CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203985Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	August 29, 2012
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	N 203985
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	February 29, 2012
PDUFA Goal Date	August 29, 2012
Proprietary Name / Established (USAN) Name	AFINITOR DISPERZ everolimus tablets for oral suspension
Dosage Forms / Strength	Tablets for oral suspension/ 2 mg, 3mg, and 5 mg
Proposed Indication(s)	AFINITOR® is indicated for the treatment of patients with TSC who have SEGA and require therapeutic intervention but are not likely to be cured by surgery. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume *[see Clinical Studies (14.314.2)]*. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Vaishali Jarral
Medical Officer Review	Martha Donoghue
Statistical Review	Weishi Yuan
Pharmacology Toxicology Review	Andrew McDougal
CMC Review	Sue Ching Line
Product Quality Microbiology Review	Steven P. Donald
Biopharmaceutics Review	Kareen Riviere
Clinical Pharmacology Review	Jian Wang
CDTL Review	Suzanne Demko
OPDP/DPP Reviews	Carole Broadnax (PI) & Karen Munoz (PPI)
OSE/DMEPA	James Schlick
OSE/DRISK	Suzanne Robottom
Patient Labeling Team Review	Sharon Mills

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DPP=Division of Professional Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Division Directory Summary Review

1. Introduction

All reviewers/review disciplines recommended approval. Specific issues identified in the review of the application and further discussed in this review are:

- The basis for accelerated approval under 21 CFR 314 Subpart H
- The rationale for limitation of this new dosage form to use in patients with tuberous sclerosis complex (TSC) requiring treatment for subependymal giant cell astrocytoma (SEGA)
- The rationale for the limited description of the results of the key secondary endpoint, time-to-angiomyolipoma progression, in product labeling.

Novartis Pharmaceuticals Corporation (Novartis) submitted NDA 203985 under 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50. The purpose of this application was (1) to support a new dosage form, Afinitor (everolimus) dispersible tablets (Afinitor® DISPERZ™) for the treatment of patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) and require therapeutic intervention but are not likely to be cured by surgery, that would be appropriate for treatment of patients under 3 years of age, (2) to provide the Agency with all outstanding components outlined in the Written Request (WR) issued for everolimus, and (3) to support inclusion in product labeling of additional data from the randomized, placebo-controlled trial in patients with TSC who have SEGA (Study M2301), and longer-term follow-up from the Phase-2 trial (Study C2485).

Data which support approval of the new dosage form are the chemistry, manufacturing, and control information and two single-dose bioavailability studies conducted in healthy volunteers comparing the approved dosage form Afinitor Tablets (everolimus) with the new dosage form, Afinitor DISPERZ (everolimus tablets for oral suspension). The bioavailability studies demonstrated that the $AUC_{0-\infty}$ of Afinitor DISPERZ is equivalent to that of Afinitor Tablets, however the C_{max} of Afinitor DISPERZ is 20-36% lower than that of Afinitor Tablets. The predicted trough concentrations at steady-state were similar after daily administration. Because the two dosage forms do not meet all of the criteria for bioequivalence, the new dosage form is limited to the SEGA indication since this is the only approved regimen in which doses are adjusted based on therapeutic drug monitoring (everolimus trough levels).

The new dosage form is appropriate for administration to children less than 3 years of age, supporting expansion of the approved indication for treatment of SEGA to include this age group, extrapolating safety and efficacy from older to younger patients and based on population pharmacokinetic (PK) analyses in the cross-referenced NDA 22334.

Novartis received accelerated approval for the treatment of SEGA in patients with TSC who were greater than 3 years of age based on the results of a single-arm trial (C2485), which demonstrated a 50% or greater reduction in SEGA tumor volume, with post-marketing requirements to submit the results of long-term follow-up data (4-year minimum follow-up

from M3201 and 5-year follow-up from C2485), as cited in the October 29, 2010 approval letter for NDA 22334/S-006. The data provided in this application, which include the protocol-specified efficacy analysis of M2301 and updated efficacy data from C2485, do not satisfy the post-marketing requirements and are inadequate to support regular approval. However, these data, together with the new dosage form, are identified in FDA's Written Request letter of April 1, 2010 and support the additional safety and efficacy data included in sections 6 and 14 of the physician package insert regarding the approved SEGA indication. In addition, the safety and pharmacokinetic data obtained from M2301 support the revisions to the recommended dose for the SEGA indication, from a recommended dose of (b) (4) m^2/day in the initial approval on October 29, 2010 to a new recommended dose of 4.5 mg/m /day in patients with SEGA who are not also taking strong CYP3A4 inducers (such as enzyme-inducing anti-epileptic drugs or EIAEDs) and 9.0 mg/m^2/day in patients with SEGA who are taking strong CYP3A4 inducers; these revisions enhance the safe and effective use of Afinitor Tablets and Afinitor Disperz for the treatment of SEGA.

