

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206406Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 206406
Supporting document/s: SDN049
Applicant's letter date: 6-12-2015
CDER stamp date: 6-12-2015
Product: Envarsus®
Indication: Prophylaxis of organ rejection in patients
receiving allogeneic kidney transplant
Applicant: Veloxis Pharmaceuticals Inc
499 Thornall St, 3rd Floor
Edison, NJ 08837
Review Division: Division of Transplant and Ophthalmology
Products
Reviewer: Aaron M Ruhland, PhD
Supervisor/Team Leader: Lori Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Lois Almoza

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Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206406 are owned by Veloxis Pharmaceuticals Inc. or are data for which Veloxis Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 206406 that [Veloxis Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206406.

1 Executive Summary

1.1 Introduction

In this submission, the sponsor has submitted updated draft labeling. In its current version, no changes were made to Sections 8.1, 13.1 or other sections that required further review from a nonclinical pharmacology/toxicology perspective. The current version of the labeling is acceptable.

See Nonclinical Pharmacology/Toxicology reviews dated 10-30-2014 and 9-24-2014 for more details.

Labeling (sections relevant to nonclinical Pharmacology/Toxicology)

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy in humans has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus given orally to pregnant rabbits at 0.7 times the maximum clinical dose and pregnant rats at 1.1 times the maximum clinical dose was associated with an increased incidence of fetal death *in utero*, fetal malformations (cardiovascular, skeletal, omphalocele, and gallbladder agenesis) and maternal toxicity. Envarsus should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.7 and 2.3 times the maximum clinical dose based on body surface area, respectively) was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (3.7 times the maximum clinical dose) was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1.0 and 3.2 mg/kg (1.2 and 3.7 times the maximum recommended clinical dose, respectively) was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0 mg/kg/day (0.84 times the AUC at the maximum clinical dose of 0.14 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.24 times the AUC at the maximum clinical dose of 0.14 mg/kg/day) [see *Boxed Warning*].

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03%-3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m²/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment; 2.5-fold the human exposure in stable adult renal transplant patients converted from Prograf to Envarsus). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Impairment of Fertility

Tacrolimus given orally at 1.0 mg/kg (1.2 times the maximum clinical dose based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryoletality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryoletal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (3.7 times the maximum clinical dose based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

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/s/

AARON M RUHLAND
06/30/2015

LORI E KOTCH
06/30/2015

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION ADDENDUM

Application number: 206406
Supporting document/s: SDN001
Applicant's letter date: 12-28-2013
CDER stamp date: 12-30-2013
Product: Envarsus®
Indication: Prophylaxis of organ rejection in patients
receiving allogeneic kidney transplant
Applicant: Veloxis Pharmaceuticals Inc
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Review Division: Division of Transplant and Ophthalmology
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1 Executive Summary

1.1 Introduction

At the time of the original nonclinical review filing, the maximum recommended starting dose of Envarsus[®] was proposed as (b) (4) mg/kg/day. All of the proposed nonclinical safety margins found in the labeling were calculated based on this dose for body surface area conversion of the dose or comparison of exposure (i.e. AUC values). However, following discussion and agreement with the applicant the recommended starting dose was lowered to 0.14 mg/kg/day. This document represents an addendum to the original review revising the safety margins in the pertinent sections of the labeling based on this lower dose.

Labeling

1.3.3.1 Applicant's version

Deletions from the Prograf[®] labeling are noted as strikethrough font and additions are noted as double underlined font.

8.1 Pregnancy

Pregnancy Category C

(b) (4)



