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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
 NDA 203985

Date	August 13, 2012
From	Suzanne G. Demko
Subject	Cross-Discipline Team Leader Review
NDA#	203985
Supplement#	0
Applicant	Novartis Pharmaceuticals
Date of Submission	February 29, 2012
PDUFA Goal Date	August 29, 2012
Proprietary Name / Established (USAN) names	Afinitor® Disperz/everolimus tablets for oral suspension
Dosage forms / Strength	2 mg, 3 mg, and 5 mg tablets for oral suspension
Proposed Indication(s)	Subependymal Giant Cell Astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected
Recommended:	Approval and Pediatric Exclusivity Granted

TABLE of CONTENTS

Acronyms used throughout this review:.....2

1. Introduction.....2

2. Background.....5

3. CMC/Device.....7

4. Nonclinical Pharmacology/Toxicology9

5. Clinical Pharmacology/Biopharmaceutics.....9

6. Clinical Microbiology.....10

7. Clinical/Statistical- Efficacy.....10

8. Safety.....16

9. Advisory Committee Meeting17

10. Pediatrics17

11. Other Relevant Regulatory Issues18

12. Labeling.....18

13. Recommendations/Risk Benefit Assessment19

Acronyms used throughout this review:

OND=	Office of New Drugs
DOP2=	Division of Oncology Products 2
CMC=	Chemistry, Manufacturing, and Controls
ONDQA=	Office of New Drug Quality Assessment
OSI=	Office of Scientific Investigations
OPDP=	Office of Prescription Drug Promotion (formerly DDMAC)
OSE=	Office of Surveillance and Epidemiology
DRISK=	Division of Risk Management
DHOT=	Division of Hematology Oncology Toxicology
DARRTS=	Document Archiving, Reporting & Regulatory Tracking System

1. Introduction

NDA 203985 was submitted to FDA on 29-Feb-2012 to respond to a pediatric Written Request (WR) that was issued by FDA on 01-Apr-2010 in which information from two studies conducted in patients with Tuberous Sclerosis Complex (TSC) and Subependymal Giant Cell Astrocytoma (SEGA) [Study C2485 and Study 2301] and an age-appropriate formulation of everolimus were requested. The Applicant accepted the WR on 16-Apr-2010. The WR resulted from a Proposed Pediatric Study Request (PPSR) submitted by the Applicant on 10-Jul-2009 and amended on 01-Sep-2009. Additional FDA comments on the PPSR were sent to the Applicant on 07-Oct-2009 and 22-Feb-2010. Responses to FDA's comments were received on 28-Oct-2009 and 09-Mar-2010 respectively. The current application also submits a request for Pediatric Exclusivity Determination.

The data submitted to support this application revises the product label to include updated results from Study C2485, the single arm study that provided supporting evidence for the 29-Oct-2010 accelerated approval (under 21 CFR 314 Subpart H) of Afinitor (everolimus) for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection (NDA 22,334, Supplement 006). In addition, labeling will be revised to include the results from Study M2301, a randomized trial comparing the SEGA response rate in patients receiving everolimus to that in patients receiving placebo.

The data submitted in support of this NDA are not intended by the Applicant to fulfill the outstanding postmarketing requirements placed during the original accelerated approval of Afinitor for this indication. These data do not reflect patient follow-up of sufficient duration to convert the status of the marketing authorization for the indication sought (i.e., SEGA that requires therapeutic intervention but cannot be curatively resected) from accelerated approval to full approval. However, it is noted that the updated safety and efficacy data submitted are consistent with the results of the primary analysis of data that provided the basis for the 2010 accelerated approval. Additionally, the new clinical data from these studies enable fuller characterization of the consistency of objective SEGA tumor responses, response duration, and further inform the adverse event profile of everolimus in children and adults with TSC who require treatment for SEGA.

Everolimus

Everolimus is a selective inhibitor of mammalian target of rapamycin (mTOR) which specifically targets the mTOR-raptor signal transduction complex (mTORC1). The drug was developed initially to prevent allograft rejection following solid organ transplantation. It is approved in the United States currently for the following indications:

For the treatment of:

- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced or metastatic
- 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
- 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

As of 13-Jan-2012, everolimus had been approved in 41 countries for the treatment of patients with TSC who have SEGA. These approvals represent the first pharmacologic treatment option for the patient population with TSC and SEGA.

The chemical name for everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-((1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl)-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza-tricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is C₅₃H₈₃NO₁₄ and the molecular weight is 958.2.

Everolimus is supplied in two formulations. Afinitor Tablets (hereinafter referred to as Afinitor) contain 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus. Afinitor Tablets also contain butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and anhydrous lactose as inactive ingredients.

Afinitor Disperz (everolimus tablets for oral suspension, hereinafter referred to as Afinitor Disperz), the product under review in the current application and a new pediatric formulation, contains 2 mg, 3 mg, or 5 mg of everolimus. Afinitor Disperz also contains butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, mannitol, microcrystalline cellulose, and colloidal silicon dioxide as inactive ingredients

Tuberous sclerosis complex with SEGA (Excerpt from the clinical review of Dr. Donoghue)

Tuberous sclerosis complex (TSC) is an autosomal dominant condition caused by inherited or sporadic mutations of the TSC1 or TSC2 genes. Patients with TSC typically develop hamartomatous tumors in multiple organ systems, including the central nervous system, lung, kidney, and skin. TSC affects approximately 1 in 6,000 to 10,000 live births, 25,000 to 40,000 people in the United States and 1 to 2 million people worldwide.

The pathophysiology of TSC remains incompletely understood. However, it is known that the characteristic features of TSC arise due to aberrant activation of cellular pathways normally regulated by hamartin and tuberlin. Hamartin and tuberlin, encoded by the TSC1 and TSC2 genes, respectively, form a tumor suppressor complex within the cell that acts via several intermediate cellular signaling pathways. By promoting the conversion of Rheb (Ras homologue enriched in brain) from its active GTP-bound state into an inactive GDP-bound state, the hamartin-tuberlin complex inhibits activity of the mammalian target of Rapamycin (mTOR) pathway. mTOR is a major effector of cell growth. The signs and symptoms of TSC arise from constitutive activation of the mTOR pathway resulting from upregulation of RHEB due to dysfunctional activity of the hamartin/tuberlin complex.

Although the genetic mutations resulting in TSC manifestations can be identified by laboratory tests, the diagnosis of TSC is based on clinical criteria established at the 1998 Tuberous Sclerosis Complex Consensus Conference. At this conference, the revised diagnostic criteria for TSC were subdivided into “major” and “minor” features as noted in the table below:

“Major features” of TSC	“Minor features” of TSC
Facial angiofibromas or forehead plaques	Multiple randomly-distributed pits in dental enamel
Three or more hypomelanotic macules	Hamartomatous rectal polyps
Nontraumatic ungula or periungual fibromas	Bone cysts
Shagreen patch (connective tissue nevus)	Cerebral white matter radial migration lines
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tuber	Non-renal hamartomas
Subependymal nodules	Retinal achromic patch
Subependymal giant cell astrocytoma	“Confetti” lesions (multiple hypomelanotic macules)
Cardiac rhabdomyoma	Multiple renal cysts.
Lymphangiomyomatosis	
Renal angiomyolipoma.	

The definitive diagnosis of TSC requires the presence of two major features. The only exception to this rule is in some women who have angiomyolipomas of the kidney associated with pulmonary lymphangiomyomatosis, but no other TSC-related features, and are not considered to have TSC. Children with one major plus one minor feature are classified as having probable TSC, while those with one major feature only, or two or more minor features but no major features, are classified as possible TSC.