As with the original approval for the SEGA indication, this NDA for Afinitor Disperz is approved under the provisions of 21 CFR 314.510, which states that "FDA may grant marketing approval for a new drug product…..on the basis of the effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relationship of the observed clinical benefit to the ultimate outcome." The same post-marketing requirements cited in the October 29, 2010 approval for NDA 22334/S-006 are also required for conversion of the SEGA indication to regular approval for this new dosage form.

2. Background

Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma (SEGA)

Tuberous sclerosis complex (TSC) is a genetic disorder affecting the TSC1 or TSC2 gene in 85% of clinically diagnosed patients. The diagnosis is based on the presence of two major or one major plus two minor criteria (Roach et al J Child Neurol 13:524-8, 1998) and can be confirmed with genetic testing. In patients with TSC1 or TSC2 mutations, there is loss of the TSC suppression of the m-TOR signaling pathway, resulting in uncontrolled constitutive expression and the development of benign tumors in multiple organs, most commonly skin and brain, as well as epilepsy, neurocognitive disorders, and dental pitting. Both inherited (autosomal dominance) and sporadic cases occur. The most recent reported estimated incidence was 1 in 5800 births (Osborne et al. Ann NY Acad Sci 615:125-7. 1991).

As noted in FDA's Written Request letter, "[S]ubependymal giant cell astrocytoma (SEGA) is a common manifestation of tuberous sclerosis, occurring in up to 20% of patients. It is the leading cause of death in children with tuberous sclerosis. SEGAs develop in the central nervous system in the subependymal layer of the lateral ventricle (often in the area of the

caudate nucleus) and can protrude into the ventricle causing obstructive hydrocephalus. Case series have found the mean age at diagnosis to vary from 4.3 to 9.4 years. SEGAs are typically slow growing with annual growth rates of 20-30%, although rates of 200-300% are possible. Treatment involves total or subtotal resection. However, surgery remains a high risk procedure and incompletely resected tumors may recur after several years. Additional interventions are needed in this population."

Regulatory history

March 30, 2009: The original NDA for Afinitor, submitted June 28, 2008, was approved for the treatment of advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. 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.

April 20, 2010: The approval of NDA 21560 was for Zortress (everolimus) for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Zortress is to be administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids. Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients receiving these products.

October 29, 2010: Accelerated approval was granted for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS), who require therapeutic intervention but are not candidates for curative surgical resection. 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 were placed to verify clinical benefit under 21 CFR 314.510, Subpart H:

- 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. These two PMRs were:

- 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 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).

May 5, 2011: Approval was granted for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced, or metastatic disease. Approval was based on 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) and 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" based on the results of a randomized, double-blind, multi-center trial in 429 patients with carcinoid tumors where the addition of Afinitor to octreotide did not improve progression-free survival and overall survival was numerically superior in the octreotide alone arm in an interim analysis.

April 26, 2012: Afinitor was approved for the treatment of patients with tuberous sclerosis complex who have renal angiomyolipoma not requiring immediate surgery. This supplement was supported primarily by the results of a single, multinational, randomized (2:1), placebo-controlled trial, M2302, which enrolled a total of 118 patients over 20 months with renal angiomyolipoma requiring intervention (at least one lesion ≥ 3 cm in diameter). The basis for accelerated approval was demonstration of a clinically important reduction in objective tumor shrinkage with an angiomyolipoma response rate of 42% confirmed by central radiology review for which the median duration of response is more than 5.3 months (as of the data cut-off, none of the 33 responding patients had suffered disease progression with ongoing response durations ranging from 2.3 months to 19.6 months). This was also supported by a significant reduction in time to angiomyolipoma progression [HR 0.076 (95% CI: 0.016, 0.371); p<0.001, one-sided] and a significantly higher skin lesion response rate among the subset of patients with skin lesions at entry (26% versus none) for the everolimus arm compared to the placebo arm in M2302.

July 20, 2012: Afinitor was approved 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. Approval was based on the results of a randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane conducted in 724 postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. The trial demonstrated statistically significant improvements in progression free survival. The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the AFINITOR and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank p < 0.0001]. The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy. The overall survival results were not mature at the time of the interim analysis, and no statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)].

Pre-submission history
Clinical development of everolimus for patients with TSC who required treatment for SEGA, but were not candidates for surgical resection of SEGA lesions, was conducted under IND 66,279. This IND was submitted in November 2002.

