

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203985Orig1s000

**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
Office of Medication Error Prevention and Risk Management**

Risk Management Plan Review

Date: July 24, 2012

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Drug Name(s): Everolimus

Therapeutic Class: kinase inhibitor

Dosage and Route: Tablets for oral suspension: 2 mg, 3 mg and 5 mg

Application Type/Number: 203985

Applicant/sponsor: Novartis

OSE RCM #: 2012-562

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1 INTRODUCTION

This review documents the Division of Risk Management review and agreement with Novartis' proposed risk management plan for everolimus (Afinitor; tablets for oral suspension), a mammalian target of rapamycin (mTOR) inhibitor. Novartis' risk management plan consists of routine measures (labeling) and post-marketing pharmacovigilance.

1.1 BACKGROUND

This NDA for everolimus is for a new formulation, tablets for oral suspension. It is a dispersible tablet with a (b) (4) compared to the immediate release tablets. The proposed indication is for the treatment of pediatric and adult patients with subependymal glial cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC) who require therapeutic intervention but are not likely to be cured by surgery. Dosing is consistent with the current approved dosing in the Afinitor label with changes to the target trough concentration (from 5-(b) (4) ng/mL to (b) (4) 15 ng/mL).

1.2 REGULATORY HISTORY

Everolimus is approved in the US as two different products:

- Afinitor (everolimus) Tablets: initial US approval (2009)
 - Indications:
 - treatment of patients with progressive neuroendocrine tumors (PNET) of pancreatic origin that is unresectable, locally advanced or metastatic
 - advanced renal cell carcinoma (RCC) after failure of sunitinib or sorafenib
 - SEGA associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection.
 - Dose:
 - PNET and RCC: 10 mg orally once daily
 - SEGA: initial dose based on body surface area (2.5-(b) (4) mg once daily) then based on therapeutic drug monitoring (trough concentrations of 5-(b) (4) ng/mL)
 - Risk Management Plan: routine labeling (includes patient package insert (PPI)) and post-marketing pharmacovigilance
- Zortress (everolimus): initial US approval (2010) with Boxed Warning
 - Indication: prophylaxis of organ rejection in adult patients ... receiving a kidney transplant in combination with other immunosuppressants.
 - Dose 0.75 mg orally twice daily
 - Risk Management Plan: With initial drug approval, a REMS consisting of MG and Communication Plan was required to inform healthcare providers about

wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when Zortress is co-administered with standard doses of cyclosporine. The MG was removed from the REMS in November 2011.

There are two additional mTOR inhibitor products approved in the US as follows

- Rapamune (sirolimus): initial US approval (1999) with Boxed Warning
 - Indication: prophylaxis of organ rejection in patients aged ≥ 13 years receiving renal transplants
 - Dose: Supplied as 0.5, 1, and 2 mg tablets. Taken orally once daily and dose based on therapeutic drug monitoring (2-20ng/mL; 40 mg maximum daily dose).
 - Risk Management Plan: Initially, routine labeling and post-marketing pharmacovigilance was sufficient. REMS was required consisting of a MG in 2010 to be consistent with Zortress. Rapamune was released from REMS requirement in June 2011 and MG is maintained as part of labeling.
- Torisel (temsirolimus): initial US approval (2007)
 - Indication: advanced renal cell carcinoma (RCC)
 - Dose: 25 mg infusion
 - Risk Management Plan: routine labeling (no patient labeling) and post-marketing pharmacovigilance.

2 MATERIALS REVIEWED

- Novartis “Safety Risk Management Plan” dated January 30, 2012 and submitted to FDA on February 29, 2012.
- Afinitor Prescribing Information. Novartis. March 2012.
- Zortress Prescribing Information. Novartis. November 2011.
- Rapamune Prescribing Information. Wyeth. July 2011.
- Torisel Prescribing Information. Wyeth. June 2011.
- O’Connell K. DRISK Zortress Review of Risk Management Options. Signed by C. Karwoski on January 19, 2010.
- Perla J. DRISK review of Afinitor Risk Management Plan. Signed by C. Karwoski on March 19, 2009.
- Berkman, S. Torisel Risk Management Plan Review. Signed by E. Unger on April 5, 2007.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

Novartis estimates that worldwide exposure is 8,814 patient-treatment-years as of September 30, 2011.

3.2 SAFETY CONCERNS

Novartis included the following identified risks in their proposed risk management plan:

- Non-infectious pneumonitis
- Increased creatinine/proteinuria/renal failure
- Cardiac failure
- Hemorrhage
- Thromboembolism

Two risks identified in the Warnings section of the label (infections, oral ulceration) are not listed in among the identified risks in the risk management plan.

Novartis included the following “potential risks:”

- Developmental toxicity
- Reproductive toxicity
- Intestinal obstruction/ileus
- Infertility
- Secondary amenorrhea

The risks listed above are represented in some manner in the current approved labeling for Afinitor. Novartis stated that no new safety issues have been identified.

Division of Pharmacovigilance was also consulted and the safety evaluator stated that there were no notable safety signals in AERS at this time.

During the Mid-Cycle Meeting on June 13, 2012, the clinical reviewer also stated that she did not uncover any new safety concerns with this formulation/application that have not been addressed in the approved everolimus/Afinitor label.

3.3 PROPOSED RISK MANAGEMENT PLAN

To address the above safety concerns, Novartis proposed a global “safety risk management plan” which is referred to as “Afinitor Version 6 / Votubia RMP Version 4 Updated with SEGA” in the February 29, 2012 sponsor submission. The plan proposes the following measures:

- Labeling including a patient package insert.
- Routine post-marketing pharmacovigilance.

4 DISCUSSION

The risk management proposal for everolimus is consistent with routine pharmacovigilance.

Largely, it appears that the risks identified by the sponsor and DOP are consistent with other approved chemotherapeutic agents, immunosuppressive drugs, and/or mTOR inhibitors. And, in general, these products manage such risks through routine measures (labeling and spontaneous adverse event reporting). In oncology, temsirolimus and everolimus are marketed without additional risk management measures beyond labeling and routine pharmacovigilance.

Based on the information provided at this time, Novartis' proposal is a reasonable approach to manage the risks.

5 CONCLUSION AND RECOMMENDATION

In absence of any unique or additional serious safety concerns for everolimus tablets for oral suspension, we agree with the sponsor that the routine labeling and post-marketing pharmacovigilance is adequate at this time and consistent with other mTOR inhibitors approved to treat cancer.

Should the DOP raise further concerns with the risks outlined above 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.

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/s/

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