CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director 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

OFFICE DIRECTOR'S REVIEW

INDICATION: The treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

MECHANISM OF ACTION: 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.

CLINICAL EVAULUATION: The efficacy and safety of everolimus tablets (AFINITOR®, Novartis Pharmaceuticals Corporation) were evaluated in an international, multicenter, randomized, double-blind trial comparing everolimus to placebo. All patients received best supportive care. The trial was conducted in patients with metastatic renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Prior therapy with bevacizumab, interleukin-2, or interferon-α was also permitted. Randomization was stratified according to prognostic score and prior anticancer therapy.

A total of 416 patients were randomized (2:1) to receive everolimus (n=277) or placebo (n=139). Demographics were well balanced between the two arms. Progression-free survival (PFS) was the trial's primary endpoint. The median PFS was 4.9 and 1.9 months in the everolimus and placebo arms, respectively (HR = 0.33, p value < 0.0001). The treatment effect was similar across prognostic scores and prior treatment status. The overall survival results are not mature; 32% of patients had died by the time of data cut-off. The objective response rates were 2% and 0% for everolimus and placebo, respectively. After documented radiological progression, patients receiving placebo could receive everolimus.

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. Anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine were the most common laboratory abnormalities (incidence ≥50%). 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%) occurred on the everolimus arm but not on the placebo arm.

The recommended dose of everolimus for treatment of advanced renal cell carcinoma is 10 mg once daily at the same time either with or without food.

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

Approval is recommended. 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 Post-marketing Risk Management Activities: Routine postmarketing surveillance with special emphasis on non-infectious pneumonitis, infections, and renal dysfunction.

Recommendation for other Post-marketing 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 everolimus should not be used in these patients. Because of an unexpected serious risk of increased drug exposure when 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 post-marketing 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 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

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