October 2, 2007 (EOP2 meeting)
Key agreements reached (for SEGA indication) were

- The proposed application would be based on a single, multi-center 99-patient, randomized (2:1) trial. (b) (4) alone would be inadequate to support approval and demonstration of clinical benefit resulting from a reduction in SEGA volume would also be required.
- Data characterizing long-term treatment effects, including toxicity, would need to be provided
- The plan for addressing effects on QTc should be submitted to the IND
- Data and analysis of the absolute or relative bioavailability of new dosage forms would be required
- Analyses exploring exposure-response and exposure-toxicity relationships should be included in the NDA in support of the proposed therapeutic drug monitoring plan for treatment of patients with SEGA

July 15, 2008 (Type A meeting to discuss proposed SPA (b) (4))
Key agreements reached were:

- (b) (4)
-

June 8, 2009: FDA issued a letter designating everolimus (request #09-2836) as an orphan drug for the following indication: "Treatment of patients with TSC including TSC-associated

SEGA, TSC-associated renal angiomyolipoma, and TCS-associated lymphangioleiomyomatosis (LAM)."

July 20, 2009: Novartis Pharmaceuticals Corporation submitted a Proposed Pediatric Study Request (PPSR) for everolimus on 7/20/2009; this request was amended on 9/1/2009 to reflect protocol amendments. and on 10/28, 2009 in response to FDA's 10/7/2009 request for additional revisions to the PPSR. Novartis also submitted a responses, dated 3/9/2010, to FDA's 2/22/2010 comments on the PPSR.

September 29, 2009 (Pre-sNDA meeting for treatment of SEGA in patients with TSC)
Key agreements reached were:

- The results of the Phase 2 trial were promising in light the unmet medical need; an application based on C2485 should have a minimum one-year safety and efficacy data for all patients enrolled and be supplemented with available additional safety data from other trials.
- The application should contain a rationale for reduction in SEGA volume at 6-months (from baseline) as likely to predict clinical benefit or as a direct measure of benefit.
- Given the limited sample size, the randomized trial (M2301) should be completed and may be required for approval
- Bridging data would be required to support new strengths (b) (4) tablets) or new dosage regimens that were not evaluated in C2485.

April 1, 2010: FDA issued a Written Request (WR), which Novartis accepted on 4/15/2010. The WR identified the following data to be submitted:

- Results from CRAD001C2485 (Study 1), a single-arm trial conducted in patients with tuberous sclerosis complex (TSC), who required treatment for subependymal giant cell astrocytoma (SEGA). This trial was to enroll a minimum of 28 patients ages 3 years and older, with a minimum of 22 patients less than 18 years of age. The primary endpoint of this trial was demonstration of reduction in SEGA tumor volume from study entry.

- Results from Protocol CRAD001M2301 ('Study 2'), a randomized, open-label trial conducted in patients with tuberous sclerosis complex (TSC), who required treatment for subependymal giant cell astrocytoma (SEGA). This trial was to enroll a minimum of 99 patients of any age, with at least 74 patients less than 18 years of age. The primary endpoint of this trial was demonstration of

- The specified studies were to be conducted using an age-appropriate formulation. If an age-appropriate formulation was not available during the conduct of the studies, the WR required that an age-appropriate formulation be developed and tested and, if found to be safe and effective in the studied pediatric population(s), marketing approval must be sought for that age-appropriate formulation.

September 27, 2011 (pre-NDA meeting - new dosage form & response to WR)
Key agreements reached

- Clinical data would include updated results from C2485 and final efficacy analyses of M2301 and two bioequivalence trials (X2105 and X2106) to satisfy the WR; these data would **not** support conversion of the SEGA indication to regular approval
- Separate labeling and new trade name could be proposed for new dosage form
- Agreement on CMC data needed to support new dosage form.

Application Summary
The NDA was submitted on February 29, 2012, with amending submissions dated March 2, April 3, April 12, April 16 (3), April 24, May 4, May 8, May 15, May 29, June 8, June 21, June 22, July 13, July 19, July 20, July 25, July 26, August 9, August 13, August 27, and August 29, 2012. As discussed below, an ODAC meeting was not convened to seek advice on this NDA.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry dating period of 18 months for the drug product, when stored at 25°C (77°F) excursions permitted between 15°C to 30°C (59°F to 86°F), protected from light and moisture. There are no outstanding issues.

As with Afinitor Tablets, the drug substance for Afinitor Disperz is (b) (4)

The drug product, Afinitor Disperz, is supplied as 2 mg, 3 mg and 5 mg tablets for oral suspension. The outer phase of the drug product differs from that of Afinitor Tablets, and was developed to minimize disintegration time and to release the fine particles of the solid dispersion within 3 minutes.