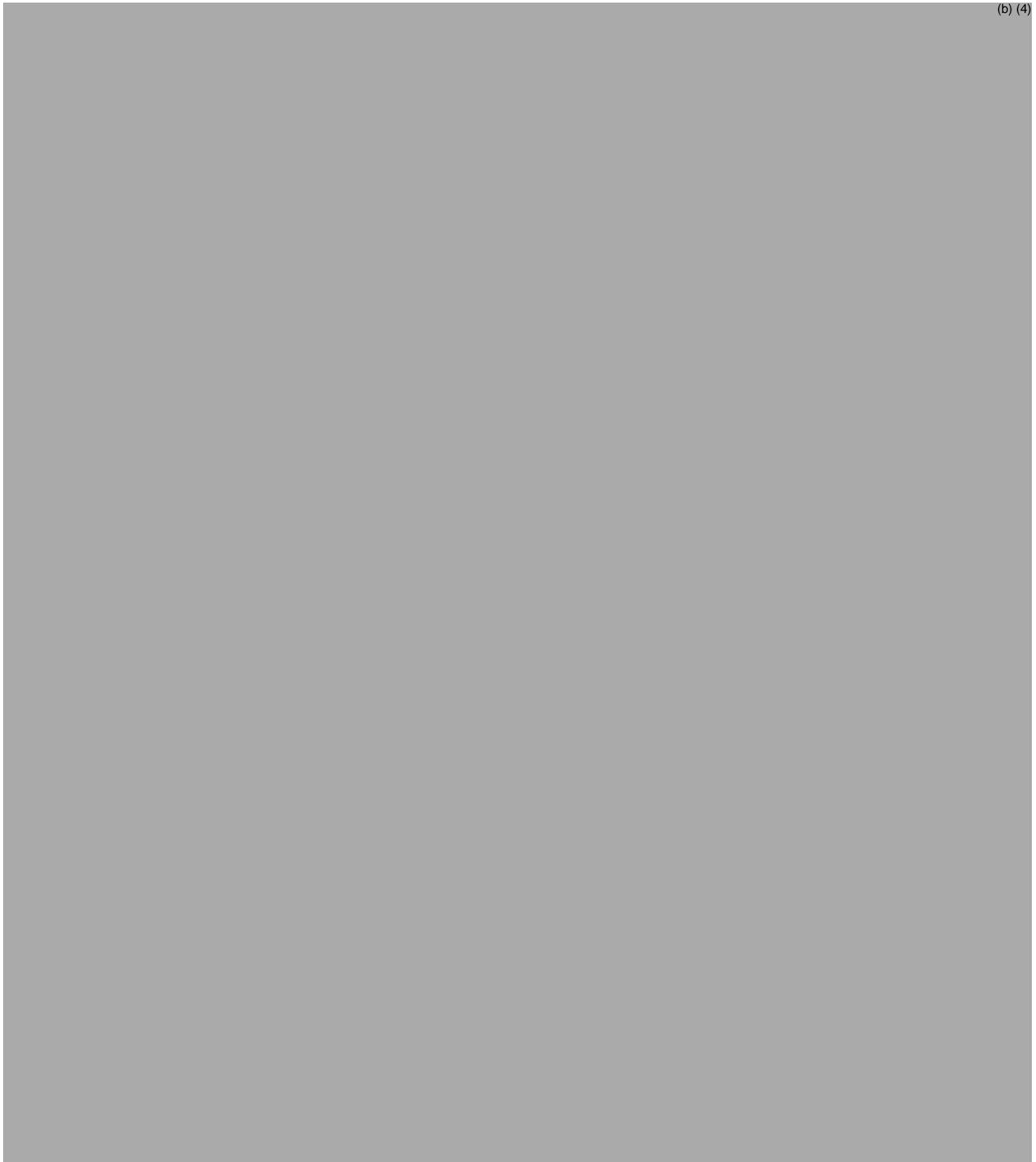
(b) (4)

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

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1.3.3.2 Suggested FDA version (Redline):

Note: Additions to the Applicant's version are noted as double underlined font and deletions are noted as ~~strikethrough font~~.

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy in humans has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus given orally to pregnant rabbits at 0 ^{(b) (4)}7 times the maximum clinical dose and pregnant rats at ^{(b) (4)}1.1 times the maximum clinical dose was associated with an increased incidence of fetal death *in utero*, fetal malformations (cardiovascular, skeletal, omphalocele, and gallbladder agenesis) and maternal toxicity. Envarsus should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0. ^{(b) (4)}7 and ^{(b) (4)}2.3 times the maximum clinical dose based on body surface area, respectively) was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (3.7 times the maximum clinical dose ^{(b) (4)}) was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1.0 and 3.2 mg/kg ^{(b) (4)}1.2 and 3.7 times the maximum recommended clinical dose ^{(b) (4)}, respectively) was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.

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Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0

mg/kg/day [redacted] (b) (4)
 [redacted] -0.84 times the AUC at the maximum clinical dose of 0.14 mg/kg/day) and
 in the rat was 5.0 mg/kg/day [redacted] (b) (4)
 [redacted] 0.24 times the AUC at the maximum clinical dose of 0.14
 mg/kg/day) [see *Boxed Warning*].

Reviewer's note: Post-approval, the Prograf® labeling was updated to base the carcinogenicity safety margins on tacrolimus exposure (AUC values) instead of direct dose comparisons (mg/m²) because exposure to tacrolimus was low following its incorporation into the feed of the test animals (probably due to less feed consumed by higher dose animals due to toxicity). These exposure values were compared to the AUC values obtained in kidney transplant recipients. Since the safety margins and steady state kidney transplant recipient AUC values are listed in the Prograf® labeling, a reverse calculation of the AUC value obtained in the nonclinical study can be made:

- Prograf labeling: AUC_{0-inf} in kidney transplant recipient (0.2 mg/kg/day): 203 ± 42 ng·hr/mL
- Prograf labeling: Safety margin based on AUC in the mouse: 0.9-fold
- Mouse AUC = 203 * 0.9 = 183 ng·hr/mL
- AUC_{0-inf} in kidney transplant recipient (0.2 mg/kg/day): 203 ± 42 ng·hr/mL
- Safety margin based on AUC in the rat: 0.265-fold
- Rat AUC = 203 * 0.265 = 53.8 ng·hr/mL

Safety margins based on AUC for Envarsus can now be calculated. In the labeling for Envarsus, the AUC for stable kidney transplant patients is reported as 216 (± 63) ng·hr/mL. Therefore, the safety margin comparisons based on AUC would be 0.84 and 0.24 for the mouse and rat AUC values, respectively. These values approximate those reported in the labeling for Prograf.

