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TGUGCTEJ**

APPLICATION NUMBER:

4262; 8Qt k 3u222

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 204096
Supporting document/s: SDN-039; (eCTD 038)
Applicant's letter date: 6/28/2013
CDER stamp date: 6/28/2013
Product: ASTAGRAF XL
Indication: Prophylaxis of organ rejection in adult patients receiving kidney transplant
Applicant: Astellas Pharma US Inc
1 Astellas Way
Northbrook, IL 60062
Review Division: DTOP
Reviewer: Aaron M. Ruhland, Ph.D.
Supervisor/Team Leader: Lori E. Kotch, Ph.D., DABT
Division Director: Renata Albrecht, M.D.
Project Manager: Jacquelyn Smith

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1 Executive Summary

1.1 Introduction

The subject of this NDA application is an extended release tacrolimus (Tac-XL) for the prophylaxis of organ rejection in adult patients receiving a renal transplant. Tacrolimus was originally approved as an immediate release formulation (Prograf[®]) and is currently marketed by the applicant. In this submission, the applicant updated the nonclinical sections of the product labeling to reflect recommendations made by the Division during review of the original NDA application. In this review, a finalized version of the nonclinical sections of the labeling will be submitted.

1.3.3 Labeling

The applicant made changes recommended following review of the original NDA application and communicated to the applicant (Division letter dated 6-14-2013). Specifically, nonclinical information was updated in Section 8.1 Pregnancy, Section 10 Overdosage, and Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

Section 8.1: Pregnancy

The applicant accepted all recommended changes made by the Division. These changes were related to recalculation of the safety margins based on the maximum clinical dose for Astagraf and the doses which produced toxicity in the nonclinical studies. Comparisons were calculated based upon body surface area (BSA) conversion of the doses. No additional changes are proposed. The final version will read as:

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 0.5 times the maximum clinical dose and pregnant rats at 0.8 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. ASTAGRAF XL 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 (0.5 and 1.6 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 (2.6 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 (0.8 and 2.6 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.

Section 10 Overdosage

In the NDA submission, [REDACTED] (b) (4)

[REDACTED]). The applicant was asked to include relevant information in the labeling regarding the doses which caused lethality in nonclinical studies conducted with tacrolimus and that only information pertinent to the oral dosage form in adults and non-adults be included. The applicant has updated the labeling for Astagraf® to include the following version:

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Reviewer’s note: The applicant based the calculations on nonclinical study reports GLR880181 and GLR910392 which were submitted with the NDA application for Prograf® (NDA 50708). The applicant has right of reference to this NDA. In those studies, the lethal dose in the adult rat following oral administration of tacrolimus was 100 mg/kg (15 mg/rat or 600 mg/m² based on a reference body weight and body surface area of 0.15 kg and 0.025 m²/rat, respectively). For the adult human dose of 0.2 mg/kg (12 mg/patient or 7.41 mg/m² based on a reference body weight and body surface area of 60 kg and 1.62 m², respectively), this calculates as an 80-fold safety margin. For non-adults the applicant assumes an 4 kg infant with a body surface area of 0.25 m² being administered a dose of 0.15 mg/kg (0.6 mg/infant or 2.4 mg/m²) which calculates as a 250-fold safety margin. The information regarding infant body mass and body surface area were taken from “Body surface area for infants” (Geigy Scientific Tables eighth edition, Volume 3 Physical Chemistry Composition of Blood Hematology Somatometric Data Page 329, C Lentner ed, Medical Education Division, Ciba-Geigy Corporation West Caldwell, NJ. 1984.) [REDACTED] (b) (4)

[REDACTED]
[REDACTED] Information regarding the doses which caused lethality in

juvenile animals is more relevant to the possibility of overdose in human juveniles and is included in the next statement.

In order to estimate the risk of overdose in non-adult humans, the safety margin of the adult dose was compared to the lethal dose in juvenile rats. The lethal dose in the juvenile rat was 32 mg/kg. The applicant calculates this as 15 mg/rat or 600 mg/m² which upon reverse calculation would assume a body mass of 0.46 kg. The source of this reference body mass was not provided and does not appear appropriate since the adult rat reference weight is 0.15 kg. No ICH guidance exists which provides a reference body weight and body surface area for juvenile rats. In the review of this study (Study GLR910392) for the approval of Prograf (NDA 50-708 and 50-709 conducted by Lauren E. Black and dated 12/16/1993), the reviewer notes that these 21-day old rats weighed approximately 50 grams. The standard formula for converting rat body mass to body surface area in cm² is: $9.1 * \text{body mass(g)}^{0.66}$ (i.e. 9.1 times the body mass in grams raised to 0.66 power; commonly cited source: Pass D, Freeth G. The rat. ANZCCART News. 1993;6(4):1-4). This appears to fit nearly perfectly with ICH guidance in that the rat reference weight of 150 grams calculates to 250 cm² or 0.025 m². For a 50 gram rat, the body surface area would then be 120 cm² or 0.012 m². Therefore a dose of 32 mg/kg in 50 gram juvenile rats would calculate as 1.6 mg/rat or 133 mg/m². This then yields a safety margin of 18-fold over the adult dose of 0.2 mg/kg (12 mg/patient or 7.41 mg/m²). The labeling should be updated to reflect this change.

