



Pediatric Focused Safety Review: Afinitor[®] (everolimus)

**Pediatric Advisory Committee Meeting
September 11, 2012**

Amy M. Taylor, MD, MHS

**Pediatric and Maternal Health Staff
Office of New Drugs**

**Center for Drug Evaluation and Research
Food and Drug Administration**

Outline

- Background Information
- Pediatric Studies
- Post-Marketing Requirements
- Labeling Changes
- Safety Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information

Afinitor® (everolimus)

- **Drug:** Afinitor®, Afinitor Disperz® (everolimus)
- **Formulations:** oral tablets, tablets for oral suspension
- **Therapeutic Category:** Antineoplastic agent
- **Sponsor:** Novartis Pharmaceuticals Corporation
- **Original Market approval:** March 30, 2009
- **Pediatric Exclusivity Granted:** July 10, 2012
- **Related product:** Zortress® (everolimus) oral tablet
 - indicated in adults for prophylaxis of organ rejection in renal transplantation.

Background Drug Information

Afinitor® (everolimus)

Indications

Afinitor® and Afinitor Disperz® are kinase inhibitors indicated for the treatment of:

- Pediatric and adult patients with tuberous sclerosis (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention, but cannot be curatively resected.
- Pediatric use is recommended for patients 1 year of age and older.

Background Drug Information

Afinitor® (everolimus)

Indications continued:

Afinitor® is indicated in adults for:

- postmenopausal women with advanced hormone receptor positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced or metastatic. The safety and effectiveness of Afinitor® in the treatment of patients with carcinoid tumors have not been established.

Background Drug Information

Afinitor® (everolimus)

Indications continued:

- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
- adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of Afinitor® in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

Pediatric Studies

Afinitor® (everolimus)

- Study 1 - A randomized (2:1), double-blind, placebo-controlled study in 117 pediatric and adult patients with SEGA associated with TSC
- Study 2 - An open-label, single arm study of the safety and efficacy of everolimus in 28 patients with SEGA associated with tuberous sclerosis complex (TSC)

*Studies numbered as they appear in Afinitor® labeling.

Pediatric Studies

Afinitor® (everolimus)

Efficacy results

- Study 1
 - The primary efficacy outcome measure was SEGA response defined as a $\geq 50\%$ reduction in the sum of SEGA volume relative to baseline in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, and new or worsening hydrocephalus.
 - There were 27 (35%) patients with SEGA responses in the Afinitor® arm and no SEGA responses in the placebo arm.
 - With a median follow-up of 8.4 months, SEGA progression was detected in 6 of 39 (15.4%) patients randomized to receive placebo and none of the 78 patients randomized to receive Afinitor®.

Pediatric Studies

Afinitor® (everolimus)

Efficacy results continued:

- Study 2
 - the primary endpoint was reduction in primary SEGA volume from baseline to Month 6.
 - Twenty eight patients received treatment (median age was 11, range 3 to 34 years). 9 out of 28 patients (32%) had a $\geq 50\%$ reduction in the tumor volume of their largest SEGA lesion.
 - Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving Afinitor® treatment. Three of these 4 patients experienced a $\geq 50\%$ reduction in the tumor volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions.



Pediatric Studies Afinitor® (everolimus) Safety Results

Adverse Reactions Reported in $\geq 10\%$ of Afinitor-treated Patients with SEGA in Study 1

	AFINITOR N=78			Placebo N=39		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any adverse reaction	97	36	3	92	23	3
Gastrointestinal disorders						
Stomatitis ^a	62	9	0	26	3	0
Vomiting	22	1	0	13	0	0
Diarrhea	17	0	0	5	0	0
Constipation	10	0	0	3	0	0
Infections and infestations						
Respiratory tract infection ^b	31	1	1	23	0	0
Gastroenteritis ^c	10	4	1	3	0	0
Pharyngitis streptococcal	10	0	0	3	0	0
General disorders and administration site conditions						
Pyrexia	23	6	0	18	3	0
Fatigue	14	0	0	3	0	0
Psychiatric disorders						
Anxiety, aggression or other behavioral disturbance ^d	21	5	0	3	0	0
Skin and subcutaneous tissue disorders						
Rash ^e	21	0	0	8	0	0
Acne	10	0	0	5	0	0