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03%-3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m²/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment; 2.5-fold the human exposure in stable adult renal transplant patients converted from Prograf to Envarsus). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The

relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

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1.3.3.3 FDA Final Version

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4 Integrated Summary and Safety Evaluation

This addendum represents changes in the labeling for Envarsus® to reflect changes in the dosing range and pharmacokinetics based on the revised recommended daily starting dose of 0.14 mg/kg/day.

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/s/

AARON M RUHLAND
10/30/2014

LORI E KOTCH
10/30/2014

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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 206406
Supporting document/s: SDN001
Applicant's letter date: 12-28-2013
CDER stamp date: 12-30-2013
Product: Envarsus XR
Indication: Prophylaxis of organ rejection in patients
receiving allogeneic kidney transplant
Applicant: Veloxis Pharmaceuticals Inc
499 Thornall St, 3rd Floor
Edison, NJ 08837
Review Division: Division of Transplant and Ophthalmology
Products
Supervisor/Team Leader: Lori Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Lois Almoza

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1 Executive Summary

At the time of the original Pharmacology/Toxicology review signing (9-24-14), the maximum recommended starting dose of Envarsus[®] was stated to be (b) (4) mg/kg/day. All of the proposed nonclinical safety margins found in the labeling were calculated based on this dose for body surface area conversion of the dose, or for comparison of exposure (i.e. AUC values).

The maximum recommended starting dose of Envarsus[®] has since been reduced to 0.14 mg/kg/day, requiring recalculation of the safety margins. These changes have been incorporated into the final labeling, as submitted to the NDA on 10-29-2014 (Supporting Document 38).

I agree that the changes made to the labeling (presented in SD38) accurately reflect the new safety margins, based on a MSRD of 0.14mg/kg/day.

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/s/

LORI E KOTCH
10/29/2014

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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

 1.1 INTRODUCTION 3

 1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3

 1.3 RECOMMENDATIONS 3

2 DRUG INFORMATION 12

 2.1 DRUG 12

 2.2 RELEVANT INDS, NDAs, BLAs AND DMFs 13

 2.3 DRUG FORMULATION 13

 2.4 COMMENTS ON NOVEL EXCIPIENTS 14

 2.5 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 14

 2.6 REGULATORY BACKGROUND 15

3 STUDIES SUBMITTED 16

 3.1 STUDIES REVIEWED 16

 3.2 STUDIES NOT REVIEWED 16

4 INTEGRATED SUMMARY AND SAFETY EVALUATION 19

1 Executive Summary

1.1 Introduction

The subject of this New Drug Application (NDA) is Envarsus[®] for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplant. Envarsus[®] is an extended release formulation of tacrolimus. Tacrolimus was originally approved as an immediate release formulation (Prograf[®]) and is currently marketed for prophylaxis of organ rejection. The applicant has filed a 505(b)(2) NDA application and will rely on nonclinical studies previously submitted for the approval of Prograf[®] (NDA 050708) to support the nonclinical safety of Envarsus[®]. Alterations to the nonclinical sections of the product labeling predominantly reflect changes in the safety margins resulting from comparing the dose based on body surface area (mg/m²) or exposure (AUC) following oral administration.

Reviewer's note: At the time of this review's signing, the maximum recommended starting dose of Envarsus[®] is proposed as (b) (4) mg/kg/day. All of the proposed nonclinical safety margins found in the labeling were calculated based on this dose for body surface area conversion of the dose or comparison of exposure (i.e. AUC values). However, there has been internal discussion regarding lowering the recommended starting dose to 0.14 mg/kg/day. If this lower starting dose is accepted and incorporated into the labeling, the safety margins calculated in this review will no longer be accurate. If this is the case, a follow-up review will be written revising the safety margins in the labeling based on this lower dose.

1.2 Brief Discussion of Nonclinical Findings

- Envarsus represents an extended release formulation of oral tacrolimus previously approved under NDA 050708 (tacrolimus capsules; Prograf)
- Applicant submitted a 505(b)2 NDA application relying on the Agency's previous nonclinical findings for the Prograf NDA application
- Applicant proposes similar labeling to the listed drug with labeling changes based on changing calculated safety margins due to differences in conversion of the proposed dose or resultant exposure to previous nonclinical data
- No new nonclinical studies were submitted to support any labeling changes

