CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Afinitor (everolimus)

Date: March 24, 2009
To: File for NDA #22-334
From: John K. Leighton, PhD, DABT
Associate Director for Pharmacology
Office of Oncology Drug Products

I have examined pharmacology/toxicology supporting review, memoranda and labeling provided by Drs. Luan Lee and Haleh Saber. I concur with their conclusions that Afinitor may be approved. No additional pharmacology or toxicology studies are necessary for the proposed indication.

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/s/

John Leighton
3/24/2009 03:32:48 PM
PHARMACOLOGIST

MEMORANDUM

Date: March 23, 2009
From: Haleh Saber, Ph.D.
Pharmacology Acting Team Leader
Division of Drug Oncology Products
To: File for NDA #22,334
Afinitor® (everolimus) tablets
Re: Approvability for Pharmacology and Toxicology

Afinitor® (everolimus) is indicated for the treatment of patients with advanced renal cell carcinoma after disease progression following treatment with sunitinib or sorafenib. Nonclinical studies that investigated the pharmacology and toxicology of everolimus were provided in support of the NDA. Everolimus, an ether derivative of sirolimus, is an inhibitor of the mTOR pathway. mTOR is a serine-threonine kinase downstream of PI3K/AKT pathway, which acts as a growth factor and nutrient sensor. Inhibition of mTOR by everolimus was shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies. In the Highlight section of the label, the pharmacologic class of Afinitor is defined as "kinase inhibitor" to be consistent with other products in this class. Of note, everolimus is approved in Europe as an immunosuppressive agent, under the name Certican®.

Pharmacology, safety pharmacology, pharmacokinetic/ ADME, and toxicology studies supporting the marketing application of Afinitor for the proposed indication were conducted in *in vitro* systems and in animal species. Based on the general toxicology studies, toxicities associated with everolimus were comparable to those reported for temsirolimus, another mTOR inhibitor approved for the treatment of renal cell carcinoma. Everolimus-related findings included effects in the male reproductive system, coagulation pathway, GI tract, lungs, metabolism/endocrine system, and lymphoid tissues. Nonclinical studies in rodents indicated that everolimus and/or its metabolites crossed the blood-brain barrier and the placenta, and were excreted into milk of lactating animals.

Everolimus was negative for evidence of genetic toxicity in the standard battery of tests described by ICH S2. Everolimus was negative for evidence of carcinogenicity in two rodent studies. Reproductive toxicology studies conducted with everolimus included the male fertility, embryo-fetal toxicity and prenatal/ postnatal development toxicity studies. Everolimus resulted in infertility in male rats, with partial recovery after 10-13 weeks of treatment-free period. Oral doses of everolimus in female rats resulted in increased pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus was embryo-fetal toxic when administered to pregnant rats; toxicities included decreased number of fetus, malformation (e.g., sternal cleft) and retarded skeletal development. In rabbits, embryo-fetal toxicity was evidenced as increased resorption. Because of the embryo-fetal effects, Pregnancy Category D is recommended for everolimus. The prenatal and postnatal development study in rats at doses tested showed no adverse

effects on delivery and lactation and no drug-related effects on the developmental parameters in the offspring (morphological development, motor activity, learning, or fertility assessment). However, reduced body weight and slight reduction in survival were noted in offspring.

The nonclinical studies were reviewed in detail by Dr. Shwu-Luan Lee. The nonclinical findings are summarized in the "Executive Summary" and "Discussion and Conclusions" of the review, and reflected in the product label.

Recommendation: I concur with Dr. Lee's conclusion that pharmacology and toxicology data support the approval of NDA 22,334 for Afinitor. There are no outstanding non-clinical issues related to the approval of Afinitor for the proposed indication.

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