Adequate data have been provided to ensure the quality of the drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. The biopharmaceutics reviewer (Dr. Kareen Riviere) issued a recommendation for approval in a review dated 03-Aug-2012. An overall acceptable recommendation was issued by the Office of Compliance on 23-Aug-2012.

The Quality reviewers found the description of the dosage form of (b) (4) as proposed by Novartis, to be unacceptable as it was inconsistent with nomenclature conventions applied by FDA for dosage forms. The reviewers stated that the correct term for this dosage form is "tablets for oral suspension" and the nonproprietary name was revised to "everolimus tablets for oral suspension" because the proprietary name, Afinitor Disperz, refers to a specific dosage form. All product labeling has been revised to incorporate this terminology.

The post-marketing commitments have been agreed-upon with Novartis to further address CMC issues

- **PMC 1917-1:** To 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 1917-2:** To provide the dissolution method development report and prior approval supplement (including the revised dissolution method and information to support the dissolution acceptance criterion).

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

One new nonclinical study was submitted in this NDA, a brain distribution study in rats (report # 1000720). Pre-treatment 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 in rats. No toxicity endpoints were measured. Dr. McDougal agreed with the applicant's conclusion.

Additional non-clinical information was incorporated by cross-reference to Novartis's IND 66279, NDA 22334, and NDA 21560. Dr. McDougal evaluated the cross-referenced IND and NDAs; no additional nonclinical studies or information were identified as relevant to this new dosage form.

Dr. McDougal verified Novartis' statements that no new impurities and no increased exposures to unqualified impurities will result from this formulation because the drug substance specifications are the same as previously approved specifications.

No labeling revisions were recommended based on the nonclinical information submitted to NDA 203985; however, nonclinical revisions were recommended for concordance across indications and pending supplements in the following sections of the product label: Warnings and Precautions (current section 5.10), Use in Special Populations (8.1), Mechanism of Action (12.1), and Nonclinical Pharmacology/Toxicology (13.1).

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

Clinical pharmacology data were provided from four studies:

- Studies M2301 and C2485, assessing the safety and efficacy of Afinitor Tablets for the treatment of SEGA in patients with TSC. The studies employed a starting dose of Afinitor

4.5 mg/m^2/day and 3.0 mg/m^2/day, respectively, with therapeutic drug monitoring and titration to achieve and maintain everolimus trough levels of 5-15 ng/mL. Data from C2485 were previously reviewed under NDA 22334/S-006, supporting the approval of Afinitor Tablets for the treatment of SEGA in patients, 3 years of age and older, with TSC.

- Studies X2105 and X2106, which were bioequivalence trials conducted in healthy subjects comparing the pharmacokinetics of Afinitor Tablets either as five tablets of 1 mg each or a single 5 mg tablet prepared as an oral solution) to Afinitor Disperz (5 mg tablets as an oral solution).

Dr. Wang assessment of the bioavailability studies were that data from Studies X2105 and X2106 indicated that AUC0-∞ of the 5-mg [Afinitor Disperz] tablet when administered as oral suspension in water was equivalent to the five 1-mg [investigational everolimus tablets] and to the 5-mg [Afinitor Tablets]. Although C_{max} following administration of the 5-mg [Afinitor Disperz] tablet was 64% of that following administration of five 1-mg everolimus tablets and 80% of that following administration of 5-mg Afinitor Tablet, the predicted C_{min} values at steady-state were similar after daily administration of all the three formulations. Dr. Wang concluded that the lower C_{max} of the Afinitor Disperz tablet when administered in suspension is not likely to affect the efficacy response of everolimus since its dosing in patients with TSC who have SEGA will be based on therapeutic drug monitoring (TDM) with dose titration to attain a C_{min} within the target range of 5 to 15 ng/mL

As previously determined from data submitted under NDA 22334, age and gender do not affect everolimus clearance as determined in a population pharmacokinetic evaluation in patients with cancer. The analyses of PK data from M2301 identified patient age less than 18 years as a factor affecting everolimus pharmacokinetics. In patients with SEGA, the geometric mean C_{min} values (trough levels), normalized to a mg/m^2 dose in patients less than 10 years of age and patients 10 to 18 years of age, were lower by 54% and 40% respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults.

An additional analysis evaluating the relationships between gender and everolimus trough levels and between concomitant use of EIAED and everolimus trough levels did not identify significant differences, however the quartile with the highest median trough levels (10-15 ng/mL) had no patients taking EIAED as compared to the lower three quartiles (based on median trough levels) where 20-25% of the patients were taking concurrent EIAEDs. A relationship is biologically plausible given the known effects of strong CYP3A4 inducers on everolimus clearance.

