CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review/CDTL Review
NDA/BLA # Supplement #	22-334
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	June 30, 2008
PDUFA Goal Date	March 30, 2008
Proprietary Name / Established (USAN) Name	Afinitor/everolimus
Dosage Forms / Strength	Tablets/ 5 mg and 10 mg
Proposed Indication(s)	AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	X
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	X
DSI	X
CDTL Review	N/A
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DRISK	X
Other – IRT Review	X

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This new drug application seeks approval of AFINITOR® (everolimus) tablets for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. This review will summarize the safety and efficacy data and the conclusions and recommendations of each review discipline. This review will also serve as the Cross-Discipline Team Leader Review.

2. Background

The application was received on 6/30/08 and was designated a priority review. However, the review clock was extended to 3/30/09 because of the submission of major amendments.

The mechanism of action of Afinitor is described in the following excerpt from the agreed-upon package insert.

> Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), 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 and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), 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.

3. CMC/Device

The Chemistry Review of the drug substance made the following recommendation and conclusion on approvability.

Sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance, everolimus. The drug substance manufacturing facilities have acceptable cGMP status. From the chemistry, manufacturing and controls perspective, applications making reference to everolimus drug substance CMC in NDA ___ can be approved. b(4)
The adequacy of drug product CMC is being evaluated under separate NDA reviews.

The Chemistry Review of the drug product made the following recommendations.

A. Recommendation and Conclusion on Approvability:

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

In order to achieve proper dose reductions the following post marketing commitment was agreed to by Novartis in their submission dated 03-Mar-2009:

Develop and propose a 2.5 mg dosing form (tablet) to allow for proper dose reductions when everolimus needs to be co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dose form should be sufficiently distinguishable from the 5 mg and the 10 mg tablets. Full chemistry, manufacturing and controls (CMC) information for the 2.5 mg dosage form including the batch data and stability data, labels, updated labeling; updated environmental assessment section is required in a prior approval supplement.
Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol

The ONDQA Division Director's Memo stated that "ONDQA recommends approval (AP) of the 5 mg and 10 mg tablet strengths as provided in the original submission and as provided in the twelve amendments cited herein."

Comment: I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and with the proposed post-marketing commitment. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation made the following recommendations.

A. Recommendation on approvability
There are no pharmacology/toxicology issues which preclude approval of everolimus (Afinitor®) for the requested indication.

B. Recommendation for nonclinical studies
No additional non-clinical studies are required for the proposed indication.

C. Recommendations on labeling
Recommendations on labeling have been provided within team meetings and communicated to the sponsor.

The Pharmacology Acting Team Leader Memorandum concurred that the pharmacology and toxicology data support the approval of Afinitor and noted that "There are no outstanding non-clinical issues related to the approval of Afinitor for the proposed indication."

The Associate Director for Pharmacology Memorandum concurred with the reviewers' conclusions that Afinitor may be approved and that no additional pharmacology or toxicology studies are necessary for the proposed indication.

Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review provided the following executive summary and recommendations.

> Everolimus is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). The current submission is the original NDA for everolimus for the treatment of advanced renal cell carcinoma (RCC). Everolimus has also been evaluated under ——— b(4)
> indications.
>
> To support the efficacy in advanced renal cell carcinoma, the sponsor conducted one randomized, controlled phase 3 study. Patients in the phase 3 study were randomized to receive best supportive care plus placebo or 10 mg of everolimus daily. Progression free survival was the primary endpoint and the median PFS for the everolimus treatment arm ranged from 3.71 to 5.52 months compared to 1.87 months for patients receiving placebo.
>
> Everolimus is a CYP3A4 substrate. Multiple drug-drug interaction studies were conducted under the NDAs for the transplant indications. Based on the results from the drug-drug interaction studies with ketoconazole, erythromycin and verapamil no dose adjustments will be provided in the label since the increases in everolimus exposures can not be adjusted by lowering the dose to 5 mg QD. For strong CYP3A4 inducers, a dose increase to 20 mg would compensate for the decrease in everolimus exposure. For strong CYP3A4 inhibitors because of the significant increase in exposure labeling instructions co-administration is not recommended. Currently, for moderate CYP3A4 inhibitors generic 'use with caution' statements will be proposed until the sponsor can develop a 2.5 mg dose for market.

A study in patients with normal hepatic function and patients with moderate hepatic impairment supported the labeling recommendation of a 50% dose reduction for patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied and that everolimus should not be used in this patient population.

The IRT review of the thorough QT study suggested that everolimus has a low potential to prolong the QT interval. IRT proposed labeling has been added to the package insert.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-334. This NDA is considered acceptable from a clinical pharmacology perspective.

Post Marketing Requirements

1. A study in patients with severe hepatic impairment.
2. Make available a 2.5 mg formulation.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

Comment: I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. I also concur with the recommended post-marketing requirement for a study in patients with severe hepatic impairment. The availability of a 2.5 mg formulation will be a postmarketing commitment.