Grading according to CTCAE Version 3.0

^a Includes mouth ulceration, stomatitis, and lip ulceration

^b Includes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral

^c Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection

^d Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder

^e Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria

Pediatric Studies

Afinitor® (everolimus)

Safety results (continued)

- There was a higher per patient incidence of infectious serious adverse events in patients < 3 years of age. Six of 13 patients (46%) < 3 years receiving everolimus had at least one serious adverse event due to infection, compared to 2 of 7 patients (29%) receiving placebo.
- Amenorrhea occurred in 17% of Afinitor® treated females aged 10-55 years and none of the females in the placebo group.
- The following additional adverse reactions occurred in Afinitor® treated patients: nausea (8%), pain in extremity (8%), insomnia (6%), pneumonia (6%), epistaxis (5%), hypersensitivity (3%) and pneumonitis (1%).

Pediatric Post-Marketing Requirements

Afinitor® (everolimus)

- Submit the final report (at least 4 years of follow-up) and datasets from the randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with everolimus versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Due March 2015
- Submit the long-term (at least 5 years) follow-up efficacy and safety data from the single-arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Due November 2014
- Both reports will include an evaluation of the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth and development for pediatric patients.

Pediatric Labeling Changes Afinitor® (everolimus)

- 1 Indication and Usage – 1.5 indication is described for pediatric and adult patients
- 2 Dosage and Administration – 2.3-2.7 recommended dose, therapeutic drug monitoring, dose modifications, administration of Afinitor® tablets and administration and preparation of Afinitor Disperz® in patients with SEGA is described
- 6 Adverse Reactions – 6.5 adverse reactions seen in the clinical studies are described

Pediatric Labeling Changes

Afinitor® (everolimus) continued

- 8 Use in Specific Populations – 8.4 Pediatric Use – The clinical trials are briefly described. Use is recommended in patients with SEGA who are aged 1 year and older.
- 12 Clinical Pharmacology – 12.2 Pharmacodynamics – the relationship between trough concentrations and reductions in SEGA volume is described.
 - 12.3 Pharmacokinetic – Dose proportionality in patients with SEGA is described. Use of everolimus in patients with SEGA with hepatic impairment is described.
- 14 Clinical Studies – 14.5 the clinical studies in patients with SEGA associated with TSC are described.

Relevant Safety Labeling

Afinitor® (everolimus)

- 4 Contraindications – Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients.
- 5 Warnings and Precautions
 - Non-infectious Pneumonitis – class effect of rapamycin derivatives
 - Infections – Afinitor® has immunosuppressive properties
 - Oral Ulceration
 - Renal Failure – cases of renal failure (including acute renal failure, some with a fatal outcome have been observed.
 - Laboratory Tests and Monitoring – elevations of serum creatinine and proteinuria, hyperglycemia, hyperlipidemia, hypertriglyceridemia, decreased hemoglobin, lymphocytes, neutrophils and platelets

Relevant Safety Labeling

Afinitor® (everolimus) continued

5 Warnings and Precautions continued

- Drug-drug interactions – avoid co-administration with strong CYP3A4 inhibitors, reduce dose with co-administration with moderate CYP3A4 and/or PgP inhibitor and increase dose with co-administration with strong CYP3A4 inducers
- Hepatic impairment – exposure to everolimus was increased in patients with hepatic impairment
- Vaccinations – use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor®
- Embryo-fetal Toxicity – Women of childbearing potential should be advised to use an effective method of contraception while using Afinitor® and for up to 8 weeks after ending treatment

Afinitor[®] Drug Utilization Settings of Care April 2009 - March 2012

- The majority of Afinitor[®] sales were to mail-order/specialty pharmacies (54% of sales) during the 12-month period ending in March 2012¹
 - Due to the inability to obtain national estimates of drug utilization in the mail-order/specialty pharmacy settings, outpatient retail pharmacy utilization data (24% of sales) was examined

¹ IMS Health, IMS National Sales Perspectives™. Extracted May 2012. File: 2012-1020 Everolimus NSP BPCA May 2012.xlsx

Afinitor® Drug Utilization

U.S. Outpatient Retail Pharmacy Settings, April 2009 - March 2012

Nationally estimated number of prescriptions and patients receiving dispensed prescriptions for Afinitor® products stratified by age, from U.S. outpatient retail pharmacies