SEGA, classified as WHO Grade I tumors by histology, are generally characterized as discrete, slow growing tumors with low proliferative potential. Diagnosis of SEGA is based on clinical and radiological findings. SEGA are typically slow-growing tumors that usually become symptomatic after causing obstructive hydrocephalus; this natural history has led to recommendations for periodic radiological evaluation of patients with SEGA.

Hamartomas in the brain usually present in the form of subependymal nodules (SENs) which can remain static throughout an individual’s lifetime. However, up to 20% of patients with TSC present with progressive growth of SENs such that they become subependymal giant cell astrocytomas (SEGA). SEGA carry with them a significant medical risk for patients, including the potential for sudden death resulting from acute hydrocephalus. This risk of hydrocephalus is directly proportional to tumor volume. As SEGA enlarge, increased intracranial pressure, new neurologic deficits, or deterioration of seizure control can occur. Asymptomatic lesions can progress to obstruct the foramen of Monro in as few as 18 months. SEGA are seen more frequently in childhood and adolescence; but have also been reported in patients in their 3rd and 4th decades.

Surgery is potentially curative. However, due to the location of SEGA tumors, surgery is not always possible. SEGA are usually resected if they exhibit progressive growth, cause hydrocephalus or cause other symptoms. Although there are no definitive guidelines currently regarding the optimal timing for surgical intervention for SEGA, experts generally recommend intervention when SEGA progression is documented by serial radiographic scans.

Although surgical resection has historically been the primary mode of treatment for SEGA, not all SEGA are amenable to curative resection. SEGA can also recur after surgical resection. Additionally, patients with SEGA may have multiple SEGA lesions, making surgery challenging. Finally, surgery

for SEGA can result in significant morbidities, such as memory impairment, hemiparesis, infection and the requirement for ventriculoperitoneal shunts.

Historically, surgical resection has been used as the standard of care to treat patients with TSC who have SEGA. Despite some chances for success, considerable peri- and post-operative risks and complications exist for such patients and resection of SEGA can be incomplete, necessitating repeat operative procedures. Surgical resection is an option once serial SEGA growth has occurred. However, the deep location of these tumors within the brain can make resection difficult because the dissection needed to reach the tumor may entail removal of substantial amounts of viable cerebral tissue. No consensus exists on the optimal approach to SEGA resection; frontal transcortical, endoscopic, or interhemispheric transcallosal approaches can be used, and the choice is likely to be based on the surgeon's experience. Certain SEGA are non-resectable due to their location (e.g., in the region of the hypothalamus or pineal gland), the presence of peritumoral edema, or invasion of surrounding normal brain tissue. In any case, resection of SEGA can be associated with significant morbidity and mortality and can recur in up to 10% of patients during the first year post-operatively. Potential complications reported by the applicant from the medical literature include:

- Perioperative mortality risk as high as 10% to 20% due to hydrocephalus or infections
- Need for reintervention for intracerebral hematoma or subdural effusion or hydrocephalus
- Late deaths due to tumor growth or hydrocephalus
- New or worsening post-operative hydrocephalus
- Development of transient or permanent hemiparesis
- Visual loss
- Post-operative meningitis, ventriculitis, sepsis, syndrome of inappropriate antidiuretic hormone secretion
- Post-operative cognitive decline

2. Background

Everolimus is a rapamycin derivative that inhibits the mTOR pathway by acting on mTOR complex-1; mTOR is a serine-threonine kinase, downstream of the phosphatidylinositol-3-kinase/Akt (PI3K/AKT) pathway. Dysregulation of the mTOR pathway is observed in a number of cancers. Everolimus binds to an intracellular protein, the 12-kDa FK506-binding protein, resulting in an inhibitory complex formation and subsequent inhibition of mTOR kinase activity. Everolimus reduces the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein, downstream effectors of mTOR. In addition, everolimus inhibits the expression of hypoxia-inducible factor and reduces the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been demonstrated to reduce cell proliferation and angiogenesis both *in vitro* and *in vivo*.

References from the scientific literature indicate that dysregulation of mTOR, which is targeted by everolimus, has been reported in lesions derived from patients with TSC.¹ Additional literature reports identify *TSC1*- or *TSC2*-mutant experimental animal models which emulate the pathology, behavioral and neurological aspects of TSC^{2,3} and are sensitive to mTOR inhibition⁴.

¹ Astrinidis A, Henske EP (2005) Tuberous sclerosis complex: linking growth and energy signaling pathways with human disease. *Oncogene*; 24: 7475-7481.

² Onda H, Lueck A, Marks PW, et al (1999) *Tsc2*(+/-) mice develop tumors in multiple sites that express gelsolin and are influenced by genetic background. *J Clin Invest*; 104: 687-95.

³ Uhlmann EJ, Wong M, Baldwin RL, et al (2002) Onda H, Kwiatkowski DJ, Yamada K, Gutmann DH. Astrocyte-specific *TSC1* conditional knockout mice exhibit abnormal neuronal

Other approved mTOR inhibitors include sirolimus and temsirolimus. The known associated risks identified with these agents include non-infectious pneumonitis, severe infections (including reactivation of hepatitis, BK-virus associated nephropathy, and CMV reactivation), hypersensitivity (including anaphylactic reactions), creatinine elevations, and hyperglycemia (new onset diabetes mellitus). Important potential risks that are noteworthy from this class of medications include cardiac failure, wound healing complications, lymphopenia, hypophosphatemia, and dyslipidemia.

Everolimus is approved in more than 80 countries worldwide for the prevention of rejection after solid organ transplant, including in the United States (US) where it was granted approval on 20-Apr-2010 for patients undergoing renal transplantation. Development of the drug for cancer indications began in 2002 and resulted in FDA-approval for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib on 30-Mar-2009. The approval was based on a randomized, placebo-controlled trial demonstrating a statistically significant and clinically important improvement in progression-free survival [HR 0.33 (95% CI 0.24, 0.43), $p < 0.0001$] in patients with metastatic renal cell carcinoma following disease progression on sorafenib, sunitinib or both. Everolimus was subsequently granted accelerated approval by FDA for patients with TSC and associated SEGA on 29-Oct-2010. Accelerated approval was based on a single-arm, single-center trial demonstrating a 32% objective tumor response rate, with median duration of response of 266 days, in patients with radiologically-documented progressive SEGA. At the time of approval, the following two post-marketing requirements (PMRs) were placed to verify clinical benefit:

- To submit the final report (at least 4 years of follow-up) and datasets from M2301, a 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).
- To submit the long-term (at least 5 years) follow-up efficacy and safety data from C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS)

Two additional post-marketing requirements, under 505(o) were identified in the approval letter. These PMRs were based on non-clinical data indicating that there exists dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females, and increased latency time during the learning and memory phases in juvenile rat toxicity studies. Furthermore, cases of low testosterone concentrations associated with high levels of follicle-stimulating hormone have been reported in the broader everolimus transplant program and no specific evaluation for the presence of hypogonadism has been performed. The two PMRs were as follows:

- To evaluate the potential for serious risk of adverse long-term effects of Afinitor (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with Afinitor® (everolimus) versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).
- To evaluate the potential for serious risk of adverse long-term effects of Afinitor (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on C2485, a

organization and seizures. *Ann Neurol*; 52: 285-96.