6. Clinical Microbiology

The Product Quality Microbiology Review recommended approval.

7. Clinical/Statistical-Efficacy

A single randomized trial was submitted in support of the application. A summary of the study design and results is provided in the following excerpt from the agreed-upon package insert.

An international, multicenter, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score[1] and prior anticancer therapy.

Progression-free survival (PFS), documented using RECIST (Response Evaluation Criteria in Solid Tumors) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR 10 mg daily.

In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

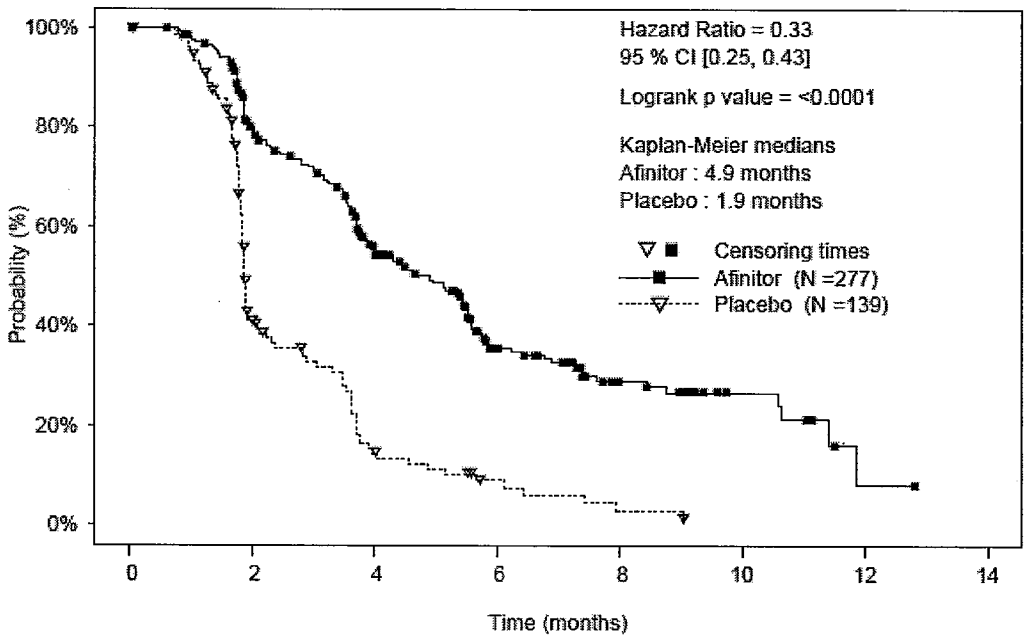
AFINITOR was superior to placebo for progression-free survival (see Table 3 and Figure 1). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. The overall survival (OS) results were not mature and 32% of patients had died by the time of cut-off.

Table 3 Efficacy Results by Central Radiologic Review

	AFINITOR N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value[a]
Median Progression-free Survival (95% CI)	4.9 months (4.0 to 5.5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.0001
Objective Response Rate	2%	0%	n/a[b]	n/a[b]

[a] Log-rank test stratified by prognostic score.
[b] Not applicable.

Figure 1 Kaplan-Meier Progression-free Survival Curves



The Clinical Review recommended approval of everolimus for the proposed indication with the following phase 4 commitments.

1. Develop and propose a 2.5 mg dosing form (tablet) to allow for proper dose reductions when everolimus needs to be co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dose form should be sufficiently distinguishable from the 5 mg and the 10 mg tablets.

2. Conduct a trial in patients with severe hepatic impairment (Child Pugh Class C). This study need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.

3. Submit the final, per-protocol overall survival analysis of study C2240, which was to be conducted at time of 2 years after randomization of the last patient.

The Statistical Review and Evaluation provided the following conclusions and recommendations.

> The applicant has submitted results from one phase III, randomized, double-blind, comparative clinical trial (Study C2240) comparing Afinitor (everolimus or RAD001) plus best supportive care (BSC) and placebo plus BSC in patients with advanced renal cell carcinoma (RCC) who were previously treated with sunitinib, sorafenib or both sequentially. The study showed benefit of RAD001 over placebo in terms of progression-free survival (PFS) as determined by independent radiologic review in this patient population based on the data from a planned interim analysis. However, the overall survival, a secondary endpoint, was not improved with RAD001 with approximately 32% overall deaths, but a trend favoring RAD001 was observed. RAD001 also did not show statistically significant superiority over placebo in terms of overall response rate (another secondary endpoint) as determined by independent radiologic review. The data and statistical results provide adequate evidence to support the claims about PFS proposed in the NDA.

The Statistical Team Leader's Memo provided the following conclusion.