	Prescription	Share %	Patient (N)*	Share %
	19,189	100%	5,206	100%
0-16 years	830	4%	133	3%
0-2 years	61	0%	10	0%
3-16 years	769	4%	129	3%
17+ years	18,345	96%	5,106	98%
Unspecified Age	14	0%	5	0%

Source: IMS Health Vector One® National, extracted May 2012, File:2012-1020 Everolimus Vona BPCA May 2012.xls

Source: IMS Health Vector One®, National Total Patient Tracker. Extracted May 2012 File: 2012-1020 Everolimus TPT BPCA May 2012.xls

**Due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across time periods. Summing across patient age bands is not advisable and will result in overestimates of patient counts*

Afinitor[®] Drug Utilization: Prescribing Specialty and Diagnosis U.S. Outpatient Retail Settings, April 2009 - March 2012

- Top prescribing specialty for Afinitor[®] was Hematology* (42% of prescriptions)¹
 - **Pediatricians** accounted for 1% of Afinitor[®] prescriptions

* Sub-specialties of Hematology could not be determined

¹IMS Health Vector One[®] National, extracted May 2012, File:2012-1020 Everolimus Vona BPCA May 2012.xls

Total Number* of Adverse Event Reports everolimus (March 30, 2009 to March 31, 2012)

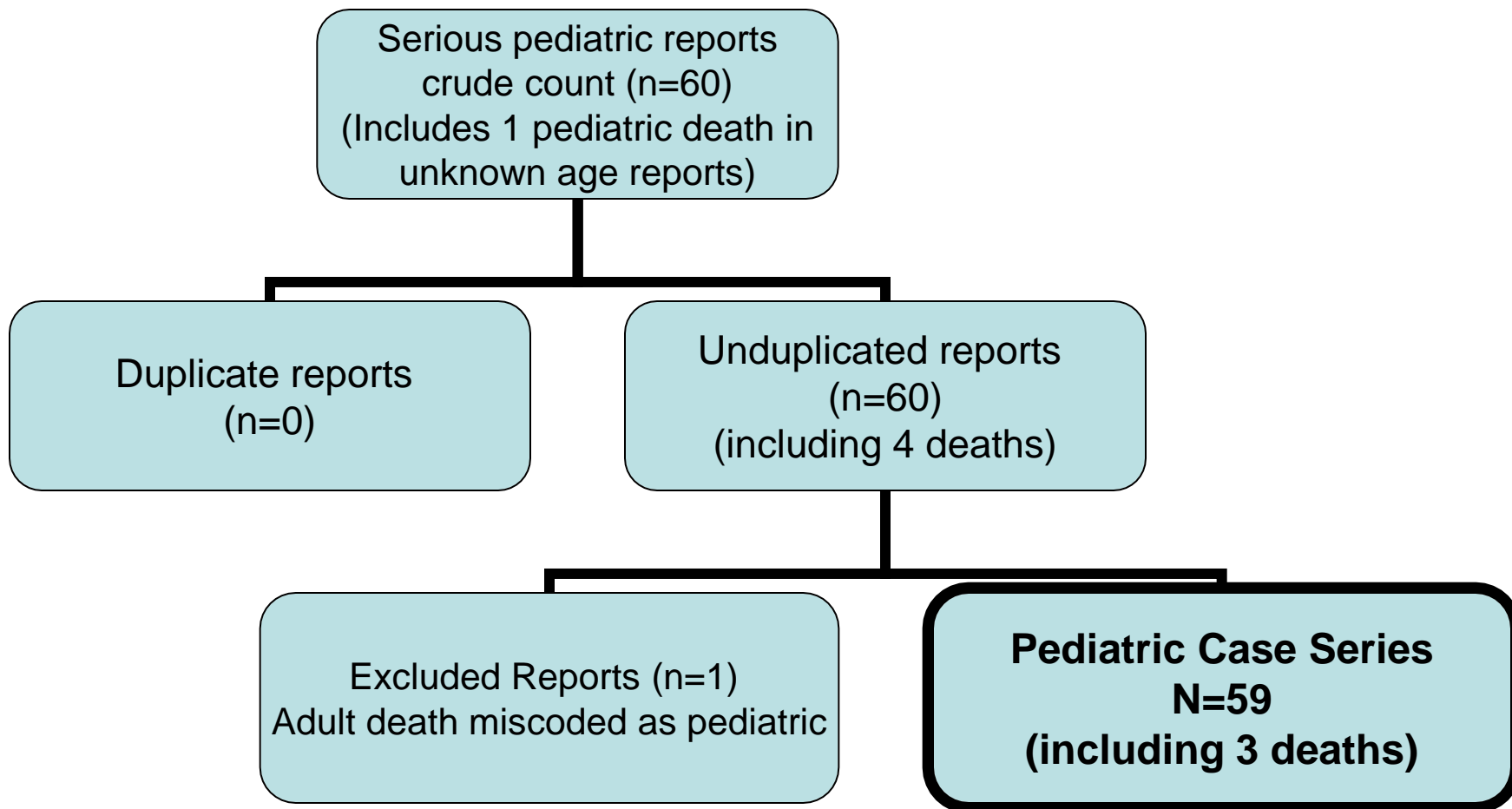
	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	3440 (1295)	3281 (1141)	695 (255)
Pediatrics (0-16 yrs.)	88 (66)	59 (40)	3 (0)
Unknown Age (Null values)	1105(563)	966 (429)	388 (154) [†]
All ages	4633 (1924)	4306 (1607)	1086 (409)