1.3 Recommendations

1.3.1 Approvability: The application is approvable from a Pharmacology/ Toxicology perspective.

1.3.3 Labeling

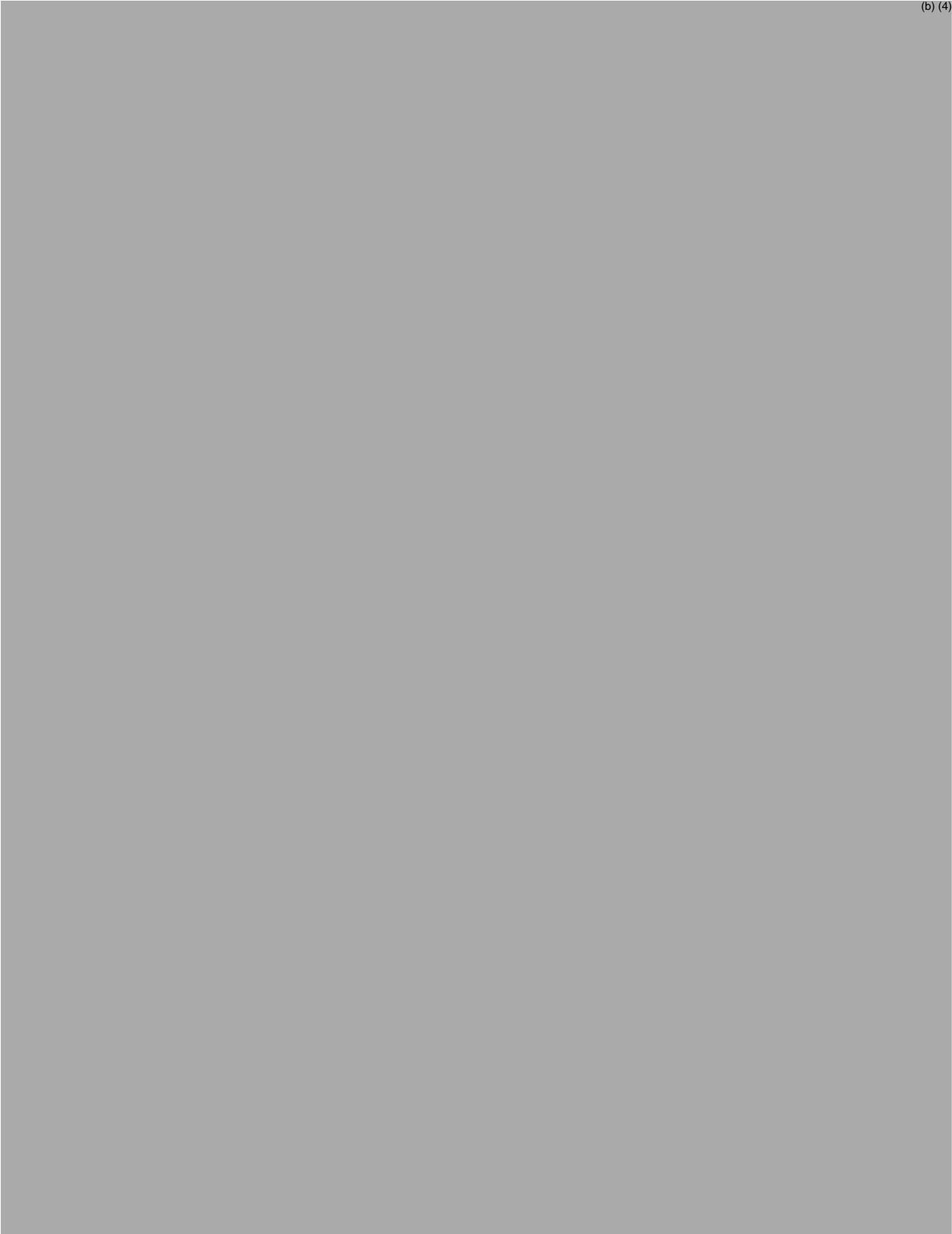
1.3.3.1 Applicant's version

(b) (4)



(b) (4)





(b) (4)



1.3.3.2 Suggested FDA version (Redline):

Note: Additions to the Applicant's version are noted as double underlined font and deletions are noted as strikethrough font.

