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 [redacted] indications. b(4)

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.

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