Since dosing in SEGA is adjusted based on therapeutic drug monitoring, this should not limit the abiliy to achieve therapeutic levels. In addition, the label has been strengthened for the SEGA indication to initiate Afinitor Tablets or Afinitor Disperz at 9.0 mg/m^2/day in patients taking strong CYP3A4 inducers, which may be included in an EIAED regimen.

Dr. Wang also conducted exploratory analyses of exposure- response and exposure-toxicity relationships. There was no evidence of an exposure-toxicity relationship but there was evidence of an exposure response relationship which supports the original therapeutic drug level (5-15 ng/mL) but does not support Novartis' proposed expansion of the therapeutic trough levels down to (b) (4). I concur with Dr. Wang's recommendation that this proposal be rejected based on the potential for

increasing the already high incidence of patients (44% in M2301) with subtherapeutic trough levels, lack of toxicity and lack of increased toxicity at greater exposures.

6. Clinical Microbiology

I concur with the conclusions reached by the product quality microbiology reviewer, Dr. Donald, that there are no outstanding microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

This NDA contained efficacy data from two clinical trials, C2485 and M2301. The results of Study C2485 were reviewed under NDA 22334/S-006 and formed the basis for accelerated approval for treatment of SEGA requiring therapeutic intervention in patients with TSC. The results of Study M2301 have not been previously reviewed, however the results of the M2301 trial confirm the results obtained in Study C2485, which was the basis for approval of the supplemental indication of treatment of SEGA approved under NDA 22334/S-006. Specifically, the results of M2301 re-demonstrate the effects on reduction in tumor volume (SEGA response rate) previously demonstrated in Study C2485.

Study 2485: "Everolimus (RAD001) "Therapy of Giant Cell Astrocytoma in Patiners with Tuberous Sclerosis Complex"

Study C2485 is an open-label, single-arm trial conducted to evaluate the safety and efficacy of Afinitor Tablets (2.5 mg or 5 mg strengths) in patients with SEGA and TSC. Twenty-eight patients were enrolled and received Afinitor beginning at an initial dose of 3.0 mg/m^2/day, with titration to maintain everolimus trough levels between 5-15 ng/mL. The study consisted of two phases, a 6-month treatment phase and an extension phase of up to 3.5 years (total treatment 4 years). The primary objective of the study was determination of the proportion of patients with ≥ 50% reduction in total SEGA tumor volume at the end of 6 months of Afinitor treatment. Patients who continued treatment on the extension phase were assessed for tumor growth (SEGA tumor volume) every 6 months and safety including assessment on growth and development and endocrine function.

Results
The median age of the patient population was 11 years (range 3-34 years), 61% of patients were male and 86% were White. The median duration of treatment in the updated report submitted to this NDA was 34.2 months (range 4.7-47.1 months).

The response rate was unchanged from the previous review, 32% (9 of 28 patients) with ≥ 50% reduction in SEGA volume) however the median duration of response was for these 9 patients was 11.8 months (range 3.2 to 39.1 months). Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff.

Study CRAD001M2301 (Study M2301):"A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)"

Study M2301 is a placebo-controlled, randomized (2:1), double-blind, multicenter trial of everolimus versus placebo conducted in adult and pediatric patients with TSC with SEGA requiring therapeutic intervention. Key eligibility criteria were at least one SEGA lesion ≥ 1.0 cm in longest diameter on MRI based on local radiology 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.

Patients were randomized to receive Afinitor Tablets (1 mg strength) /matching placebo at a starting dose of 4.5 mg/m^2 daily. Randomization was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs). The dose of everolimus was titrated to achieve and maintain trough levels of 5 -15 ng/mL and for toxicity. Treatment continued until SEGA progression, unacceptable toxicity, or completion of 5 years of treatment. MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter. The protocol consisted of two phases: a double-blind, placebo-controlled efficacy phase which was completed when the last randomized patient had completed 6 months of treatment at which time the final analysis of efficacy would occur and an open-label extension phase of up to 5 years of Afinitor treatment. Patients receiving placebo were offered open-label Afinitor at the time of SEGA progression during the blinded treatment phase.

In Study M2301, the primary endpoint was SEGA response rate. Secondary endpoints included change from baseline to week 24 in frequency of epileptiform events (seizures); time to SEGA progression (TTSP); and skin lesion response rate. SEGA response rate as determined by independent central radiology review. Identification of patients with a SEGA response was defined as a 50% or greater reduction in SEGA volume relative to baseline (where SEGA volume was the sum of all target SEGA lesion volumes identified at baseline) with no evidence of (1) unequivocal worsening of non-target SEGA lesions, (2) new SEGA lesions (≥ 1 cm in longest diameter), or (3) new or worsening hydrocephalus.