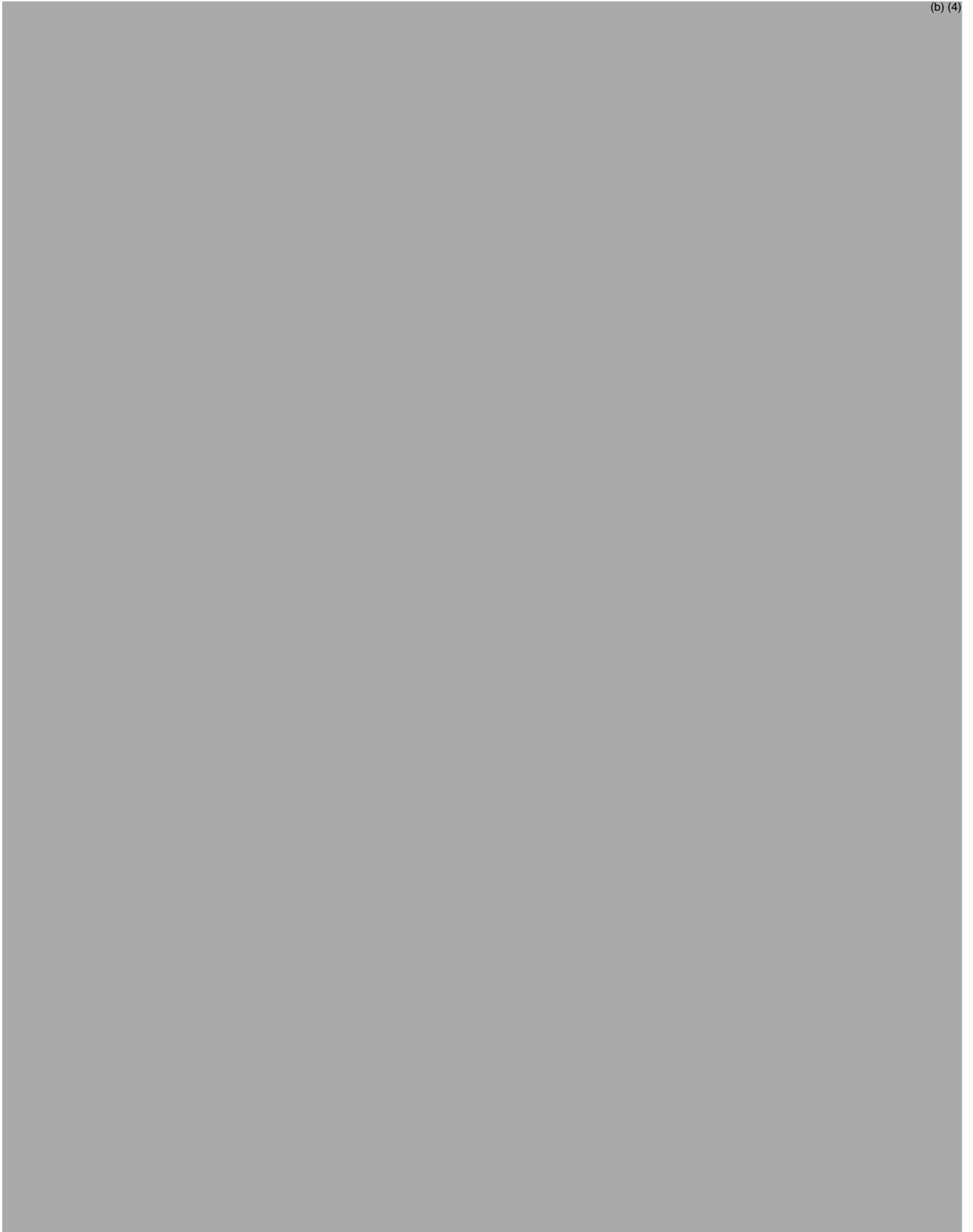
8.1 Pregnancy

Pregnancy Category C



(b) (4)

