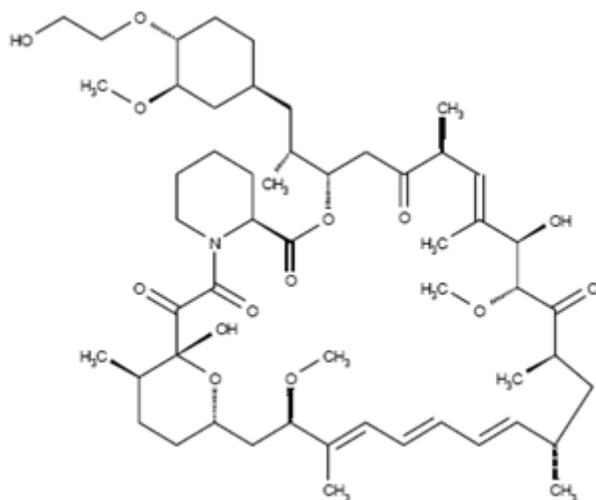
1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-((1R)-2-((1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl)-1-methylethyl)-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0<sup>4,9</sup>]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

### 2.1.5 Molecular Formula/Molecular Weight

$C_{53}H_{83}NO_{14}$   
958.2 Daltons

### 2.1.6 Structure

Figure 1: Structure of everolimus



### 2.1.7 Pharmacologic class

Kinase inhibitor, inhibitor of mTOR, antineoplastic agent

## 2.2 Relevant IND/s, NDA/s, and DMF/s

The applicant references IND 66279, NDA 22334, NDA 21560, DMB (b) (4) DMB (b) (4), and DMF (b) (4), (b) (4)

### 2.3.1 Drug Formulation

AFINITOR DISPERZ (everolimus tablets for oral suspension) are supplied for oral administration and contain 2 mg, 3 mg, or 5 mg of everolimus. Inactive ingredients in the tablets include butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, mannitol, microcrystalline cellulose, and colloidal silicon dioxide.

From the NDA (module 3.2.P.1 Description and Composition of the Drug Product):

**Table 1: Composition of the 2, 3 and 5 mg dispersible tablet**

Ingredient	Amount per 2mg tablet [mg]	Amount per 3mg tablet [mg]	Amount per 5mg tablet [mg]	Function	Reference to standards
(b) (4)	2.00	3.00	5.00	Active ingredient	Novartis monograph
(b) (4) Butylated hydroxytoluene/					(b) (4) Ph. Eur., NF, JPE
(b) (4) Lactose monohydrate/					Ph. Eur., NF, JP
(b) (4) Hypromellose/					Ph. Eur., USP, JP
(b) (4) Microcrystalline cellulose					Ph. Eur., NF, JP
Crospovidone					Ph. Eur., NF, JPE
Magnesium stearate					Ph. Eur., NF, JP
(b) (4) Colloidal silicon dioxide					Ph. Eur., NF, JP
(b) (4)					Ph. Eur., USP
(b) (4)					Ph. Eur., NF
(b) (4)					Ph. Eur., NF
<b>Tablet</b>	<b>250.00</b>	<b>375.00</b>	<b>625.00</b>		

### 2.4 Proposed Clinical Population and Dosing Regimen

This NDA proposes to add a new clinical population to the currently approved label for Afinitor: “children and adults with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but is unlikely to be curatively resected. Effectiveness is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC has not been demonstrated.”

For the proposed population of patients with subependymal giant cell astrocytoma with TSC, the proposed dosing regimen is 4.5 mg/m<sup>2</sup> administered once daily with the following qualifications:

“Monitor everolimus whole blood trough levels routinely in all patients. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Assess trough concentrations approximately two weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4 and/or Pgp inducers or inhibitors, a change in hepatic function, or a change in formulation between AFINITOR Tablets and AFINITOR DISPERZ.

Titrate the dose to attain trough concentrations of 5 to 15 ng/mL.

