CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 19, 2009
To:	Robert Justice, M.D., Director Division of Drug Oncology Products (DDOP)
Thru:	Claudia Karwoski, Pharm.D., Acting Director Division of Risk Management (DRISK)
From:	Scientific Lead: Jeanne Perla Ph.D., Risk Management Analyst, DRISK Team Members: Suzanne Berkman Pharm.D., Senior Risk Management Analyst and (acting) Team Leader, DRISK Mary Dempsey, Risk Management Program Coordinator, DRISK
Subject:	Review of Proposed "Safety Risk Management Plan" dated June 6, 2008 and submitted June 30, 2008
Drug Name(s):	Afinitor (everolimus)
Submission Number:	0000
Application Type/Number:	NDA 22-334
Applicant/sponsor:	Novartis
OSE RCM #:	RCM 2009-83

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EXECUTIVE SUMMARY

Everolimus (Afinitor) is a rapamycin derivative; mTOR (mammalian target of rapamycin) inhibitor. The proposed indication is for the treatment of patients with advance renal cell carcinoma (RCC). Afinitor for will be available in 5 mg and 10 mg tablets; the recommended dose is 10 mg daily; dose reduction to 5 mg daily may be needed to manage adverse drug reactions.

Novartis has identified the following risks associated with Afinitor: non-infectious pneumonitis, severe infection, stomatitis, and increased creatinine. Potential safety concerns identified by the Novartis are: cardiac failure, wound healing and drug-drug interactions.

To manage these risks, the Sponsor proposes labeling, including a Patient Package Insert and routine pharmacovigilance. The Division of Drug Oncology Products (DDOP) has not identified any additional safety concerns for Afinitor that warrant consideration of a REMS at this time for the proposed indication. The risks and the routine risk management approach are consistent with other approved chemotherapeutic agents, immunosuppressive drugs, and mTOR inhibitors approved for the treatment of RCC.

Should the DDOP raise further concerns with the risks outlined within this review or identify additional/new risks associated with everolimus warranting a risk evaluation and mitigation strategy, please send a consult to OSE Division of Risk Management.

1 BACKGROUND

1.1 INTRODUCTION

This review follows a request from the DDOP for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed "safety risk management plan" for Afinitor (everolimus) 5 and 10 mg Tablets dated June 6, 2008 (submitted on June 30, 2008, with the original NDA) and submitted to OSE for consultation on December 30 2008.

Everolimus is a mTOR (mammalian target of rapamycin) inhibitor. In vivo, everolimus appears to reduce cell proliferation, glycolysis and angiogenenesis of solid tumors. It has been submitted for review for the treatment of patients with advanced renal cell carcinoma (RCC). The proposed dose is 10 mg to be taken by mouth once daily at the same time every day ——— b(4)
——— Dose reduction to 5 mg daily may be needed to manage adverse drug reactions. The medical officer's review recommends approval of everolimus for the treatment of patients with advanced RCC "after disease progression following treatment with sunitinib or sorafenib."

Everolimus is marketed in more than 60 countries under the tradename Certican for prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. The initial dose for this indication is 1.5mg/day, a substantially lower dose than the proposed dose for RCC. Total exposure based solely upon commercial usage currently exceeds 10,000 patient-years.

The sponsor notes that three products are approved for the treatment of advanced RCC: sorafenib (Nexavar; tyrosine kinase inhibitor (TKI) that targets the vascular endothelial growth factor receptor, (VEGF)), sunitinib (Sutent; TKI-VEGF), and temsirolimus (Torisel). Temsirolimus is the ester analog of sirolimus (Rapamune)[1], and administered as a once weekly intravenous infusion. Temsirolimus and sirolimus are marketed without additional risk management measures beyond labeling and routine pharmacovigilance.

1.2 REGULATORY HISTORY

Everolimus is not approved in the United States. It has been in clinical development as an investigational immunosuppressant drug for transplantation ——— since 1996. Two NDAs for everolimus have been previously submitted by Novartis Pharmaceuticals for use in b(4)
transplant patients: ——— for the prophylaxis of organ rejection in allogeneic kidney transplantation and NDA 21-628 for the prophylaxis of organ rejection in cardiac transplantation. Both NDAs have received two Approvable actions on October 20, 2003, and on August 27, 2004, both letters cited insufficient evidence of a safe dosing regimen for everolimus when used in combination with cyclosporine.

Since November 2002, everolimus has also been in development to treat cancer patients both as monotherapy ——— under IND 66,279. b(4)
Novartis submitted an NDA for Afinitor on June 30, 2008 for priority review for the treatment of advance RCC. The goal date was extended by three months following submission of a major amendment. The extended user fee goal date is March 30, 2009.

2 MATERIAL REVIEWED

The following materials were reviewed:

- Everolimus "Safety Risk Management Plan" dated June 6, 2008 and submitted on June 30, 2008

[1] Rapamune (Wyeth; FDA approved in 1999]) is indicated for the prevention of organ rejection in renal transplant recipients aged 13 years or older who are at low to moderate risk of acute rejection. Rapamune is available as a tablet and oral solution.

- Everolimus draft labeling submitted June 30 2008.
- Ryan Q. Clinical Review of NDA 22-334; Afinitor (everolimus). DRAFT provided on March 11, 2009.
- Berkman, S. "Torisel Risk Management Plan Review." Signed by E. Unger on April 5, 2007.
- Rapamune Prescribing Information. Wyeth. March 2008.
- Torisel Prescribing Information. Wyeth. September 2008.
- MO Mid-cycle Slides dated February 11 2008

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

3.1.1 Sponsors' Safety Concerns

The sponsor has identified the following safety concerns:

- Non-infectious pneumonitis: In study CRAD001C2240[2], baseline non-infectious pneumonitis was reported in approximately 20% of patients in both groups. New cases of pneumonitis were reported in 24 (8.9%) patients in the everolimus group and no one from the placebo group. The maximum severity grading was as follows: 4 patients (1.5%) with grade 1, 12 patients (4.5%) with grade 2, and 9 patients (3.3%) with grade 3. No grade 4 cases were evident.
- Severe infection: In study CRAD001C2240[2], severe infections were diagnosed in 67 patients (24.9%) in treatment group and 15 patients (11.1%) in the placebo group.
- Stomatitis: In study CRAD001C2240[2] stomatitis was experienced in 41.6% of the patients in the treatment group and 8.1% of the patients in the placebo group.
- Increased creatinine: In study CRAD001C2240[2], 7.8% of patients in the everolimus arm and 0.7% in the placebo arm had increases in serum creatinine concentrations.

The sponsor has identified the following potential safety concerns:

- Cardiac failure: In study CRAD001C2240[2], cardiac disorders were reported for 6.3% (n=17) of everolimus–treated patients vs. 3% (n=4) of placebo-treated patients.
- Wound healing: Wound healing complications were not identified in this study but have been observed in patients treated with other members of the rapamycin class.
- Drug-Drug interactions: Everolimus is extensively metabolized by CYP3A4. Concurrent treatment with CYP3A4 inhibitors will decrease everolimus metabolism. Other inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood levels.

3.1.2 DDOP SAFETY CONCERNS

The Medical Officer identifies the following adverse reactions in the draft clinical review[3] which "should be watched and managed appropriately during treatment:"

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[2] Study CRAD001C2240 had a total of 410 patients; Afinitor n= 272, control n=138.

[3] Ryan Q. Clinical Review of NDA 22-334; Afinitor (everolimus). DRAFT provided on March 11, 2009.

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