A total of 99 patients were planned for this study. Assuming the response rates are 0% in the placebo arm and ≥ 20% in everolimus arm, a total of 99 patients would provide 93% power for a 2:1 randomization at a significance level of 0.025 using a 1-sided exact Cochran-Mantel-Haenszel (CMH) test. The analysis of SEGA response rate was to be stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Results

From August 2009 to August 2010, the study enrolled 117 patients from 24 centers in 10 countries, among which 78 were randomized to the everolimus arm and 39 to the placebo arm. Sixty seven patients were in the USA. The cut-off date for this submission clinical study report is March 2, 2011.

During the blinded treatment phase, 2 of the 78 patients in the everolimus arm and 8 of the 39 patients in the placebo arm have discontinued study treatment. One patient in each arm discontinued treatment prematurely for withdrawal of consent, one patient in the everolimus

arm was lost-to-follow-up, and one patient in the placebo arm was removed from the study by the investigator due to non-compliance with study visits. Six patients (15%) discontinued study treatment prior to the final efficacy analysis in the placebo arm due to disease progression compared to no discontinuations for disease progression in the everolimus arm.

Given the small sample size and limited stratification factors, the treatment arms was not balanced for gender or country of origin, neither of which is considered to have prognostic importance. Treatment arms were balanced for EIAED use (likely due to stratification), race (White vs. non-White), and age subgroups.

Demographic and Baseline Entry Variables by Treatment Arm in M2301

Baseline Entry Variable	Everolimus (n=78)	Placebo (n=37)
Gender		
Male	49 (63%)	18 (46%)
Female	29 (37%)	21 (54%)
Age		
<3 years	13 (17%)	7 (19%)
3-10 years	55 (70%)	26 (67%)
>10 years	10 (13%)	6 (15%)
EIAED use		
Yes	15 (19%)	7 (18%)
No	63 (81%)	32 (82%)
Race		
White	73 (94%)	36 (92%)
Other	5 (6%)	3 (8%)
Country		
US	49 (63%)	18 (46%)
Other	29 (37%)	21 (54%)
Baseline SEGA volume (target lesions)		
Median	1.63 cm^3	1.30 cm^3
Range	(0.17 -25.15 cm^3)	(0.32 – 9.75 cm^3)

For the overall study population, the median age was 9.5 years (range 0.8 to 26 years; 69% were 3 to < 18 years at enrollment; 17% were < 3 years at enrollment), 57% were male, and 93% were Caucasian. Based on central radiology review at baseline, 98% of patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter, 79% had bilateral SEGAs, 43% had ≥ 2 target SEGA lesions, 26% had growth in or into the inferior surface of the ventricle, 9% had evidence of growth beyond the subependymal tissue adjacent to the ventricle, and 7% had radiographic evidence of hydrocephalus. Eight (7%) patients had prior SEGA-related surgery.

At the time of the final efficacy analysis, the median duration of follow-up was 8.4 months (range 4.6 to 17.2 months).T he SEGA response rate was statistically significantly higher in AFINITOR-treated patients. Results are displayed in the table below. At the time of the final analysis, all SEGA responses were ongoing and the median duration of response was 5.3 months (range 2.1 to 8.4 months). No patient in either arm required surgical intervention during blinded treatment phase of M2301.

SEGA response rates in Study M2301

	AFINITOR N=78	Placebo N=39	p-value
SEGA response rate[a] - (%)	**35**	**0**	**<0.0001**
95% CI	24, 46	0, 9	

[a] Per independent central radiology review

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.

The three key secondary endpoints were tested according to the pre-defined fixed-sequence testing procedure used to control for multiplicity. Change in seizure frequency from baseline to week 24 was the first of the secondary endpoint to be tested. Neither the proposed analysis using last-observation carried forward (change in frequency -1.24 vs. -0.24 from baseline to week 24, p=0.20) nor a sensitivity analysis based on patients with complete data and no imputation, demonstrated significant differences in change in seizure frequency between treatment arms. Therefore the two other secondary points could not be formally tested. Since the assumptions regarding treatment frequency were not met in this trial, the trial was not adequately powered nor designed to test this endpoint at the seizure frequency observed in this trial. The FDA statistical reviewer also conducted exploratory analyses of the other secondary endpoints. For time to SEGA progression, the outcome was favored the everolimus arm in that no patient in the everolimus arm progressed while 6 patients (15.4%) in the placebo arm progressed. For best overall skin lesion response, the outcome again favored the everolimus arm and is consistent with findings observed in a related population (patients with TSC treated for renal angiomyolipoma). Thirty of 72 patients (41.7%) in the everolimus arm achieved skin responses compared to 4 of 38 patients (10.5%) in the placebo arm.