- For trough concentrations less than 5 ng/mL, increase the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- For trough concentrations greater than 15 ng/mL, reduce the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- If dose reduction is required for patients receiving the lowest available strength, administer every other day.”

## 2.5 Regulatory Background

The applicant reports that everolimus was initially developed for treatment of allograft rejection following organ transplantation (Zortress®, NDA 21560), and the development program was expanded to treatment of patients with cancer (e.g. Afinitor®, NDA 22334).

Among other approvals, everolimus was approved on October 29, 2010 for treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.

The applicant states (NDA section 2.5 Clinical Overview) that the purposes of this NDA submission include:

- “To update the label based on data from the Phase-III randomized placebo-controlled trial in patients with TSC who have SEGA (Study M2301), and longer-term follow-up from the Phase-II trial (Study C2485). Of note, the longer-term follow-up from Study C2485 provides relevant data pertaining to sustained efficacy and safety of everolimus in this patient population.”
- “To support an age-appropriate formulation” for patients under 3 years of age”

### 3 Studies Submitted

#### 3.1 Studies Reviewed

The February 29, 2012 NDA included one nonclinical study report, "Brain distribution of RAD001 in rats after oral administration of 3 mg/kg RAD001 with and without oral co-administration of 10 mg/kg cyclosporine", report # 1000720.

No nonclinical reports have been submitted to the NDA subsequently (as of July 19, 2012).

#### 3.2 Studies Not Reviewed

None.

#### 3.3 Previous Reviews Referenced

The reviews for IND 66379, NDA 22334 and NDA 21560 are referenced, including particularly Dr. Shwu-Luan Lee's review<sup>1</sup> and Dr. William H. Taylor's review<sup>2</sup>.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

**Study title: Brain distribution of RAD001 in rats after oral administration of 3 mg/kg RAD001 with and without oral co-administration of 10 mg/kg cyclosporine**

Study no.:	1000720
Report date:	January 18, 2012
Study report location:	NDA module 4.2.2.3 Distribution
Conducting laboratory and location:	Novartis Institute for BioMedical Research, DMPK, Basel, Switzerland
Date of study initiation:	Not reported
GLP compliance:	No
Drug, lot #, and % purity:	Everolimus (RAD001) batch # 13179-YL (purity 100%)

<sup>1</sup> Lee/NDA 22334/March 12, 2009. Publically-available version accessed online via: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2009/022334s000\\_PharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000_PharmR.pdf)

<sup>2</sup> Taylor/NDA 21560/December 18, 2009. Publically-available version accessed online via: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/021560s000pharmr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021560s000pharmr.pdf)

## Key Study Findings

- In Wistar rats dosed orally with 3 mg/kg of everolimus in a microemulsion formulation, pre-treatment with cyclosporine increased the concentration of everolimus in the brain cortex
- Cyclosporine is a P-gp inhibitor; the purpose of this study was to investigate whether inhibition of this efflux pump would affect everolimus concentrations in target tissue (brain and CSF)
- The authors conclude, and this reviewer concurs, that the results “should be considered with reservation” due to analytical limitations.

## Methods

- Dosing information:
- 3 rats were untreated (as blank control)
  - 12 rats were pre-treated by oral gavage with vehicle microemulsion, and one minute later were treated by oral gavage with 3 mg/kg of everolimus microemulsion
  - 12 rats were pre-treated by oral gavage with 10 mg/kg of cyclosporine as a “neural microemulsion”, and one minute later were treated by oral gavage with 3 mg/kg of everolimus microemulsion
- Frequency of dosing: Once (acute dose study)
- Route of administration: Oral gavage
- Dose volume: Not reported
- Formulation/Vehicle:
- Everolimus was formulated in 3% microemulsion (not specified in more detail in the report), 97% saline
  - Cyclosporine was formulated in 2% “Neoral microemulsion” (not specified in more detail in the report), 98% saline
- Species/Strain: Male Wistar rats (HAN:WIST)
- Number/Sex/Group: 3 or 12 males/group
- Age: Not specified
- Weight: 250 to 280 grams