⁴ Kenerson H, Dudon TA, Yeung RS (2005) Effects of rapamycin in the Eker rat model of tuberous sclerosis complex. *Pediatr Res*; 57: 67-75.

single-arm, single-institution, phase 2 trial evaluating treatment with Afinitor® (everolimus) in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

On 5-May-2011, approval was granted for Afinitor for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced, or metastatic disease. The approval was based on a demonstration of a statistically significant improvement in progression-free survival [HR 0.35 (95% CI: 0.25, 0.45); $p < 0.001$] in a randomized, double-blind, multi-center trial of Afinitor plus best supportive care (BSC) versus placebo plus BSC conducted in patients with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (PNET) who had disease progression within the prior 12 months. Labeling was also revised to state that “The safety and effectiveness of Afinitor in the treatment of patients with carcinoid tumors have not been established”. This was based on the results of a randomized, double-blind, multi-center trial in 429 patients with carcinoid tumors in which Afinitor plus depot octreotide (Sandostatin LAR®) was compared to placebo plus depot octreotide. The addition of Afinitor did not improve progression-free survival and overall survival was numerically superior in the octreotide alone arm in an interim analysis.

In addition, two Supplemental New Drug Applications (sNDA) for Afinitor were approved under NDA 22334 on 30-Mar-2012. Supplement 14 was a Prior Approval Supplement adding revisions to the label to include a final survival analysis for patients with advanced renal cell cancer. Supplement 15 added results to the label from hepatic impairment and drug interaction studies. Both supplements fulfilled PMRs that were included in the original approval letter. Supplement 17 was also recently granted accelerated approval by DOP2 on 26-April-2012 for the treatment of adults with renal angiomyolipoma and TSC, not requiring immediate surgery. Verification of clinical benefit associated with this accelerated approval is required by the following PMR:

- To complete the ongoing clinical trial CRAD001M2302 entitled “A Randomized, Double-blind, Placebo-controlled Study of RAD001 in the Treatment of Angiomyolipoma in Patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangiomyomatosis (LAM)” to further verify and describe the ultimate clinical outcomes of the duration of objective responses, incidence of nephrectomy and of renal embolization four years after randomization of the last patient in the study, as specified in the original protocol. You will submit the final comprehensive clinical study report, inclusive of all data collected in the clinical trial, as described in ICH E3.

Lastly, on 20-Jul-2012, another Prior Approval Supplement was approved for Afinitor for the treatment of 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.

Everolimus is also marketed under the trade name Zortress® (NDA 021560). FDA approved Zortress on 20-Apr-2010 for the prophylaxis of organ rejection in adult patients at low to moderate immunologic risk receiving a kidney transplant.

In Europe, everolimus is approved as Votubia® for patients with advanced neuroendocrine tumors (NET), as well as for SEGA associated with TSC.

3. CMC/Device

The information in this section was derived from the primary reviews of Sue-Ching Lin, Ph.D. and Kareen Riviere, Ph.D., Office of New Drug Quality Assessment.

Both the reviewing chemist, Dr. Lin and the biopharmaceutics reviewer, Dr. Riviere have concluded that this NDA application is approvable, pending an acceptable recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product. At the date of this CDTL review, information on the inspection results for this application was still pending. I agree with the conclusions and recommendations of both CMC reviewers.

CMC Review Issues

The stability data for the bulk tablets provided in the application as initially submitted was insufficient. FDA sent a deficiency letter on 05-Jul-2012 requesting additional data capable of demonstrating that the bulk tablets are stable in the proposed containers during the transportation from the manufacturing site in Switzerland to the packaging site in (b) (4). In addition, a time limit between the production of the bulk tablets and the packaging of the tablets into blisters was requested of the applicant. The applicant responded in an amendment to the NDA on 13-Jul-2012. The data submitted, which included information that the container closure system proposed for the marketed product (i.e., the commercial blister package) was different than the container closure system used in the registration stability studies, support a bulk holding time proposal of (b) (4). In addition, an 18-month expiration dating period was granted by ONDQA for the drug product when it is stored under the proposed storage conditions. The expiration dating period can be extended to 24 months upon fulfillment of a post-marketing commitment (PMC) negotiated between CMC and the applicant the substance of which follows:

Novartis will conduct pre-validation as well as validation activities for the blistering process for the container closure system that will be used for the US market. The USP <671> Water Vapor Transmission Rate test (WVTR) will be performed with blister cards derived from Pre-Validation trials. The most stringent requirement, Class A <0.5 mg/day will need to be met before proceeding with validation and launch activities.

To bridge the registration stability and the launch batches Novartis will ensure that the WVTR result is comparable to that measured for the registration stability batches.

Because water uptake is the most critical attribute as relates to stability of the Afinitor Tablets for Oral Suspension an acceptable WVTR result in combination with successful pre-validation and validation on the packaging process will provide assurance that the registration stability data is bridged to the intended commercial product. Novartis will provide the comparable USP<671> WVTR data before the end of November 2012.

Additionally, the ONDQA review team determined that the Applicant's proposed dissolution method was not acceptable. The ONDQA Biopharmaceutics Team requested that the Applicant use phosphate pH 4.5 as the dissolution medium because it is biorelevant and discriminating. Additionally the ONDQA Biopharmaceutics Team asked the Applicant to provide complete dissolution profile data using phosphate buffer pH 4.5 for the clinical batches of the proposed product. During a teleconference held on 25-July-2012, the Applicant acknowledged the Agency's recommendations and agreed to conduct additional studies to develop a discriminating dissolution method. The Applicant agreed to a postmarketing commitment to submit a dissolution method development report on or before 29-Feb-2013 and a Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion) on or before 29-Aug-2013. FDA agreed to review the dissolution development report and provide feedback to the Applicant within 30 days of its submission.

Lastly, the Applicant requested a biowaiver for the 2 mg and 3 mg strengths of Afinitor Disperz. ONDQA determined that the Applicant provided sufficient data to meet the requirements of 21 CFR 320.22(d)(2), and a biowaiver was granted.

4. Nonclinical Pharmacology/Toxicology

The information in this section was derived from the primary review of Andrew J. McDougal, Ph.D., Division of Hematology Oncology Toxicology.

The Applicant submitted one new nonclinical study report in the current NDA for a brain distribution study in rats (report # 1000720). Pre-treatment of the rats with cyclosporine (to inhibit P-gp efflux pumps in the blood-brain barrier) resulted in higher concentrations of everolimus in the brain following oral dosing. No toxicity endpoints were measured.

Dr. McDougal also reviewed the cross-referenced IND and NDAs for nonclinical information that was potentially relevant to the change in formulation represented under this NDA. He identified no other studies of particular relevance.

After review of the Afinitor Disperz NDA submission, as well as the cross-referenced NDA and IND, Dr. McDougal recommended approval of NDA 203985. Labeling recommendations were also conveyed during labeling meetings. No Postmarketing Requirements or Commitments were deemed necessary. I concur with the recommendations of the nonclinical reviewer.

5. Clinical Pharmacology/Biopharmaceutics

The information in this section was derived from the primary Clinical Pharmacology and Pharmacometrics review of Jian Wang, Ph.D., Division of Clinical Pharmacology 5 and the primary Clinical review of Martha Donoghue, M.D., Division of Oncology Products 2.

Based upon their reviews of the clinical pharmacology data, the Clinical Pharmacology and Clinical reviewers recommended approval of this application. Detailed labeling recommendations were also made by both review teams and no Postmarketing Requirements or Commitments were deemed necessary. I concur with these recommendations.

Reviewed for this NDA were clinical pharmacology data from four studies, two clinical efficacy and safety studies in patients with TSC and SEGA (M2301 and C2485) and two bioequivalent studies in healthy subjects with the market formulation (MF)/ final market image (FMI) everolimus tablets and the dispersible tablet (X2105 and X2106).