8. Safety

There is an adequate safety database in the cross-referenced NDA 22334, which contains safety data from clinical studies supporting all of the approved indications for Afinitor Tablets, and in particular, all of the multiple-dose safety information in patients with TSC requiring treatment for SEGA. The extrapolation of data obtained with Afinitor Tablets to the new dosage form, Afinitor Disperz, is justified by the similar bioavailability of the two dosage forms as described in section 5 of this summary review.

This application also contains a modification to the recommended dose for the approved SEGA indication, which is based on the safety data from M2301, conducted with Afinitor Tablets. These data are summarized in section 6.5 of the product label and reproduced below. No new safety signals were identified in M2301 and no new post-marketing requirements or REMS were required to ensure safe and effective use of this new dosage form.

"The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (Study 1) of AFINITOR in 117 patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC). The median age of patients was 9.5 years (range 0.8 to 26 years),

93% were Caucasian, and 57% were male. The median duration of blinded study treatment was 52 weeks (range 24 to 89 weeks) for patients receiving AFINITOR and 47 weeks (range 14 to 88 weeks) for those receiving placebo.

The most common adverse reactions reported for AFINITOR (incidence ≥ 30%) were stomatitis and respiratory tract infection. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pyrexia, pneumonia, gastroenteritis, aggression, agitation, and amenorrhea. The most common key laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia.

There were no adverse reactions resulting in permanent discontinuation. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 55% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.
Table 10 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 11.

Table 10: Adverse Reactions Reported in ≥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/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

	AFINITOR N=78			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
[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						

Amenorrhea occurred in 17% of AFINITOR-treated females aged 10 to 55 years (3 of 18) and none of the females in the placebo group. For this same group of AFINITOR-treated females, the following menstrual abnormalities were reported: dysmenorrhea (6%), menorrhagia (6%), metrorrhagia (6%), and unspecified menstrual irregularity (6%).

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%).

Table 11: Key Laboratory Abnormalities Reported in 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 %
Hematology						
Elevated partial thromboplastin time	72	3	0	44	5	0
Neutropenia	46	9	0	41	3	0
Anemia	41	0	0	21	0	0
Clinical chemistry						
Hypercholesterolemia	81	0	0	39	0	0
Elevated aspartate transaminase (AST)	33	0	0	0	0	0
Hypertriglyceridemia	27	0	0	15	0	0
Elevated alanine transaminase (ALT)	18	0	0	3	0	0
Hypophosphatemia	9	1	0	3	0	0
Grading according to CTCAE Version 3.0						

Longer-term follow-up of 34.2 months (range 4.7 to 47.1 months) from a non-randomized, open-label, 28-patient trial resulted in the following additional notable adverse reactions and key laboratory abnormalities: cellulitis (29%), hyperglycemia (25%), and elevated creatinine (14%)."

9. Advisory Committee Meeting

This NDA is for a new dosage form of everolimus; the data provided in this application through cross-reference to NDA 22334, support revisions to a single approved indication (treatment of SEGA) and new dosing recommendations. No issues were identified in the review of this NDA which required the advice of the Oncologic Drugs Advisory Committee.

10. Pediatrics

Novartis was granted Orphan Drug designation for everolimus for "Treatment of patients with TSC including TSC-associated SEGA, TSC-associated renal angiomyolipoma, and TCS-associated lymphangioleiomyomatosis (LAM)" on June 8, 2009. Therefore, this indication is exempt from the requirements of PREA.

The data provided in this supplement were presented to the Pediatric Exclusivity Board on July 10, 2010. The Board determined that Novartis fairly responded to the WR and pediatric exclusivity was tentatively granted, effective July 10, 2010.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: There were no objections from DMEP, OPDP, or the review team to the proposed proprietary name of Afinitor Disperz.

- Physician labeling

  - Indications and Usage: The indication for treatment of SEGA in patients with TSC was amended to remove the restriction of the indication to patients 3 years of age or older. The description of the basis for approval was modified to reflect the primary endpoint(SEGA response rate) as described in M2301, and editorial changes as proposed by Novartis were incorporated.
  - Dosage and Administration: As discussed in section 5 of this review, Novartis' proposed modification to the range for therapeutic dosing (from 5-15 ng/mL to (b) (4) (b) (4) was rejected based on concerns of exposure of patients to potentially ineffective doses based on exposure-response logistic regression analyses. Novartis' proposal to increase the starting dose from (b) (4) to 4.5 mg/m2/day was accepted based on the results of M2301. In addition, the D&A section was place all recommended dosing information for treatment of SEGA, which applies both to Afinitor Tablets and Afinitor Disperz, together and to title these subsections for clarity as limited to patients receiving treatment for SEGA due to the differences in dosing regimen for this indication and the failure to demonstrate bioequivalence between the two dosage forms. More specific and detailed direction on therapeutic monitoring and dose modification, as supported by pop PK studies and PK analyses of M2301, were incorporated into this section.
  - Warnings and Precautions: Section 5.8 (Hepatic Impairment) and related information in Sections 8.7 and 12.3 revised to provide specific advise for dose modification when everolimus is administered for treatment of SEGA in patients