## Method notes

- Stability of everolimus was verified experimentally
- Blood, brain cortex, and CSF samples were collected from untreated rats (i.e. N =3, multiple time points not necessary).
- For the everolimus-treated rats, 3 rats were sacrificed at each time point (15 minutes, 1 hour, 4 hours and 24 hours post-dose); blood, brain cortex, and CSF samples were collected
- The lower limit of quantification (LLOQ) for everolimus in blood was 0.3 ng/ml

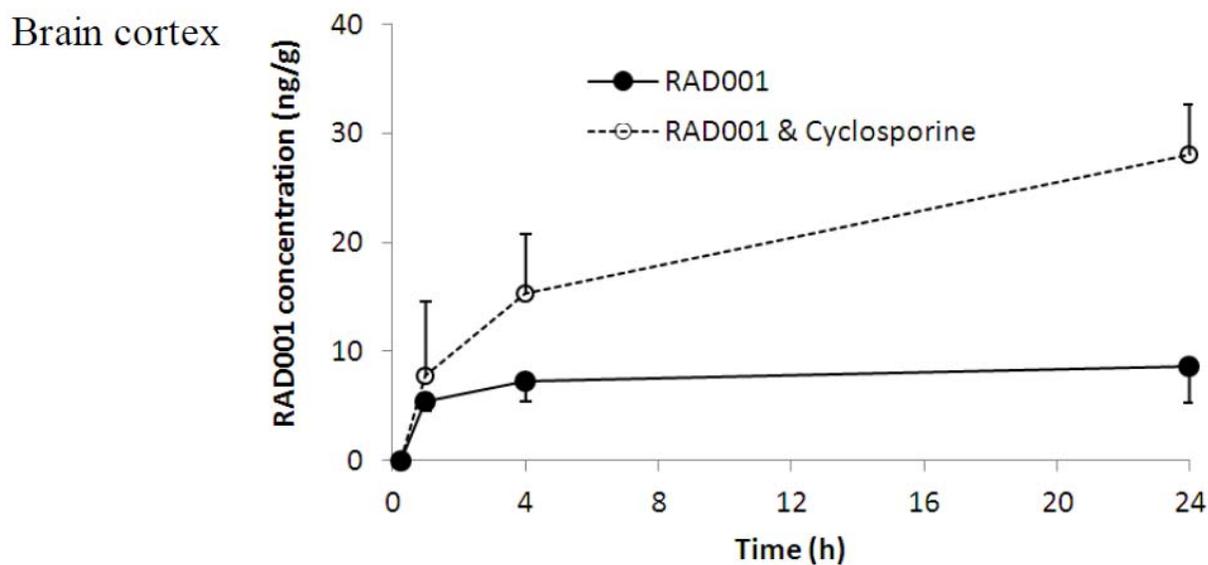
- The LLOQ for brain and CSF tissue was dependent on the homogenization procedure (i.e. samples were diluted with water). The LLOQ ranged from 2.1 to 3.7 ng/ml. The LLOQ for CSF ranged from 0.72 to 2.5 ng/ml

### Results notes

- Under the conditions tested, everolimus did not appear to be stable in CSF over 4 hours. The authors speculate that everolimus adsorbed to protein, confounding the analytical procedure.
- Without cyclosporine pre-treatment, everolimus was detected in the brain and CSF of rats after oral dosing.
- Pre-treatment had a clear effect on everolimus's concentration in the brain.
- The effect of cyclosporine pre-treatment on CSF concentration is unclear.