*May include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 3414.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

[†]One pediatric death

Pediatric Case Selection



Characteristics of Serious Pediatric Cases everolimus (n=59)

- Gender
 - Male – 27
 - Female – 30
 - Unknown - 2
- Age
 - 0-1 month – 0
 - 1 month - < 2 years – 4
 - 2-5 years – 17
 - 6-11 years – 16
 - 12-16 years – 21
 - Unknown – 1

Pediatric Deaths (n=3) everolimus

- A 6 year old male with a hepatic transplant for an unknown indication and chronic hepatic transplant rejection started on everolimus in addition to Neoral® because no other immunosuppressive agents were effective. The patient died due to the progression of multiple organ failure.
- A 14 year old female with metastatic renal cell carcinoma was started on everolimus. She developed nephritic syndrome and pneumonia eventually requiring hospitalization for fungal pneumonia. The patient's clinical condition worsened and she died 5 months later.

Pediatric Deaths (n=3) everolimus continued

- A nurse report of a male adolescent started on everolimus 5mg daily for renal cell carcinoma. On an unknown date, the patient died. No additional information including the cause of death was provided.

Pediatric Serious Non-Fatal Adverse Events everolimus

(more than 1 adverse event may have been reported for each case)

- Infections (n=27)
 - General infections (n=16)
 - Pneumonia (n=11)
- Nervous system disorders (Convulsion, n=16)
- Gastrointestinal events (Stomatitis, n=10)
- Renal dysfunction (n=8)

Pediatric Serious Non-Fatal Adverse Events everolimus continued

(more than 1 adverse event may have been reported for each case)

- Psychiatric disorders (n=8)
 - Psychiatric and behavioral disorders were reported during the randomized (2:1) placebo-controlled trial, including anxiety, aggression and other behavioral disturbances (21% in the treatment group versus 3% in the placebo group)
 - Section 6 Adverse Reactions has been updated in the labeling to reflect this finding.
- Organ transplant rejection (n=4)
- Necrosis/abscess (n=2)
- Thromboembolic events (Arterial, n=1)
- Laboratory investigations (n=13)

Summary Pediatric Focused Safety Review Afinitor® (everolimus)

- This concludes the pediatric focused safety review
- No new safety signals identified
- FDA will continue its standard ongoing safety monitoring.
- Does the Committee concur?



ACKNOWLEDGEMENTS

DOPII

Martha Donoghue, MD
Amir Shahlaee, MD
Gregory Reaman, MD

OPT

Amy Odegaard, MPH
Judith Cope, MD, MPH
Dianne Murphy, MD
Pam Weinel, RN, MSN, MBA

PMHS

Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD
Lynne P. Yao, MD

OSE

Afrouz Nayernama, PharmD
Robert Pratt, PharmD
Ethan Hausman, MD
Bindi Nikhar, MD
Justin Mathew, PharmD
Grace Chai, PharmD
Laura Governale, PharmD