An extensive review of the pharmacokinetic data was conducted by Dr. Wang, including analyses of biocomparability between the Afinitor Disperz tablets and the MF tablets, the relationship between everolimus trough levels and toxicity, as well as the relationship between everolimus trough levels and SEGA response.

Target Trough Levels: An exposure-response relationship for efficacy was demonstrated based on data in study M2301. An increased efficacy response with increased average C_{min} was observed and the effect reached plateau at C_{min} ≥ 5 ng/mL. In 44% of patients, the C_{min} was below 5 ng/mL even though the target range was 5-15 ng/mL. Based on an indirect response model derived using the continuous data, the typical decrease in SEGA volumes for C_{min} of 3 ng/mL was 29.8% (95% CI: 22.5%, 35.6%). Combined safety data from M2301 and C2485 indicated no relationship between C_{min} and NCI CTCAE Grade 3 infections or stomatitis, both of which are related to everolimus treatment, and the incidence is consistently low when C_{min} is as high as 14.6 ng/mL. Under the submissions for PNET and RCC indications, which were cross-referenced in this NDA, there were no specific safety

concerns when C_{min} was as high as 135 ng/mL. Overall, the results of the data analyses supported the proposed dose of 4.5 mg/m² as the recommended starting dose, followed by dose titration to a target range of 5-15 ng/mL.

The Applicant originally proposed to target everolimus trough levels between (b) (4). Although SEGA responses were observed in patients with average steady state C_{min} of less than 5 ng/mL, the clinical and clinical pharmacology review teams conferred and proposed that the everolimus target trough concentration range be set at 5 - 15 ng/mL.

Test Kit for Everolimus Levels: Of further note, there is currently not an approved test kit for measuring everolimus trough levels in patients with SEGA (unlike Zortress, for which there is an approved test kit to monitor everolimus levels in the adult transplant population). Because dosage of everolimus in SEGA is based on therapeutic drug monitoring, the clinical review team consulted with the Center for Devices and Radiological Health (CDRH) to obtain advice regarding whether the current recommendation for use of a “validated test” for measuring everolimus trough levels was sufficient. CDRH concluded that it was not necessary to require the Applicant to develop a commercially available test kit for measuring everolimus trough levels in patients with SEGA because of the relatively wide therapeutic range, the relative tolerability of everolimus in the SEGA population at the proposed dose and schedule, and lack of a strong relationship between everolimus trough levels and toxicity.

Bioequivalence Studies: Data from Study X2105 and Study X2106 indicated that AUC_{0-∞} of the 5-mg dispersible tablet when administered as suspension in water was equivalent to the 5 x 1-mg MF tablets and to the 5-mg FMI tablet. Although C_{max} of the 5-mg dispersible tablet (Afinitor Disperz) was 64% of the 5 x 1-mg MF tablets and 80% of the 5-mg FMI tablet, predicted C_{min} values at steady-state were similar after daily administration of all three formulations. The lower C_{max} of the dispersible tablet when administered in suspension was not deemed by Dr. Wang to be likely to affect the efficacy response of everolimus since its dosing in patients with TSC and SEGA will be based on therapeutic drug monitoring with dose titration to attain a C_{min} within the target range of 5 to 15 ng/mL.

The clinical and clinical pharmacology review teams concluded that the lower C_{max} of the dispersible tablet was not likely to affect the efficacy in patients with SEGA because dosing is based on therapeutic drug monitoring. The FDA clinical and clinical pharmacology review teams ultimately decided that the bioavailability of everolimus tablets for oral suspension was sufficiently similar to the bioavailability of the formulations approved for commercial use (FMI) and the formulations used in prior clinical trials of everolimus (MF) in patients with SEGA to support the approval of Afinitor Disperz (everolimus tablets for oral suspension).

6. Clinical Microbiology

There were no significant clinical microbiology issues identified in this NDA. The microbiology review completed on 22-Mar-2012 recommended approval of this application.

7. Clinical/Statistical- Efficacy

The information in this section was derived from the primary reviews of Weishi Yuan, Ph.D., Division of Biometrics V, and Martha Donoghue, M.D., Division of Oncology Products 2.

The statistical reviewer, Dr. Yuan concluded that data and analyses from the current NDA demonstrated that there was a statistically significant difference in the overall SEGA response rate, the primary endpoint of the randomized trial, for patients treated with everolimus based upon central radiology review. The clinical reviewer, Dr. Donoghue concluded that the results from this trial

represented a positive benefit: risk ratio and, therefore, clinical benefit to patients. Dr. Donoghue also recommended that the application be approved based on these same results. I concur with the conclusions and recommendations of Drs. Yuan and Donoghue.

The Applicant has pursued development of everolimus for multiple clinical indications since 1996. Clinical development for the first of multiple oncologic indications began in 2002. FDA approved everolimus under the trade name Afinitor (NDA 22334) on 30-Mar-2009 for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. On 5-May-2011, FDA approved Afinitor for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. On 20-July-2012, the FDA approved Afinitor for the treatment of postmenopausal women with advanced hormone receptor-positive HER2-negative breast cancer in combination with exemestane after failure or treatment with letrozole or anastrozole.

The clinical development program for treatment of diseases associated with Tuberous Sclerosis Complex (TSC) began in 2004 with the filing of investigator-sponsored IND 70,895 for the study of everolimus in patients with angiomyolipomata associated with TSC. An investigator-sponsored study of everolimus in patients with SEGA associated with TSC (Study C2485) was submitted to FDA under IND 70,895 in August 2006, and the first patient was enrolled in January 2007.

At an End of Phase 2 (EOP2) meeting with FDA (under the Applicant's commercial IND 66, 279) on 2-Oct-2007, the Applicant proposed to conduct two randomized studies intended for registration in patients with TSC, M2301 (for SEGA) and M2302 [for renal angiomyolipoma or sporadic lymphangiomyomatosis (LAM)]. After receiving FDA feedback at the meeting, the Applicant revised both protocols and submitted them for Special Protocol Assessment (SPA). However, although the Applicant chose to conduct Studies M2301 and M2302, the Applicant subsequently withdrew the requests for SPA.

While these studies were being conducted, an analysis demonstrating favorable results from the single arm investigator-sponsored study conducted in TSC patients with SEGA (Study C2485) prompted the Applicant to reassess their initial plans for registration in this patient population. After discussion with FDA, Novartis submitted an sNDA based on data from Study C2485, which resulted in the 29-Oct-2010 accelerated approval of Afinitor for the treatment of patients with subependymal giant cell astrocytoma associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection (sNDA 22334, Supplement 6). Accelerated approval was based on SEGA response rate observed in patients enrolled in Study C2485. The approval letter included two clinical PMRs to verify the clinical benefit and two additional PMRs to assess the effects of long-term use of everolimus on the growth and development of pediatric patients.

On 1-Apr-2010, prior to submission of the sNDA (Supplement 6) by Novartis that resulted in the accelerated approval of Afinitor for the treatment of patients with SEGA, FDA issued a Written Request (WR) for the study of everolimus in pediatric patients with TSC and SEGA. In order to fulfill the terms of the WR, the Applicant was required to submit updated study results from Study C2485, and results from randomized Study M2301. Additionally, the Applicant agreed to develop an age-appropriate formulation of everolimus for pediatric patients with SEGA.

On 26-April-2012, FDA granted accelerated approval for the treatment of renal angiomyolipomas in adult patients with TSC based upon evidence of durable reduction in tumor size. The Applicant is required to complete the ongoing trial M2302 entitled "A Randomized, Double-Blind, Placebo-Controlled Study of RAD001 in the Treatment of Angiomyolipoma in Patients with Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangiomyomatosis (LAM)" to further verify and describe the

clinical outcomes of the duration of objective responses, incidence of nephrectomy and renal embolization four years after randomization of the last patient in the study.