The applicant then proposes (b) (4)
[Redacted]
[Redacted]
[Redacted]. The following is a redline version of the changes recommended to the applicant's version of the nonclinical information in Section 10:

[Redacted] (b) (4)
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]

Therefore, the final nonclinical information in Section 10 should read as:

In acute oral toxicity studies, mortality was observed at or above the following doses: in orally administered adult rats, 80-fold the maximum adult human dose; in orally

administered immature rats, 18-fold the maximum adult human dose. All doses are based on body surface area conversion (mg/m²).

Section 13.1: Carcinogenesis, Mutagenesis, Impairment of Fertility

In the Division's recommended draft labeling (letter date: 6-14-2013), the applicant was asked to include safety margins related to doses which produced lymphoma in the nonclinical dermal studies of Protopic®. The applicant was asked to base the safety margin on exposure comparisons (preferably AUC) of patients administered tacrolimus XL (at 0.2 mg/kg) and the exposures observed in the nonclinical dermal study. The following represents the applicant's redline version of the labeling for Section 13.1:

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 (0.49 times the AUC at the maximum clinical dose of 0.2 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.14 times the AUC at the maximum clinical dose 0.2 mg/kg/day) [see *Boxed Warning, and Warnings and Precautions (5.4)*].

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; (b)(4)-fold the human exposure in stable adult renal transplant patients > 6 months post transplant). 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.

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. Tacrolimus given orally at 1.0 mg/kg (0.8 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 (2.6 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.

Reviewer's note: The applicant updated the labeling according to the Division's recommendation using the AUC cited from source document F506-TX -5803 and the human AUC from the Astagraf label. A study report for F506-TX-5803 could not be located in the Protopic NDA review conducted by Dr. Barbara Hill and dated 8-2-2000. In that review, for Study 95-8005 which was a 104-week dermal carcinogenicity study in mice, a significant increase in the incidence of pleiotrophic lymphomas and undifferentiated lymphomas in the 0.1% ointment group was reported. It is not known by this reviewer if the applicant is referring to the same study described by Dr. Hill in her review. In the pharmacology/Toxicology review of Protopic, for Study 95-8005, the average AUC_{0-24hr} in male and female mice administered 0.1% Protopic ointment was 534 ng•hr/mL. In the labeling for Astagraf, the average human exposure in stable adult renal transplant patients > 6 months post-transplant was 222 ng•hr/mL. Therefore, the AUC at the oncogenic dose in mice represents a safety margin of 2.4-fold over the human dose based on exposure. The applicant's redline version should be changed to reflect this recalculation:

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 (0.49 times the AUC at the maximum clinical dose of 0.2 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.14 times the AUC at the maximum clinical dose 0.2 mg/kg/day) [see Boxed Warning, and Warnings and Precautions (5.4)].

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; **2.4-fold the human exposure in stable adult renal transplant patients > 6 months post transplant**). 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.

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.

Tacrolimus given orally at 1.0 mg/kg (0.8 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 (2.6 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.

4 Integrated Summary and Safety Evaluation

The applicant has submitted updated labeling for NDA 204096. Further changes and deletions outlined above should be communicated to the applicant as the final version of the labeling.

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/s/

AARON M RUHLAND
07/15/2013

LORI E KOTCH
07/15/2013

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 204096
Supporting document/s: SDN-001; original
Applicant's letter date: 9/20/2012
CDER stamp date: 9/21/2012
Product: ASTAGRAF XL
Indication: Prophylaxis of organ rejection in adult patients receiving kidney transplant
Applicant: Astellas Pharma US Inc
1 Astellas Way
Northbrook, IL 60062
Review Division: DTOP
Reviewer: Aaron M. Ruhland, Ph.D.
Supervisor/Team Leader: Lori E. Kotch, Ph.D., DABT
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1 Executive Summary

1.1 Introduction

The subject of this NDA application is an extended release tacrolimus (Tac-XL) for the prophylaxis of organ rejection in adult patients receiving a renal transplant. Tacrolimus was originally approved as an immediate release formulation (Prograf[®]) and is currently marketed by the applicant. The applicant relies on the nonclinical studies previously submitted for the approval of Prograf[®] to support the nonclinical safety of Tac- XL. In the NDA submission, the applicant did not update the nonclinical sections of the product labeling to reflect changes in the safety margins which result from changes in the recommended dosing regimen and clinical pharmacokinetics associated with the extended release dosage form. In this review, the nonclinical sections of the product labeling have been updated to reflect these changes.