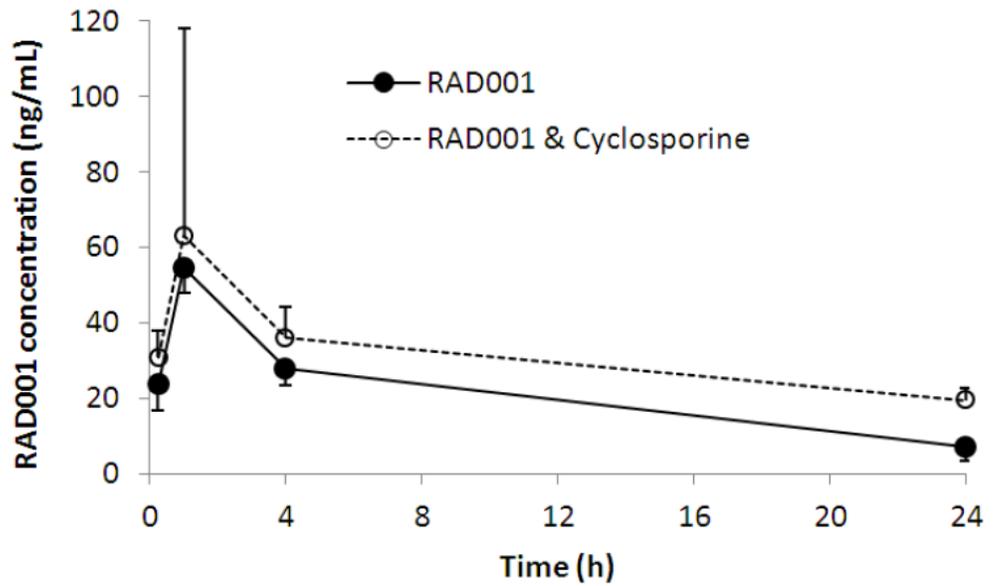
From the report (page 16, 18):

**Figure 2: Cyclosporine pre-treatment enhanced brain concentrations of everolimus following oral dosing (report # 100720)**



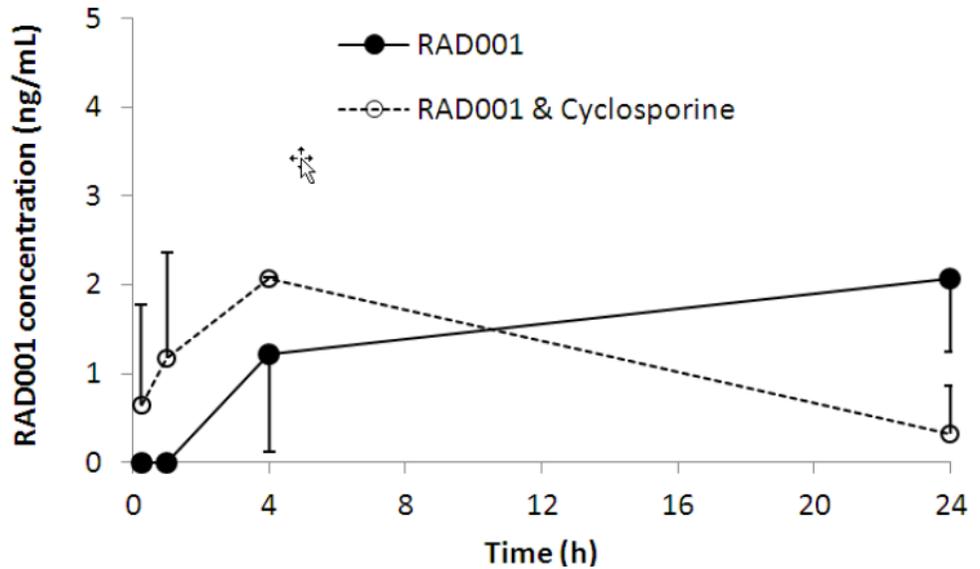
**Figure 3: Cyclosporine pre-treatment did not affect blood concentrations of everolimus following oral dosing (report # 100720)**

Blood



**Figure 4: The effect of cyclosporine pre-treatment on CSF concentrations of everolimus following oral dosing is unclear (report # 100720)**