The following table lists the clinical trials that were submitted in support of this NDA:

Clinical trials providing support for NDA 203985

Study Number	Population	Design
M2301	Patients of any age with worsening SEGA and TSC (N = 117)	Randomized (2:1) multicenter double-blind placebo-controlled study. 1° endpoint: SEGA response rate
C2485	Patients ≥ 3 years of age with worsening SEGA and TSC. (N = 28)	Single arm, single center investigator-sponsored study. 1° endpoint: change from baseline of primary SEGA lesion
1X2105	Healthy adult subjects (N=54)	Randomized, open label crossover bioequivalency study (one 5mg tab for oral suspension vs. five 1 mg tablets for oral use)
1X2106	Healthy adult subjects (N=54)	Randomized, open label crossover bioequivalency study (one 5mg tab for oral suspension vs. one 5 mg tablets for oral use)

Study M2301

Study M2301 was a randomized (2:1), double-blind, placebo-controlled, parallel group, multicenter trial of everolimus conducted in 117 pediatric and adult patients with SEGA and TSC. Randomization was stratified by presence or absence of concomitant enzyme-inducing anti-epileptic drugs at randomization. Eligible patients had at least one SEGA lesion ≥ 1 cm in longest diameter based on local MRI assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. The demographic characteristics of the patients enrolled in Study M2301 are in the table immediately below.

M2301 Demographic characteristics

Demographic Characteristic	Everolimus N=78	Placebo N=39
Age (years)		
Mean (std dev)	10.1 (5.9)	10.3 (7.3)
Median (range)	9.5 (1.0-23.9)	7.1 (0.8-26.6)
Age group (years) n (%)		
< 3	13 (16.7)	7 (17.9)
3 to < 12	38 (48.7)	16 (41.0)
12 to < 18	17 (21.8)	10 (25.6)
≥ 18 years	10 (12.8)	6 (15.4)
Gender n (%)		
Male	49 (62.8)	18 (46.2)
Female	29 (37.2)	21 (53.8)
Race n (%)		
Caucasian	73 (93.6)	36 (92.3)
Black or African American	3 (3.8)	1 (2.6)
Pacific Islander or Native Hawaiian	1 (1.3)	0
Asian	0	0
American Indian or Alaska		

Demographic Characteristic	Everolimus N=78	Placebo N=39
Native		
Other	1 (1.3)	2 (5.1)
Ethnicity n (%)		
Not Hispanic/Latino	76 (97.4)	35 (89.7)
Hispanic/Latino	2 (2.6)	4 (10.3)
Weight (kg)		
Mean (std dev)	38.7 (22.8)	39.5 (24.5)
Median (range)	31.4 (9.0 – 107.8)	27.1 (7.9 – 94.0)
BSA (m ²)		
Mean (std dev)	1.2 (0.5)	1.2 (0.5)
Median (range)	1.1 (0.4 – 2.2)	1.0 (0.4 – 2.1)

The treatment arms were well balanced with respect to key demographic characteristics except gender; there was a higher percentage of male patients randomized to the everolimus arm (63%) compared to the placebo arm (46%). The majority of patients were Caucasian, reflecting the countries that participated in the trial. The highest enrolling countries were: the US (57%), Poland (16%), Russia (10%), Germany (6%), Belgium (3%), and Canada (3%). Australia, Italy, Great Britain and the Netherlands enrolled one or two patients each.

A summary table of diagnostic characteristics for the patients enrolled in the trial is immediately below.

M2301 Summary of Diagnostic Characteristics

TSC Diagnostic Criteria	Everolimus N=78	Placebo N=39
Major features	n (%)	n (%)
Subependymal Giant Cell Astrocytoma	78 (100)	39 (100)
Subependymal nodule	73 (94)	37 (95)
Cortical Tuber	71 (91)	38 (97)
≥3 hypomelanotic macules	70 (90)	36 (92)
Facial angiofibromas or forehead plaque	60 (77)	30 (77)
Cardiac rhabdomyoma, single or multiple	49 (63)	22 (56)
Renal angiomyolipoma	47 (60)	28 (72)
Shagreen patch (connective tissue nevus)	37 (47)	23 (59)
Non-traumatic ungula or periungual fibroma	12 (15)	14 (36)
Multiple retinal nodular hamartomas	11 (14)	9 (23)
Lymphangiomyomatosis	1 (1)	0
Minor Features		
Multiple renal cysts	31 (40)	9 (23)
Cerebral white matter radial migration lines	14 (18)	6 (15)
Gingival fibromas	10 (13)	10 (26)
Multiple randomly-distributed pits in dental enamel	10 (13)	6 (15)
Confetti skin lesions	9 (12)	7 (18)
Non-renal hamartoma	6 (8)	4 (10)

TSC Diagnostic Criteria	Everolimus N=78	Placebo N=39
Retinal achromic patch	4 (5)	3 (8)
Bone cysts	2 (3)	0
Hamartomatous rectal polyps	0	0

All patients met the key eligibility criterion for serial worsening of a SEGA lesion, which required the presence of serial SEGA growth, a new SEGA lesion, or new or worsening hydrocephalus. Because the pre-defined protocol eligibility requirement for documentation of a worsening SEGA lesion was based on local reviewer assessment, all patients enrolled in Study M2301 were eligible for enrollment. Independent central radiology (IRC) review did not confirm the presence of a worsening SEGA lesion in seventeen patients, 12 (15%) enrolled on the everolimus arm and 5 (13%) on the placebo arm. However, only 1 of the 12 patients with discrepant eligibility assessments in the everolimus arm was a responder. Therefore, it is unlikely that the treatment effect observed in the everolimus arm was obscured by this finding.

Although used as a stratification factor for randomization, only 15 (19%) patients in the everolimus arm and 7 (18%) patients in the placebo arm reported use of an enzyme-inducing antiepileptic at baseline. Mutations within the TSC2 gene were more commonly observed than mutations in the TSC1 gene (73% versus 12%, respectively). One patient (randomized to the everolimus arm) had mutations in both the TSC1 and TSC2 genes.

Patients randomized to the treatment arm received everolimus 1 mg MF tablets at a starting dose of 4.5 mg/m²/day, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL. Patients received everolimus or matched placebo until disease progression or unacceptable toxicity. Notable is the fact that the new formulation, Afinitor Disperz, was not administered in this trial.

Disease status was assessed by MRI scans obtained at baseline, 12, 24, and 48 weeks, and annually thereafter. The primary efficacy endpoint was SEGA response rate based on independent central radiology review. SEGA response was defined as a $\geq 50\%$ reduction in the sum of the SEGA volume of target lesions 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. Analysis of SEGA response rate was limited to the blinded treatment period which ended 6 months after the last patient was randomized.

A total of 78 patients were randomized to everolimus and 39 patients to placebo. The median age of patients enrolled was 9.5 years (range 0.8 to 26 years). The SEGA response rate was statistically significantly higher in everolimus-treated patients. There were 27 (35%) patients with SEGA responses in the everolimus arm and no SEGA responses in the placebo arm ($p < 0.0001$; 95% CI: 24%, 46% for the everolimus arm and 0%, 9% for the placebo arm). At the time of the primary analysis, the estimated median duration of response was 5.3 months (range 2.1 to 8.4 months). With a median follow-up of 8.4 months, SEGA progression was observed in 6 of 39 (15.4%) patients in the placebo arm; no patients in the everolimus arm exhibited SEGA progression.