> This Team Leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Somesh Chattopadhyay) of this application. The study showed benefit of RAD001 over placebo in terms of progression-free survival (PFS) as determined by independent radiologic review in this patient population based on the data from a planned interim analysis. However, the overall survival, a secondary endpoint, was not improved with RAD001 with approximately 32% overall deaths, but a trend favoring RAD001 was observed. RAD001 also did not show statistically significant superiority over placebo in terms of overall response rate (another secondary endpoint) as determined by independent radiologic review. The data and statistical results provide adequate evidence to support the claims about PFS proposed in the NDA.

Comment: I concur that a clinically and statistically significant improvement in PFS has been demonstrated in this trial. Although only a single randomized trial was submitted, the PFS findings are robust.

8. Safety

The safety profile of everolimus is provided in the following summary from the agreed-upon package insert.

> The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.
>
> The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 53 from the Clinical Review compares the incidence of adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 1: Adverse reaction that occurred in the everolimus arm > 10% by selected broader terms search (Feb 28, 2008 cut-off)

	Everolimus N=274 (%)			Placebo N=137 (%)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0

Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (days)	141			60		

a Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.
b Includes all preferred terms within the 'infections and infestations' system organ class including pneumonia, aspergillosis, candidiasis, and sepsis.
c Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.
Source: Study C2240 study report and safety update

Key laboratory abnormalities are summarized in Table 2 from the package insert.

Table 2 Key Laboratory Abnormalities Reported at a Higher rate in the AFINITOR Arm than the Placebo Arm

Laboratory Parameter	**AFINITOR 10 mg/day N=274**			**Placebo N=137**		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical Chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0

Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

[a] Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

Comment: The safety database is adequate for this indication. Major safety concerns include non-infectious pneumonitis, infections, oral ulcerations, renal dysfunction, hyperglycemia, hyperlipidemia, myelosuppression, drug-drug interactions with strong or moderate CYP3A4 inhibitors or with strong CYP3A4 inducers, use in patients with impaired hepatic function, use of live vaccines, and use in pregnancy. These are all addressed in the Warnings and Precautions section of the package insert.

9. Advisory Committee Meeting

This application was not taken to a meeting of the Oncologic Drugs Advisory Committee (ODAC) because the application is based on a trial demonstrating a clinically and statistically significant improvement in progression-free survival with an acceptable benefit/risk ratio. Progression-free survival has previously been used as the basis for approval of drugs for the treatment of advanced renal cell carcinoma and the safety profile is similar to that of other drugs approved for this indication.

10. Pediatrics

The PeRC concurred with a waiver of the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since this disease does not occur in the pediatric population.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Includes:

- Proprietary name: DMEPA concurred with the proprietary name.
- Physician labeling: Agreement was reached on the physician labeling.
- Carton and immediate container labels: Agreement was reached on the final carton and blister labels.
- Patient labeling/Medication guide: Agreement was reached on patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval is recommended.
- Risk Benefit Assessment: The risk benefit assessment is acceptable for this patient population. The improvement in PFS is clinically significant, the toxicity profile is similar

to that of other agents approved for the treatment of advanced renal cell cancer, and there are no other therapies of proven benefit in patients with failure of prior treatment with sunitinib or sorafenib.

- Recommendation for Postmarketing Risk Management Activities: Routine postmarketing surveillance with special emphasis on non-infectious pneumonitis, infections, and renal dysfunction.
- Recommendation for other Postmarketing Requirements and Commitments:

Trial A2303 evaluated everolimus in patients with moderate hepatic impairment (Child Pugh Class B) and due to increases in everolimus exposure, a dose reduction is needed in these patients. No exposure data are available for patients with severe hepatic impairment and current labeling recommends that Afinitor® (everolimus) should not be used in these patients. Because of an unexpected serious risk of increased drug exposure when Afinitor® (everolimus) is administered to patients with severe hepatic impairment, the following postmarketing clinical trial will be required:

1. Conduct a trial in patients with severe hepatic impairment (Child Pugh Class C). This trial need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.

Final Protocol Submission:	May 14, 2009
Trial Start Date:	October 14, 2009
Final Report Submission:	April 14, 2011

The following are the agreed-upon postmarketing study commitments:

2. Submit the final, per-protocol overall survival analysis of protocol C2240 which was to be conducted 2 years after randomization of the last patient.

   Protocol Submission: July 27, 2006
   Trial Start Date: December 6, 2006
   Final Report Submission: June 2010

3. Develop a 2.5 mg dosage form (tablet) to allow for proper dose reductions when Afinitor® (everolimus) is co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dosage form should be sufficiently distinguishable from the 5 mg and 10 mg tablets. Full chemistry, manufacturing and controls (CMC) information for the 2.5 mg dosage form including batch and stability data, updated labeling, and an updated environmental assessment should be submitted as a prior approval supplement.

Protocol Submission Date:	May 14, 2009
Final Report Submission:	January 14, 2010

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

/s/

Robert Justice
3/27/2009 07:08:30 PM
MEDICAL OFFICER