1.2 Brief Discussion of Nonclinical Findings

The applicant included an amendment to the study report for a nonclinical proof of concept study entitled “Comparison between the effects of bolus intramuscular administration and continuous infusion of FK506 on skin allograft rejection in rats (Report No. CRR980201). This study was reviewed by Dr. Shukal Bala (see Microbiology/Immunology review dated 5-10-2013).

The applicant did not suggest any changes to the nonclinical sections of the labeling for Tac-XL and therefore the labeling proposed for approval was a facsimile of the Prograf[®] labeling for those sections. When comparing Tac-XL to Prograf[®], the recommended dosing range has changed and human pharmacokinetics are different between these two formulations. These differences change the estimated safety margins for the effects observed in the nonclinical studies. Also, there are no safety margins reported in the labeling for exposures which resulted in lymphoma following dermal application of tacrolimus in the nonclinical carcinogenicity studies. The applicant should update the labeling to reflect the safety margin calculated based on exposure to tacrolimus (i.e. direct AUC comparisons).

Additionally, the applicant removed nonclinical information from Section 10 of the labeling, “Overdosage”. While some of the information removed is no longer relevant to the oral extended release formulation being proposed in this NDA, other information pertaining to doses which caused lethality in the nonclinical studies should be included.

1.3 Recommendations

1.3.1 Approvability: Approvable from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

- The following comment should be communicated to the applicant:
 - In the labeling, please update Section 10, “Overdosage”, to include safety margins related to the doses which produced lethality in the nonclinical studies. Information should be included regarding oral dosage forms in adults and non-adults. The margins should be based on body surface area conversions of the doses which caused lethality in the acute nonclinical studies.
 - In the labeling, please update Section 13.1 “Carcinogenicity” to include safety margins related to doses which produced lymphoma in the nonclinical dermal studies of Protopic[®]. The safety margin should be based on exposure comparisons (preferably AUC) of patients administered Astagraf XL (at 0.2 mg/kg) and the exposures observed in the nonclinical dermal study.
- Other changes to the labeling are recommended (see FDA redline version of Section 1.3.3). These changes were incorporated into the draft labeling sent to the applicant.

1.3.3 Labeling

The applicant did not propose any changes from the currently approved labeling for Prograf[®] for Sections 8.1 and 13.1. The sponsor removed nonclinical information regarding overdose from Section 10:

Section 8.1: Applicant’s version

8.1 Pregnancy

Pregnancy Category C

(b) (4)

(b) (4)

Section 8.1: Suggested FDA version (Redline):

Note: Additions are noted as bold blue font and deletions are noted as strikethrough font.

8.1 Pregnancy***Pregnancy Category C***

(b) (4)

FDA rationale:

In the labeling for Prograf[®], the Dosage and Administration section of the labeling includes recommended dose ranges for liver and heart transplant recipients. The lower end of the dose range in these patient populations is 0.075 mg/kg/day for heart transplant recipients. The current labeling for Prograf includes this dose as the lower end of the clinical dose range when calculating nonclinical safety margins. This population is not indicated in the Tac- XL labeling and therefore is not relevant. The

dose range of tacrolimus in adult kidney transplant patients ranges from the maximum of 0.2 mg/kg/day with no established lower limit. Therefore, only the maximum recommended dose is used in the changes FDA suggests for the labeling.

Section 10 Applicant's version:

10. OVERDOSAGE

(b) (4)

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdose.

Reviewer's note: It is notable that the following text was included in the Prograf labeling but was not proposed for the Tac-XL labeling:

In acute oral and IV toxicity studies, mortalities were seen at or above the following doses: in adult rats, 52 times the recommended human oral dose; in immature rats, 16 times the recommended oral dose; and in adult rats, 16 times the recommended human IV dose (all based on body surface area corrections).

The applicant should be asked to include relevant information in the labeling regarding doses which caused lethality in nonclinical studies conducted with tacrolimus. Only information pertinent to the oral dosage form in adults and non-adults should be included. While Tac-XL is only proposed to be indicated for use in adults, the risk of accidental ingestion and overdose in non-adults remains a possibility.