SEGA response per central radiology review in Study M2301

	Everolimus N = 78	Placebo N = 39
Best Overall SEGA Response n (%)		
Response	27 (34.6)	0
Stable Disease	49 (62.8)	36 (92.3)
Progression	0	3 (7.7)
Not Evaluable ^a	2 (2.6)	0
Response Rate (95% CI)	34.6% (24.2%, 46.2%)	0% (0%, 9.0%)
Difference in Response Rate (95% CI)	34.6% (15.1%, 52.3%)	
p-value ^b	< 0.0001	

a. Two patients were considered unevaluable because they did not have identified SEGA target lesions by independent central review.

b. P-value was calculated using the one-sided Cochran-Mantel Haenszel test, stratified by protocol randomization stratification factor (EIAED use vs. EIAED non-use).

Three key secondary endpoints were tested according to the pre-defined fixed-sequence testing procedure used to control for multiplicity. Seizure frequency from baseline to week 24 was the first tested, and no significant difference was found between the two treatment arms (one-sided rank ANCOVA, p=0.20). Therefore, per statistical convention, the two other secondary points could not be formally tested. However, for time to SEGA progression (TTSP), no patient in the everolimus arm progressed while 6 patients (15.4%) in the placebo arm progressed. For best overall skin lesion response, 30 of 72 patients (41.7%) in the everolimus responded while 4 of 38 patients (10.5%) in the placebo arm responded.

The relatively small sample size of patients enrolled in Study M2301 limited the utility of subgroup analyses. However, analysis of SEGA response by age, gender, site, and country of enrollment (U.S. versus non U.S) by the statistical reviewer demonstrated results that were generally consistent across subgroups.

Study C2485

The updated data from Study C2485 reflects an additional year of follow-up after the 9-Dec-2009 data cut-off used for the primary analysis that provided the evidence for the original accelerated approval for the current indication. The additional data provide evidence of the durability of objective tumor responses in patients with SEGA. At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a $\geq 50\%$ reduction in the tumor volume of their largest SEGA lesion. As of 30-Dec-2010, the median duration of treatment of patients enrolled in Study C2485 was 34.2 months (range 4.7-47.1 months). As of 30-Dec-2010, the median duration of response for the 9 patients who exhibited a SEGA response at 6 months was 360 days (range 97 to 1191 days); seven of the 9 patients had an ongoing volumetric reduction of $\geq 50\%$ at the time of data-cut-off. No patient receiving everolimus had developed a new SEGA lesion.

Both Study C2485 and Study M2301 are ongoing. To fulfill the postmarketing requirements issued at the time of the 2010 accelerated approval for SEGA, the Applicant will provide long-term (at least 5 years) follow-up efficacy and safety data from Study C2485. According to the specifications of the PMR, the final study report and datasets for Study C2485 will be submitted in November 2014. Similarly, the Applicant is required to submit the final study report and datasets that include a minimum of 4 years of follow-up for patients enrolled in Study M2301 by March 2015.

Additional Efficacy Analyses

Angiomyolipoma responses were also analyzed in Study M2301. In order to qualify as a response, fulfillment of the following criteria was required:

- Reduction in angiomyolipoma volume of $\geq 50\%$ relative to baseline (angiomyolipoma volume was the sum of the volumes of all target angiomyolipomas identified at baseline)
- No new angiomyolipomas ≥ 1 cm in longest diameter
- No increases in kidney volume $> 20\%$ from nadir
- No angiomyolipoma-related \geq Grade 2 bleeding.

Angiomyolipoma responses were confirmed with a second assessment performed 8-12 weeks following original detection of the response.

Angiomyolipoma responses were observed in the everolimus arm only. A total of 16 of 30 (53%) patients in the everolimus arm who had angiomyolipoma at baseline exhibited a response (all partial responses). Angiomyolipoma progression was detected in 3 of 14 (21%) patients in the placebo arm who had angiomyolipoma identified at baseline. Angiomyolipoma progression was not observed in the everolimus arm.

8. Safety

The information in this section was derived from the primary review of Martha Donoghue, M.D., Division of Oncology Products 2.

Known safety issues with everolimus treatment that are well described and relate to the mechanism of mTOR inhibition are: stomatitis and related events, infections, rash and related events, cytopenia, hemorrhages, non-infectious pneumonitis, hyperglycemia and new-onset diabetes mellitus, renal events, hypersensitivity reactions, including anaphylactic reaction, and thromboembolism. The more common side effects reported with mTOR inhibitors include infections resulting from the immunosuppressive properties of these drugs, while metabolic events result from inhibitory effects on mTOR-regulated lipid and glucose pathways.

In general, at the proposed dose and schedule in the current NDA, the safety profile of everolimus in children and adult patients with SEGA enrolled in Study C2485 and Study M2301 was generally similar to that previously described in the approved label for Afinitor. The most common adverse event in both studies was stomatitis. In both studies, the rate of patient discontinuations was low and there were no patient deaths reported for either study.

In Study M2301, no adverse reactions resulted in treatment discontinuation of everolimus during the double-blind treatment period. Dose interruptions or reductions due to adverse reactions occurred in 56% of everolimus-treated patients. The most common adverse reaction leading to dose adjustment was stomatitis. The most common adverse reactions reported for everolimus (incidence $\geq 20\%$) were: stomatitis (62%); pyrexia (23%); anxiety, aggression, or other behavioral disturbance (21%); and rash (21%). The most common Grade 3-4 adverse reactions (incidence $\geq 2\%$) were stomatitis (9%, all Grade 3), pyrexia (6%, all Grade 3), pneumonia (3%), gastroenteritis (4%), aggression (3%), agitation (3%), and amenorrhea (3%). The most common key laboratory abnormalities (incidence $\geq 50\%$) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence $\geq 3\%$) was neutropenia (9%). Serious adverse events (SAEs) were reported for 19 (24%) of patients in the everolimus group and 5 (13%) patients in the placebo group during the double blind treatment period. Infections were the most common type of serious adverse event.

A safety signal of potential clinical significance was identified by Dr. Donoghue during her clinical review of the randomized trial. Because of the increased incidence of adverse events observed for

patients in the everolimus group under the MedDRA System Organ Class (SOC), Psychiatric Disorders, additional analyses of adverse events reported for this SOC were conducted. The majority of psychiatric adverse events analyzed were reported as mild; there were two Grade 2 adverse events of agitation, and one Grade 3 adverse event of post-ictal psychosis. Because the clinical presentation of agitation, anxiety, abnormal behavior, panic attack, and aggression can be similar in pediatric patients, Dr. Donoghue recommended combining these preferred terms into a heading entitled “anxiety, aggression, or other behavioral disturbance” in the adverse event table included in the proposed package insert. When combining these terms, the per-patient incidence of anxiety, aggression, or other behavioral disorders was 21% (16 of 78 patients) in the everolimus arm and 3% (1 of 39 patients) in the placebo arm. There was Division-wide concurrence with Dr. Donoghue’s approach to these adverse events and their inclusion in labeling.

9. Advisory Committee Meeting

No Advisory Committee meeting was planned or held for this application.