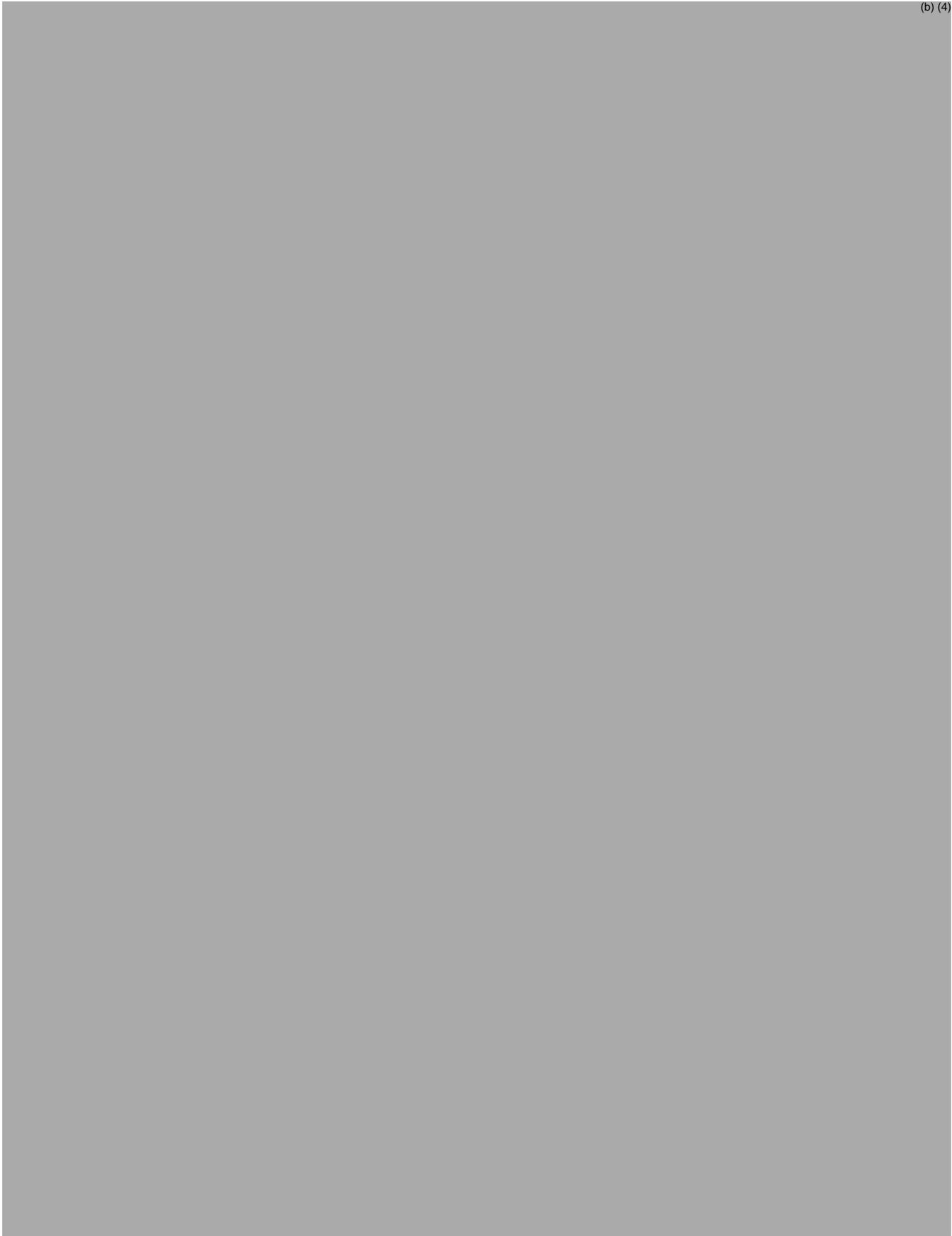




(b) (4)

(b) (4)





(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 104987-11-3

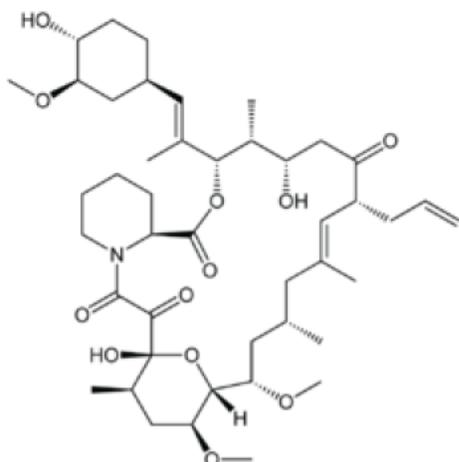
Generic Name: FK506; tacrolimus; LCP-Tacro

Proposed Trade Name: Envarsus®

Chemical Name: 3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR* -5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a -hexadecahydro-5,19-dihydroxy -3-[2-(4-hydroxy-3-methoxycyclohexyl) -1-methylethenyl]-14,16-dimethoxy -4,10,12,18-tetramethyl-8-(2-propenyl) -15,19-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclotricosine-1,7,20,21(4H,23H) -tetrone, monohydrate

Molecular Formula/Molecular Weight: C₄₄H₆₉NO₁₂ / 804.018 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Calcineurin inhibitor; immunosuppressant

2.2 Relevant INDs, NDAs, BLAs and DMFs

- NDA 050708: Prograf® Capsules
 - approved April 8, 1994 for the indication of prophylaxis of organ rejection in patients receiving allogeneic liver transplants and the additional indications of prophylaxis of organ rejection in patients receiving allogeneic kidney transplants and heart transplants were approved on April 22, 1997 and March 29, 2006, respectively.
- DMF (b) (4) Tacrolimus drug substance

2.3 Drug Formulation

Envarsus will be marketed as three strengths, 0.75 mg, 1 mg and 4 mg.

Ingredient	Composition (mg/tablet)		
	0.75 mg	1 mg	4 mg
Tacrolimus monohydrate	0.75 mg	1 mg	4 mg

(b) (4)

2.4 Comments on Novel Excipients

Per FDA inactive ingredient database:

- [REDACTED] (b) (4)

All other excipients are qualified above their proposed content in the formulation.

2.5 Proposed Clinical Population and Dosing Regimen

- *De Novo* kidney transplant recipients
 - [REDACTED] (b) (4)
- Conversion from tacrolimus immediate release formulations (e.g. Prograf)
 - When switching patients from tacrolimus immediate-release formulations (e.g. Prograf), Envarsus should be administered at a lower dose in order to achieve therapeutic blood levels. The conversion ratio when switching from immediate-release formulations to Envarsus is [REDACTED] (b) (4)
[REDACTED] following conversion, tacrolimus trough levels should be monitored and, if necessary, dose adjustments made to maintain similar systemic exposure.

Table 1. Recommended oral dose and observed whole blood concentrations in kidney transplant patients

Treatment regimen	Oral Dose	Observed whole blood trough concentrations*
Newly transplanted patients (with IL-2 receptor antagonist induction)	(b) (4)	
Conversion from tacrolimus immediate-release formulation (e.g. Prograf)		

2.6 Regulatory Background

The following Pharm/Tox reviews were found in DARRTs for IND 75,250 (LCP-Tacro):

- 3-14-2007: William Taylor
 - Review of initial IND package
 - The reviewer noted that there were no pharmacology/toxicology studies submitted with this initial IND application. At the pre-IND meeting, the reviewer notes that the sponsor asked the Division whether the “pre-clinical pharmacology and toxicology data, filed under Prograf capsules (tacrolimus) NDA No. 050708, provides sufficient basis to proceed with the proposed clinical Phase I studies.” The Division responded affirmatively in its July 27, 2006 facsimile and in its face-to-face meeting (August 2) with the sponsor.