with TSC, based on the additional safeguard afforded by therapeutic drug monitoring. Section 5.9 (Vaccinations) revised to strengthen advice on avoidance of live virus vaccinations and to include a recommendation to complete vaccinations prior to initiation of everolimus if possible.

- Adverse Reactions: The safety date from M2301 was incoporated into this section, largely replacing information on C2485 since the data was obtained in a larger study, is internally controlled, and was obtained with the new recommended starting dose.
- Description, Dosage Forms and Strengths, and How Supplied Sections: Modified to include a description of the new dosage form (Afinitor Disperz). As discussed under section 3 of this review, dosage form of (b) (4) proposed by Novartis was unacceptable to FDA; the dosage form was revised for consistency with FDA nomenclature for dosage forms (i.e., everolimus tablets for oral suspension).
- Clinical Pharmacology: New subsection (12.6) for description of effects of everolimus on QTc was created and relevant data from section 12.3 was moved to this section for consistency with current labeling recommendations from the Office of Clinical Pharmacology. Section 12.3 also revised to include results of the relative bioavailability of Afinitor Tablets and Afinitor Disperz, to include data on absorption/dose proportionality and on effects on gender and age with everolimus when used for treatment of SEGA in patients with TSC, based on PK data obtained in Study M2301.
- Clinical Experience: The description of the trial design, demographics, entry characteristics, and efficacy results from M2301 (Study 1) were added to section 14.5. In addition, the efficacy results of C2485 (renamed Study 2) were updated to include the median duration of response (previous provided only range of response duration) and median duration of treatment (from 24.4 to 34.2 months).

- Carton and immediate container labels: All issues were resolved

- Patient labeling/Medication guide: Patient labeling for Afinitor Tablets was amended to include information on Afinitor Disperz. In addition, an "Instructions for Use" document, specific to the Afinitor Disperz dosage form, which provides detailed instructions on preparation of the oral solution was developed in conjunction with the Patient Labeling Team, DMEPA, the clinical and clinical pharmacology reviewers and Novartis.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Approval of this new dosage formulation is based on demonstration of a well-controlled manufacturing process and similar relative bioavailability to the approved

Afinitor Tablets for oral administration (NDA 22334) to support initial dosing in patients with TSC receiving treatment for SEGA. Because therapeutic drug monitoring is recommended for this indication, the modest difference in bioavailability will be addressed as a result of such monitoring. This application does not support a new indication but does contain pharmacokinetic data obtained in patients with TSC undergoing everolimus treatment for SEGA which supported modification to the starting dose, dose adjustments, and frequency of therapeutic monitoring which should enhance safe and effective use by increasing the proportion of patients who remain within the therapeutic range.

Approval of this dosage form is limited to patients undergoing treatment with SEGA where therapeutic monitoring is conducted. Because of the differences, albeit modest, in bioavailability (based on C_{max}) between this dosage form and Afinitor Tablets, Afinitor Disperz is not indicated for treatment of other approved indications due to the absence of therapeutic drug monitoring.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  There were no new safety signals identified during the review of M2301 which required a REMS or new post-marketing requirements under 505(o). I concur with the recommendations of the review team that new Risk Evaluation and Mitigation strategies were not need to ensure safe and effective use as a condition of approval of this new dosage form, revised dosing recommendations, or expanded indication for the treatment of SEGA in children with TSC who are less than 3 years of age.

- Recommendation for other Postmarketing Requirements and Commitments

  The following PMRs required under 21 CFR 314.510 Subpart H for the approval of NDA 22334/S-006, as set out in the October 29, 2010 approval letter, are also required for this NDA. These PMRs are required to provide information on the long-term effectiveness of everolimus chronically administered for the treatment of SEGA in patients with TSC.

  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).

  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 following PMRs required under 505(O) for the approval of NDA 22334/S-006, as set out in the October 29, 2010 approval letter, are also required for this NDA. These PMRs are required to provide information on the long-term toxicity of everolimus when chronically administered for the treatment of SEGA in patients with TSC.

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.

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.

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/s/

PATRICIA KEEGAN
08/29/2012