10. Pediatrics

Written Request and Pediatric Exclusivity: This NDA included outstanding analyses and data required to fulfill the terms of the Pediatric Written Request issued by FDA on 1-Apr-2010 and a Request for Pediatric Exclusivity Determination submitted by the Applicant. A table outlining the items contained in the written request, along with the information and responses submitted by the Applicant, adapted from the Applicant’s submission, can be found in Dr. Donoghue’s primary clinical review (Table 54). Based on review of the data submitted, the clinical, clinical pharmacology, and statistical reviewers concluded that the Applicant fulfilled the requirements of the Written Request. On 10-Jul-2012, the review team met with the FDA Pediatric Exclusivity Board and formally recommended that pediatric exclusivity be awarded to the Applicant. One of the questions raised by the Board was that the WR was silent on why a placebo-controlled trial was acceptable in this population of patients. The clinical reviewer, Dr. Donoghue, commented in her review upon the use of a placebo in the trial as both reasonable and ethically appropriate and gave the following reasons, with which I agree:

- *The study protocol excluded enrollment of patients that required immediate surgical intervention.*
- *Surgery was not considered an appropriate control arm in this population due to the potential for surgical morbidity.*
- *There was no active pharmacologic comparator that had been shown to benefit to patients with TSC at the time this study was initiated (the first patient visit for Study M2301 occurred on August 10, 2009, and everolimus was granted accelerated approval for the treatment of SEGA on October 29, 2010).*
- *Because Study C2485 was a small single arm trial, the incorporation of a placebo control arm into this study enabled the first comparative analyses of safety and efficacy data of everolimus compared to the natural history of the disease in patients with SEGA associated with TSC.*
- *SEGA are slow-growing tumors, and Study M2301 permitted patients to crossover at the first radiologic sign of progression.*

After addressing the terms of the Pediatric Written Request in light of a summary of the contents of NDA 203985, the Pediatric Exclusivity Board concurred with the recommendation of the reviewing team and Pediatric Exclusivity was granted.

Effects of Everolimus on Growth: A meaningful analysis of the effects of everolimus on growth as required by previously placed postmarketing requirements is not yet possible due to the short period of follow up of patients in Study M2301 and Study C2485. A preliminary analysis of changes in body

mass index, weight, and height of patients enrolled in study M2301 submitted as part of this NDA did not show any clear trend in differences in growth between the everolimus and placebo groups. A more mature formal analysis of the effects of long-term use of everolimus on the growth and development of patients enrolled in Study C2485 and Study M2301 is needed and will be submitted by the Applicant to fulfill the outstanding postmarketing requirements.

Orphan Designation: Orphan designation for everolimus for the indications involving the treatment of patients with TSC was granted on 8-Jun-2009.

11. Other Relevant Regulatory Issues

Debarment Certification: The applicant provided certification that it did not and will not use in any capacity the services of any person debarred under sections 306(a) or 306(b) of the federal Food, Drug and Cosmetic Act as related to the current application.

Financial Certification: All investigators participating in the conduct of the trials submitted in support of this application filed financial disclosure information. Only one investigator disclosed two consultation grants from the Applicant totaling \$50,000.00.

Patents: A patent declaration was submitted with this supplemental application as required by 21 CFR 314.53. There were no patent issues identified with the submission.

Letters of authorization: Appropriate letters of authorization were provided for this application.

Labeling Consult Reviews: The following Offices, Divisions and FDA staff were consulted to perform reviews of physician, patient, and package labeling for Afinitor Disperz: Office of Prescription Drug Promotion (DCDP, DPDP), Office of Medical Policy Initiatives (DMPP), Office of Surveillance and Epidemiology (DRISK, DMEPA), and Pediatric and Maternal Health Staff. Reviews and comments on the relevant sponsor submissions were received and discussed during regular labeling and team meetings and the advice given was incorporated into labeling as appropriate.

12. Labeling

At the date of this review, labeling negotiations are being finalized. The most recent version of the label proposed by the applicant on 8-Aug-2012 can be found as Appendix 1 to this document. Label sections that were the primary subject of negotiations with the sponsor with regard to proposed revisions were: Indications and Usage (section 1), Dosage and Administration (section 2), Dosage Forms and Strengths (section 3), Adverse Reactions (section 6), Use in Specific Populations (section 8), Description (section 11), Clinical Pharmacology (section 12), Clinical Studies (section 14), and Patient Counseling Information (section 17).

The Applicant originally proposed the generic name “everolimus (b) (4)” for the Afinitor Disperz dosage form. The ONDQA review team concluded that this was not an acceptable dosage form recognized by FDA; the Applicant and ONDQA subsequently agreed to use “everolimus tablets for oral suspension” for the Afinitor Disperz dosage form. During labeling meetings, DOP2 and ONDQA determined that the presentation of the proprietary name and nonproprietary name should be as follows: Afinitor Disperz (everolimus tablets for oral suspension), because the proprietary name Afinitor Disperz is for a specific dosage form (tablets for oral suspension) and thus the dosage form should be displayed within the parentheses along with the nonproprietary name.

The final label agreed upon by FDA and the applicant will be attached to the action letter for this application.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval and grant pediatric exclusivity.

Risk Benefit Assessment: The current application was submitted to fulfill a pediatric Written Request (WR), support the approval of a new pediatric dosage form required under the WR, update the current everolimus label to include additional data and information regarding the efficacy and safety of everolimus in patients with SEGA, and request pediatric exclusivity. The data submitted and analyses performed by the Applicant and FDA review teams support the conclusion that the Applicant has adequately responded to the WR, developed an age-appropriate pediatric formulation, provided new and updated data and information to revise labeling, and should be granted pediatric exclusivity for Afinitor Disperz.

This NDA included the following data and analyses to fulfill the outstanding requirements of the Pediatric Written Request issued by FDA on 1-Apr-2010:

- Data from two pharmacology studies conducted in healthy adult subjects to establish bioequivalence between a single 5 mg tablet for oral suspension and five of the 1 mg market formulation (MF) tablets used in Study M2301 (Study X2105) and between the 5 mg tablet for oral suspension and the 5 mg “final market image” tablet (FMI) currently approved for commercial use and also used in study C2485 (X2106).
- Updated data and clinical study report from study C2485 (data cut-off 30-Dec-2010 compared to 9-Dec-2009 data cut-off used for the primary analysis).
- Data and clinical study report from the primary analysis of Study M2301, a randomized trial in 117 pediatric and adult patients with SEGA associated with TSC.

In addition to the review teams, relevant parts of the application were reviewed by the FDA Pediatric Exclusivity Board who agreed with the review team’s assessment that the requirements of the WR had been fulfilled by the current NDA. As a result of the Pediatric Exclusivity Board’s review, it was determined that the Applicant’s request for pediatric exclusivity was granted. In addition, the clinical, clinical pharmacology, and chemistry and manufacturing review teams concluded that Afinitor Disperz is an age-appropriate formulation for pediatric patients. Afinitor Disperz offers several advantages to young pediatric patients who are unable to swallow Afinitor Tablets. Afinitor Disperz is available in smaller dosage increments compared to Afinitor tablets, thus permitting administration of a lower dose and the capability for smaller incremental dose adjustments. Additionally, the Applicant provided data demonstrating that preparation of a suspension with Afinitor Disperz requires less time, less water, and less manipulation compared to the previously-labeled procedures for preparation of a suspension with Afinitor Tablets.

Although the clinical pharmacology review team initially concluded that everolimus tablets for oral suspension were not bioequivalent to the MF or FMI formulations of everolimus, the formulations were found to be comparable with respect to area under the curve (AUC), but the C_{max} of the everolimus tablets for oral suspension was lower compared to the C_{max} of the MF and FMI tablets. Based on further analysis of the data, however, the clinical pharmacology review team predicted that the C_{min} of the everolimus tablets for oral suspension, MF tablets, and FMI tablets would be similar at steady state. Finally, after appropriate discussion between the review disciplines, both the clinical pharmacology and clinical review teams concluded that the lower C_{max} of the everolimus tablets for oral suspension was

not likely to have a significant impact on efficacy in patients with SEGA because dosing is based on therapeutic drug monitoring of everolimus serum trough levels. The review disciplines ultimately decided that the bioavailability of Afinitor Disperz is sufficiently similar to the bioavailability of the formulations approved for commercial use (FMI) and the formulations used in prior clinical trials of everolimus (MF) in patients with SEGA to support approval of the new formulation, Afinitor Disperz (everolimus tablets for oral suspension).

