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 [redacted] b(4) [redacted] 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 [redacted] since 1996. Two NDAs for everolimus have been previously submitted by Novartis Pharmaceuticals for use in b(4) transplant patients: [redacted] 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 [redacted] 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.

- Hyperlipidemia and hyperglycemia: Two fold increases in incidence were seen in the everolimus arm comparing to the placebo arm. Both of these are known class effects for rapamycin and its derivatives. [4]
- Renal function: Treatment related creatinine elevation and renal failure[4] occurred 9% and 2% more, respectively, in the everolimus arm. The Medical Officer recommends carefully monitoring of the serum creatinine and renal function.
- Pneumonitis:[4,5] A blinded central radiology review was conducted which reported new or worsening CT changes in 48.2% and 14.6% of everolimus and placebo arm patients, respectively. Clinically reported pneumonitis occurred in only 13.5% everolimus patients and 0% placebo patients. Among patients in the placebo arm with a CT suggesting pneumonitis, no clinical cases of pneumonitis were reported. Therefore, monitoring everolimus treatment-emergent pneumonitis should combine the clinical presentation and CT results. Everolimus dose reduction was required for 50% (14/28) of grade 2 or 3 cases and treatment discontinuation for 36% (10/28). Therefore, criteria for dose reduction and discontinuation should be included in the proposed label.
- Increased bleeding events among patients on the everolimus arm (8%) were associated with thrombocytopenia, which occurred in 23% of patients. The number of thromboembolic events was similar between the two arms.
- Liver function test abnormalities were noted in everolimus treated patients with or without co-existing liver disease, 40% and 4%, respectively. It does not appear that any serious adverse events (i.e., hepatic failure) were reported.
- Mucositits:[4] Significant numbers of patients developed mucositits in the everolimus arm. However, the severity and resolution course appeared to be acceptable with necessary supportive treatment per the Medical Officer.

Deaths due to acute respiratory failure (1.9%), infection (1.1%), and renal failure (0.4%) were observed on the everolimus arm. No deaths due to an adverse reaction were seen in the placebo arm. The adverse reactions that caused treatment termination were pneumonitis, dyspnea, lung disorders, fatigue and renal failure. Mucositits, pneumonitis and symptoms related to both were the most common reasons for treatment delay or dose reduction. The most common adverse reactions requiring medical interventions during everolimus treatment were anemia, gastrointestinal, respiratory, and skin symptoms.

The most common adverse reactions to everolimus were similar to other rapamycin derivatives.

3.2 SPONSOR'S PROPOSED RISK MANAGEMENT PLAN

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[4] Risk is included in the Torisel (temsirolimus) and/or Rapamune Prescribing Information.

[5] Torisel PI refers to "interstitial lung disease" and includes the following:

- WARNINGS: Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.
- ADVERSE REACTIONS: Respiratory, Thoracic and Mediastinal Disorders – Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.

The sponsor's proposed "safety risk management plan" is consistent with the EMEA risk management template. The sponsor does not identify any risks beyond those common to chemotherapeutic agents, other immunosuppressive drugs, and/or mTOR inhibitors as a class. Therefore, Novartis proposes that routine measures (labeling and spontaneous adverse event reporting) are appropriate.

We note that the sponsor has submitted a patient package insert (PPI) for review and did not specifically cite this as part of their risk management approach. Sutent and Nexavar have PPIs while Torisel does not have FDA-approved patient labeling. None of these drugs have Medication Guides.

4 DISCUSSION AND CONCLUSION

The risk management proposal for everolimus is consistent with routine pharmacovigilance. Largely, it appears that the risks identified by the sponsor and DDOP are consistent with other approved chemotherapeutic agents, immunosuppressive drugs, and/or other rapamycin/mTOR inhibitors. And, in general, these products manage such risks through routine measures (labeling and spontaneous adverse event reporting). Temsirolimus and sirolimus are marketed without additional risk management measures beyond labeling and routine pharmacovigilance. We note that pneumonitis/interstitial lung disease is a concern however, DDOP does not believe that additional measures beyond labeling are necessary at this time. We recommend expedited reporting of spontaneously reported serious pulmonary events. In addition, DRISK recommends the use of the term [redacted] instead of pneumonitis in the product labeling to be consistent with Torisel unless there is a compelling reason otherwise. b(4)

Based on the information provided at this time and considering the patient population, severity of RCC, mortality of RCC, limited treatment options[6] (Proleukin[7], Sutent[8], Nexavar[9], interferon alfa, and Torisel[10]), comparable level of risks associated with other treatment options and with other chemotherapeutic agents in general, along with the limited scope of the prescribing population; it appears that the Sponsor's proposal is a reasonable approach to manage the risks at this time.

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

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[6] Cohen HT, McGovern FJ. Renal-cell carcinoma. [Review article]. NEJM 2005.353(23):2477-2490.

[7] Proleukin (aldesleukin) Package Insert. Chiron. September 2000.

[8] Sutent (sunitinib) Package Insert, Pfizer. November 2008.

[9] Nexavar (sorafenib) Package Insert. August 2006.

[10] Torisel Prescribing Information. Wyeth. September 2008.

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/s/

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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:	December 8, 2008
To:	Robert Justice, M.D., Director Division of Drug Oncology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Melina Griffis, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Afinitor (Everolimus) Tablets 5 mg and 10 mg
Application Type/Number:	NDA 22-334
Applicant/sponsor:	Novartis Pharmaceuticals
OSE RCM #:	2008-1236

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis reviewed the carton, container and insert labeling and noted areas of needed improvement with respect to the positioning and prominence of the product strength. Our recommendations are provided in section 5.2 of this review. Please forward these recommendations to the Applicant prior to approval.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Drug Oncology Products for assessment of the proposed labels and labeling for Afinitor.

1.2 REGULATORY HISTORY

The proposed proprietary name, Afinitor, was determined to be acceptable by DMEPA in a previous review (OSE 2008-257 dated August 11, 2008).

1.3 PRODUCT INFORMATION

Afinitor (Everolimus) is an mTOR inhibitor indicated for the treatment of advanced renal cell carcinoma. It will be available in 5 mg and 10 mg tablets and the recommended dose is 10 mg to be administered once daily at the same time every day [redacted] Dose reduction may be needed to manage adverse drug reactions, therefore, the dose may be reduced to 5 mg daily. b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff to conduct a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. The Division defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container labels communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on June 27, 2008 the following labels for our review (see Appendices A and B for images):

- Blister card container labels (5 mg, 10 mg and professional sample)
- Carton labels (5 mg, 10 mg and professional sample)

3 RESULTS

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
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Date:	February 16, 2009
To:	Robert L. Justice, M.D., Director **Division of Drug Oncology Products**
Through:	Jodi Duckhorn, MA, Team Leader **Patient Labeling and Education Team** **Division of Risk Management**
From:	Nancy Carothers, RN, BA Patient Product Information Reviewer **Patient Labeling and Education Team** **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert) #2
Drug Name(s):	Afinitor® Tablets, oral (everolimus)
Application Type/Number:	NDA 22-334
Applicant/sponsor:	Novartis Pharma Stein AG
OSE RCM #:	2008-2055

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_____ Draft Labeling (b5)

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