- 3-29-2007: William Taylor
 - Reviewer concluded that [REDACTED] (b) (4) [REDACTED] were not necessary based on independent review and levels qualified for intravenous use. The sponsor was notified of this conclusion.

3 Studies Submitted

3.1 Studies Reviewed

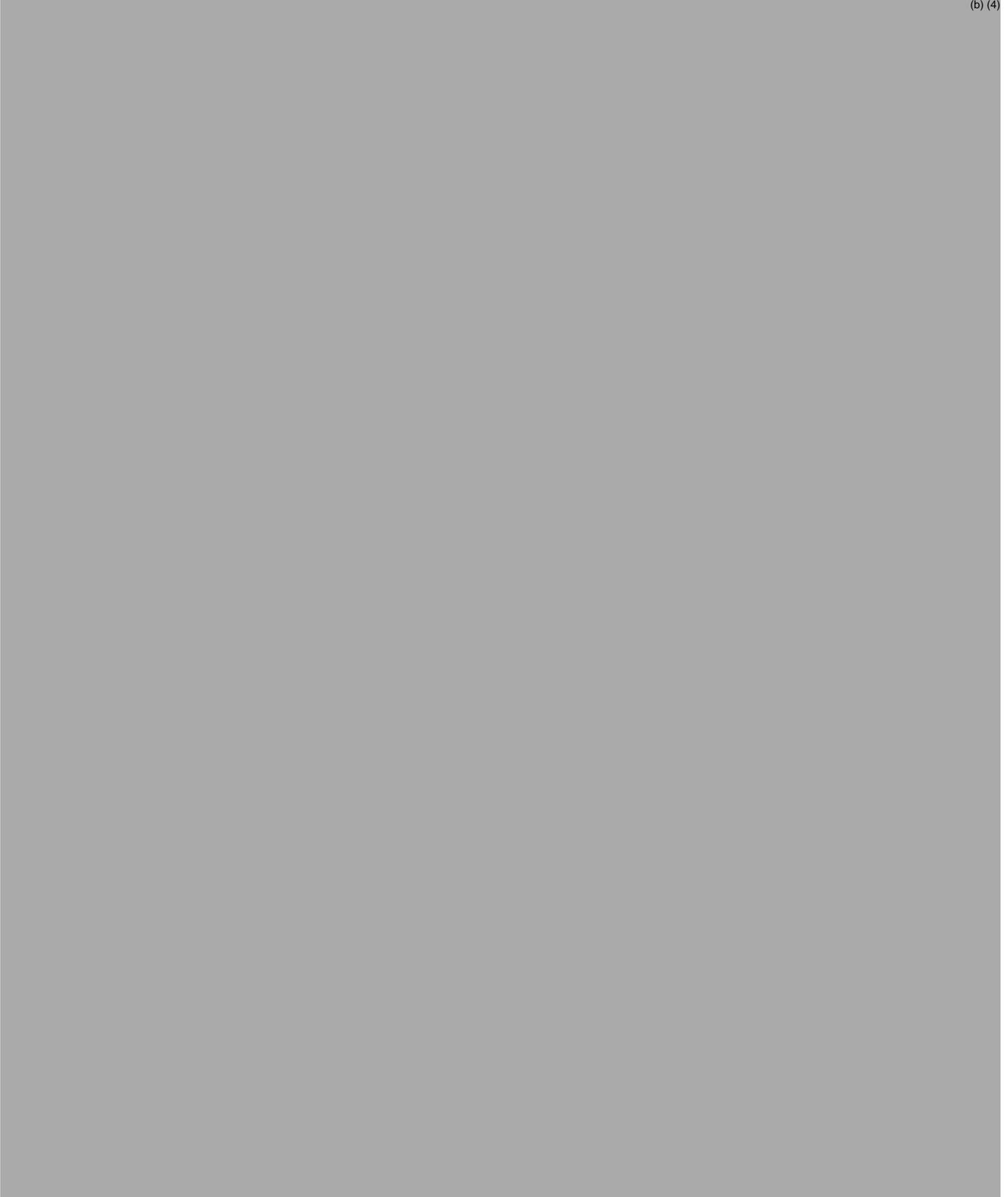
- No studies were submitted to support any changes in the labeling