The Afinitor label is being updated with the data and information derived from this application. Specifically, updated results from Study C2485, which provided the basis for the accelerated approval of everolimus for the treatment of patients with SEGA who require therapeutic intervention but are not candidates for curative surgical resection, were submitted. Study C2485 was conducted in 28 patients with TSC who had at least one SEGA tumor with evidence of serial growth on MRI. In this study, patients received adult formulation everolimus tablets at a dose of 3 mg/m²/day, with subsequent dose adjustments to achieve and maintain an everolimus trough level of 5-15 ng/mL. At the time of accelerated approval, the median duration of treatment was 24.4 months (range 4.7 months to 37.3 months). The primary endpoint of Study C2485 was the change from baseline in the volume of the primary SEGA tumor at 6 months, as determined by central radiology review. At 6 months, 9 of 28 patients (32%, 95% CI: 16% - 52%) had at least a 50% reduction in tumor volume of their largest SEGA tumor. The median duration of response for the 9 responding patients was 266 days (range: 97 to 946 days). These results demonstrate a continuing benefit to patients with SEGA who are treated with everolimus.

In addition, the submission of results from Study M2301 provides additional evidence of a favorable benefit: risk profile for everolimus in the treatment of patients with SEGA that requires therapeutic intervention but cannot be curatively resected. Study M2301 was a randomized (2:1), double-blind, placebo-controlled trial of everolimus conducted in 117 pediatric and adult patients with SEGA and TSC. Eligible patients had at least one SEGA lesion \geq 1 cm in longest diameter based on local MRI assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion \geq 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received everolimus 1 mg MF tablets at a starting dose of 4.5 mg/m²/day, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL. Patients received everolimus or matched placebo until disease progression or unacceptable toxicity. Disease assessments were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter. The primary efficacy endpoint was SEGA response rate based on independent central radiology review. SEGA response was defined as a \geq 50% reduction in the sum of the SEGA volume of target lesions relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion \geq 1 cm, or new or worsening hydrocephalus. Analysis of SEGA response rate was limited to the blinded treatment period which ended 6 months after the last patient was randomized.

A total of 78 patients were randomized to everolimus and 39 patients were randomized to placebo. The median age of patients enrolled was 9.5 years (range 0.8 to 26 years).

The SEGA response rate was statistically significantly higher in everolimus-treated patients. There were 27 (35%) patients with SEGA responses in the everolimus arm and no SEGA responses in the placebo arm ($p < 0.0001$; 95% CI: 24%, 46% for the everolimus arm and 0%, 9% for the placebo arm). At the time of the primary analysis, the estimated median duration of response was 5.3 months (range 2.1 to 8.4 months). With a median follow-up of 8.4 months, SEGA progression was observed in 6 of 39 (15.4%) patients in the placebo arm; no patients in the everolimus arm exhibited SEGA progression.

At the proposed dose and schedule, the safety profile of everolimus in children and adult patients with SEGA enrolled in Study C2485 and Study M2301 was generally comparable to that previously described in the approved label for Afinitor. The most common adverse event in both studies was stomatitis. Serious adverse events (SAEs) were reported for 19 (24%) of patients in the everolimus group and 5 (13%) patients in the placebo group during the double blind treatment period. Infections were the most common type of serious adverse event. In both studies, the rate of patient discontinuations was low and there were no patient deaths reported for either study. The clinical reviewer identified a new safety signal related to psychiatric and behavioral issues which is included in labeling; these adverse reactions are plausible in the context of the disease. However, this finding does not alter the positive benefit: risk assessment for this application.

In conclusion, the data submitted to support this NDA represents a favorable benefit: risk assessment for everolimus for the treatment of pediatric and adult patients with tuberous sclerosis complex (TSC) and subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. In addition, the requirements of the WR have been fulfilled, an acceptable pediatric formulation is now available, and pediatric exclusivity has been granted. Future submissions to respond to ongoing PMRs will provide additional experience to characterize and confirm the clinical benefit of everolimus in this patient population and will define any long-term risks in the pediatric and adult populations with this disease.

Recommendation for Postmarketing Risk Evaluation and Management Strategies: None

Recommendation for other Postmarketing Requirements and Commitment: Since it was not the purpose of this application to fulfill the postmarketing requirements (PMR) established at the time of the original accelerated approval, the following PMRs to further verify and describe clinical benefit for everolimus in the treatment of patients with SEGA associated with TSC, established under 21 CFR 314.510, remain to be fulfilled:

PMR 1700-1:

Submit the final report (at least 4 years of follow-up) and datasets from M2301, a 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).

The Applicant agreed to conduct this trial according to the following schedule:

Final Protocol Submission: January 2011

Trial Completion: September 2014

Final Report and Dataset Submission: March 2015.

PMR 1700-2:

Submit the long-term (at least 5 years) follow-up efficacy and safety data from C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

The Applicant agreed to conduct this trial according to the following schedule:

Final Protocol Submission: March 2011

Trial Completion: March 2014

Final Report and Dataset Submission: November 2014.

Additionally, under Section 505(o)(3), the Applicant is required to conduct the following postmarketing studies and clinical trials to assess the long-term effects of everolimus on the growth and development of pediatric patients:

PMR 1700-3:

To evaluate the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with Afinitor® (everolimus) versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

All patients must be evaluated for growth and development milestones annually while still treated in the extension phase of M2301 (minimum of 4 years after randomization of the last patient). Evaluations must include the following: growth as measured by weight, height (measured with a stadiometer), height standard deviation scores (SDS), height velocity, height velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Results of each evaluation must be documented. Luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls must be measured in patients who have not developed secondary sexual characteristics by age 13 in girls and 14 in boys. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The Applicant agreed to conduct this trial according to the following schedule:

Final Protocol Submission: January 2011

Trial Completion Date: September 2014

Final Report and Dataset Submission: March 2015.

PMR 1700-4:

To evaluate the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with Afinitor® (everolimus) in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

All patients must be evaluated for growth and development milestones annually while still treated in the extension phase of C2485 (at least 5 years). Evaluations must include the following: growth as measured by weight, height (measured with a stadiometer), height standard deviation scores (SDS), height velocity, height velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls must be measured in patients who have not developed secondary sexual characteristics by age 13 in girls and 14 in boys. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The Applicant agreed to conduct this trial according to the following schedule:

Final Protocol Submission: March 2011

Trial Completion Date: March 2014

Final Report and Dataset Submission: November 2014.

New postmarketing commitments agreed upon by FDA and the Applicant during the course of this review cycle are as follows:

PMC #1

Cross Discipline Team Leader Review

Afinitor Disperz NDA 203985

S.G. Demko

Provide acceptable USP<671> Water Vapor Transmission Rate test (WVTR) results for the proposed commercial packaging system. Provide 3 months accelerated stability data on the first 3 commercial batches post approval when available, to demonstrate comparable stability with that of registration batches.

PMC Schedule Milestones:

Study/Trial Completion:

Final Report Submission: (USP <671> results) 11/30/12

Other: 3 months accelerated stability data 5/31/13

PMC #2

Dissolution Method Development Report and Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion). FDA committed to review the report and provide feedback within 30 days of receipt of submission of the dissolution method development report.

PMC Schedule Milestones: Final Report Submission: 03/29/2013

Other: Prior Approval Supplement Submission: 08/29/2013

Recommended Comments to Applicant: None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE G DEMKO

08/15/2012