CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-334
Submission Date:	27 June 2008
Brand Name:	Afinitor®
Generic Name:	everolimus
Formulation:	5 mg and 10 mg tablets
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OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	Novartis
Submission Type; Code:	Original NDA; 000
Dosing regimen:	10 mg once daily
Indication:	treatment of advanced renal cell carcinoma

OCP Briefing held on February 19, 2009 attended by: Amna Ibrahim, Pengfei Song, Ramana Uppoor, Phil Colangelo, Jun Yang, Aakanksha Khandelwal, Sarah Schrieber, Nam Atiqur Rahman, Gil Burckart, Rosane Charlab-Orbach, Gerlie Gieser, Qi Liu, Chris Tornoe, Ping Zhao, Lillian Zhang, Anthony Murgo, Ellen Maher, Qin Ryan, Partha Roy.

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1 EXECUTIVE SUMMARY

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 two NDAs for transplant 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 [redacted] tatements will be proposed until the sponsor can develop a 2.5 mg dose for market. b(4)

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

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