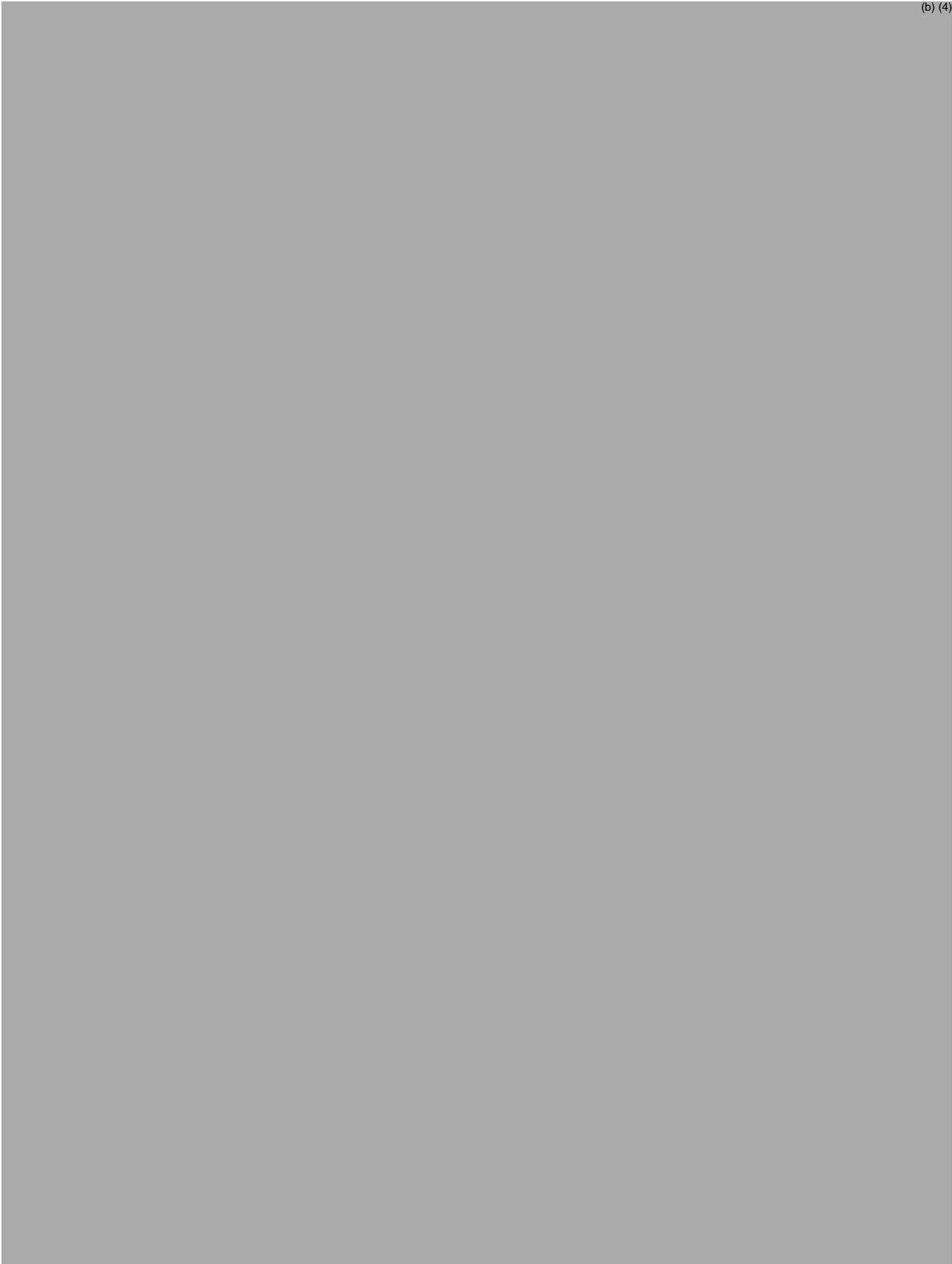
3.2 Studies Not Reviewed



(b) (4)

(b) (4)





(b) (4)

4 Integrated Summary and Safety Evaluation

The applicant has submitted a 505(b)(2) NDA application for an extended release formulation of tacrolimus, Envarsus®. The applicant lists Prograf capsules (NDA 050708) as the listed drug. Some changes in the labeling are required for Envarsus® to reflect changes in the dosing range and pharmacokinetics.

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/s/

AARON M RUHLAND
09/24/2014

LORI E KOTCH
09/24/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 206406

**Applicant: Veloxis
Pharmaceuticals**

Stamp Date: 12-20-2013

**Drug Name: Envarsus
(tacrolimus extended release
tablets)**

**NDA/BLA Type: 505(b)(2)
New NDA (SD1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		All required studies were conducted for the listed drug. A nonclinical bridging study was not included to establish a that reliance on the listed drug (Prograf NDA 50-708) and the applicant's formulation is scientifically justified. Clinical pharmacokinetic data exist that should allow a comparison between formulations.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Clinical studies compared the pharmacokinetics of the applicant's formulation to that of the listed drug.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		As a 505(b)(2), the applicant relies on pivotal studies conducted for the listed drug. Many publications are also included which are not GLP compliant.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		To date, no impurity issues have arisen.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

AARON M RUHLAND
02/25/2014

LORI E KOTCH
02/25/2014