CSF



**Table 2: Cyclosporine pre-treatment did not affect everolimus distribution to the brain or CSF (report # 1000720)**

Parameter	Blood	Brain cortex	CSF
Everolimus 3 mg/kg (no cyclosporine pre-treatment)			
T <sub>max</sub> (h)	1	24	24
C <sub>max</sub> (ng/ml)	54.5	8.65 <sup>a</sup>	2.07
AUC <sub>last</sub> (h*ng/ml)	505	180 <sup>a</sup>	34.7
AUC <sub>ratio</sub> (tissue/blood)	1.00	0.356	0.0688
Cyclosporine + Everolimus 3 mg/kg			
T <sub>max</sub> (h)	1	24	4
C <sub>max</sub> (ng/ml)	62.9	28.1 <sup>a</sup>	2.07
AUC <sub>last</sub> (h*ng/ml)	741	471 <sup>a</sup>	29.8
AUC <sub>ratio</sub> (tissue/blood)	1.00	0.636	0.0402

<sup>a</sup> For brain cortex, the units for C<sub>max</sub> are ng/g, and the units for AUC<sub>last</sub> are h\*ng/g

## 6 General Toxicology

Study title: **SDZ RAD solid dispersion. A comparative 2-week oral (gavage) toxicity study in the rat with two different batches**

Study no.: • 203-077  
• 163634.01  
• RCC project # 34678

Report date August 25, 1997

Study report location: • This NDA includes authorization of cross-reference in NDA Module 1.4.4 (Cross-reference to other applications)  
• The original study report was identified in NDA 22334 (NDA Module 4 Nonclinical Study Reports)

Conducting laboratory and location: Novartis Pharma AG  
Preclinical Safety  
Toxicology/Pathology

GLP compliance and QA statement::	CH-4002 Basel Switzerland Yes, signed
Drug, lot #, and % purity:	<ul style="list-style-type: none"> <li>• Everolimus (SDZ RAD solid dispersion), 9.09% nominal concent of active ingredient, white to off-white powder, batch #s X081 0596 and X09 0796.</li> <li>• SDZ RAD solid dispersion placebo (HPM cellulose 3 and lactose)</li> </ul>

### Key Study Findings

- This study has been reviewed previously. It was identified by this reviewer as potentially relevant to the change in formulation. Re-review determined that the formulations tested are not directly relevant to the new clinical formulation.

### Methods

Doses: 0, 1.5 or 15 mg/kg/day of either batch # 081 0596 or batch # X096 0796  
 Frequency of dosing: Daily for 2 weeks (14 doses total)  
 Route of administration: Oral gavage  
 Dose volume: 5 ml/kg  
 Formulation/Vehicle: Drinking water  
 Species/Strain: Rat (Hanlbm:WIST)  
 Number/Sex/Group: 10/sex/group  
 Age: 10 weeks at start of treatment  
 Weight: Males 203 to 298 g  
 Females 132 to 200 g

### Review Comments

- This study was identified for potential review based on the title and summary reporting.
- With vigorous stirring of the water, the solid dispersion powder was added slowly, to prevent agglomeration. After 5 minutes, a uniform dispersion was formed.
- The dispersion powder was described as “HPM-cellulose 3” and lactose, but the amounts of each were not specified in the study report.
- This reviewer concludes that this study report is not directly relevant to the clinical formulation under NDA 203985.

## **11 Integrated Summary and Safety Evaluation**

No new nonclinical data relevant to the clinical indication were submitted to NDA 203985. No new impurities, or increased exposures to unqualified impurities, are expected.

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/s/  
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ANDREW J MCDOUGAL  
07/27/2012

WHITNEY S HELMS  
07/27/2012

I concur with the opinion of Dr. McDougal that the nonclinical data provided to support the approval of Afinitor are sufficient to support the approval of Affinitor Disperz for the same indications.

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 203985**

**Applicant: Novartis  
Pharmaceutical Corp.**

**Stamp Date: February 29, 2012**

**Drug Name: Affinitor Disperz  
(everolimus) dispersible tablet**

**NDA Type: 505(b)(1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		This will be a review issue.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		This will be a review issue, no pertinent outstanding nonclinical requests have been identified

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		This will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?	X		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	Not applicable		

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. No issues identified

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/s/  
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ANDREW J MCDOUGAL  
04/05/2012