Section 13.1: Applicant's version

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility



Section 13.1: Suggested FDA version (Redline):

Note: Additions are noted as bold blue font and deletions are noted as strikethrough font.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility



2 Drug Information

2.1 Drug

CAS Registry Number: 104987-11-3

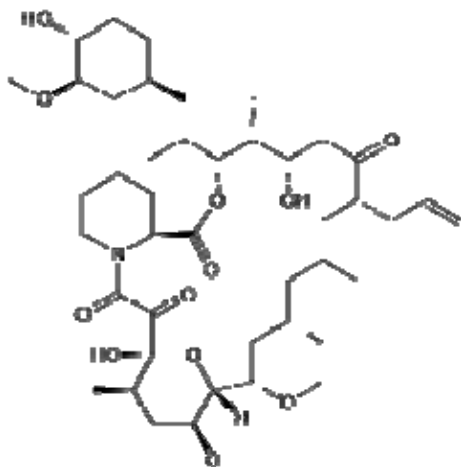
Generic Name: FK506; Tacrolimus; Tac-XL (extended release formulation)

Proposed Trade Name: Astagraf XL

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
- NA 050709: Prograf® Injection. NDA 050708 and NDA 050709 were originally approved on 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 16833: Tacrolimus (FK506) Drug Substance, Astellas Pharma Tech Co., Ltd. Letter of authorization included in application.

2.3 Drug Formulation

Ingredient	Reference Quality Standard	Function	0.5 mg Capsule	1.0 mg Capsule	5.0 mg Capsule	
Tacrolimus*	USP DMF No. 16833	Active ingredient	0.50 mg	1.0 mg	5.0 mg	
Hypromellose (b) (4)	USP					(b) (4)
Ethylcellulose	NF					
Lactose monohydrate	NF					
Magnesium stearate	NF					

(b) (4)

2.4 Proposed Clinical Population and Dosing Regimen

The applicant proposes to indicate Tac- XL for prophylaxis of organ rejection in adult patients receiving a kidney transplant. The proposed dosing regimen is as follows:

(b) (4)

3 Studies Submitted

3.1 Studies Reviewed

The applicant did not submit any new nonclinical studies to support the nonclinical safety of Tac- XL. The applicant relies on nonclinical studies conducted for the approval of Prograf® to support this extended release formulation. For details, refer to the Pharmacology review conducted by Lauren E. Black (dated 12-16-1993). A list of those studies reviewed for approval of Prograf are listed in Appendix A.

Reviewer's note: The following data were taken from the TK studies of Prograf® and used to form the basis of the calculations made for the proposed changes to the Carcinogenicity section of the labeling. These study reports can be found in the NDA application for Prograf® (NDA 50-708).

Mouse:

Study No. GLR940186: FR900506: TK study in mice by dietary administration for 13-weeks

Route: Oral

Doses: 0, 0.3, 1.0, or 3.0 mg/kg/day

TK sampling: Whole blood on Day 2, Week 8, and Week 14

Mean PK parameters of FK506 in male and female mice after dietary administration of FK506 over a period of 13-weeks

Dose (mg/kg/day)	Time Point (Day or Weeks)	C _{max} (ng/mL)	AUC (ng*hr/mL)
0.3	Day 2	0.54	7.3
	Week 8	0.48	7.7
	Week 14	0.76	11.7
1.0	Day 2	1.5	24.1
	Week 8	1.6	23.8
	Week 14	1.9	33.0
3.0	Day 2	4.2	71.4
	Week 8	5.8	97.0
	Week 14	18.0	182.4

Rat:

Study No. GLR940185: FR900506: TK study in rats by dietary administration for 13-weeks

Route: Oral, dietary feed

Doses: 0, 1.25, 2.5, or 5.0 mg/kg/day

TK sampling: Day 2, Week 8, Week 14

Mean PK parameters of FK506 in male and female rats after dietary administration of FK506 over a period of 13-weeks

Dose (mg/kg/day)	Time Point (Day or Weeks)	Cmax (ng/mL)	AUC (ng*hr/mL)
1.25	Day 2	1.2	9.4
	Week 8	2.4	10.2
	Week 14	0.45	7.2
2.5	Day 2	1.0	13.3
	Week 8	0.79	12.2
	Week 14	0.88	9.0
5.0	Day 2	1.5	22.3
	Week 8	9.0	58.4
	Week 14	3.5	53.8

Reviewer's note: The carcinogenicity studies cited in the labeling were dietary feed studies. To estimate the exposure to tacrolimus in those studies, the TK information from Studies GLR940185 and GLR940186 were used. To compare the human exposure to the high dose of 3.0 mg/kg/day in the mouse carcinogenicity study, the AUC value of 182.4 ng•hr/mL was used. To compare the human exposure to the high dose of 5.0 mg/kg/day in the rat carcinogenicity study, the AUC value of 53.8 ng•hr/mL was used. These values were then compared to the human AUC value obtained in clinical trials of TAC-XL in renal transplant patients receiving 0.2 mg/kg/day and cited in the labeling: 372 ng•hr/mL.

4 Integrated Summary and Safety Evaluation

The applicant has submitted an NDA application for an extended release formulation of tacrolimus. Data submitted from NDA 050708 and NDA 050709 (Prograf[®] Capsule and Prograf[®] Injection, respectively) support the nonclinical safety of the new formulation. Some changes in the labeling are required for Tac-XL to reflect changes in the dosing range and pharmacokinetics of Tac-XL. It is also recommended that the applicant include safety margins related to exposures observed in the dermal carcinogenicity studies. Additionally, the applicant removed some data from the Overdosage section of the labeling which should be reincorporated with changes based on relevance and the proposed dosing regimen for Tac-XL.

5 Appendix/Attachments

APPENDIX A: Nonclinical studies conducted in support of approval of NDA 050708 (Prograf capsule) and NDA 050709 (Prograf injection):

NONCLINICAL TOXICOLOGY STUDIES: OVERVIEW

Study Summary:

A. Acute

A1. Acute toxicity study of FK506 in rats following i.v. and oral dosing¹. (GILR880181; Fujisawa, non-GLP; 5/87-8/87; lot no. 016073L).

A2. Acute toxicity of FK506 in young rats following oral dosing. (GLR910392; Fujisawa; Japan GLP; 5/90-9/90; lot no. 10306YL).

A3. FK506 acute oral and i.v. toxicity to baboons by single administration.
Study no. 881636; lot # G02672S; GLP; 5/28/88)

A4. Single dose toxicity study of FK506 and its deterioration products, related compounds, and tautomer in Jcl:ICR mice (i.v. dosing). (Fujisawa; Japan GLP; GLR 910601; 7/91; lot no. not provided)

A5. Single dose toxicity study of related compound and a metabolite of FK506 in mice using i.v. dosing. (Fujisawa; Japan-GLP; lot no. not provided ; GLR920309; 1/92)

B. Subchronic

B1. Preliminary 2-wk oral toxicity study of FK506 in rats. (GLR 910477; Fujisawa; non-GLP; 2/86-4/86; lot no. 011050L).

B2. FK506 toxicity to rats by repeated oral administration for 13 weeks. (GLR 880273; GLP; 10/26/87-1/26/88; lot no. 10306YL)

B3. FK506 toxicity to rats by repeated oral administration for 52 weeks. (GLR 910589; GLP; 2/12/90-2/11/91; lot no. s 034103L, 8/27/90-2/8/91; and 018270L, 2/6-8/24/90)

B4. Four-week oral toxicity study of FK506 in young rats. (GLR 910393; Fujisawa; Japan GLP; 7/90-3/91; lot no. 018178L)

B5. FK506 toxicity to rats by repeated i.v. administration for 4 weeks. (GLR 900160; GLP; 12/8/88-1/5/89; lot no. 018178L).

B6. FK506 preliminary toxicity study in baboons by repeated oral administration for 28 days.
Study no. 880271; 6/24/87; GLP; lot no. G00371S)

B7. FK506 toxicity to baboons by repeated oral administration for 13 weeks.
; Study no. 880272; GLP; lot no. G02672S; 11/4/87)

B8. FK506 toxicity to baboons by repeated oral administration for 13 weeks II.
Study no. 890443; GLP; lot no. G02672S; 7/15/88)

B9. FK506 toxicity to baboons by repeated administration for 52 weeks.
Study no. 910520; GLP; lot no. 239684K; 3/13/91)

B10. FK506 toxicity to baboons by repeated i.v. administration for 4 weeks.
Study no. 890444; GLP; lot no. 111385K, 111285K, and 111185K; 8/11/88)

B11. Four week i.v. toxicity of FK506 in rabbits with 4-wk recovery. (GLR 930031; non-GLP; lot no. 718619K; 4/2/92)

B12. Dose-range finding study in rats by dietary administration for 13 weeks.
Lot no. 203001K; GLR 910196; GLP; 3/23/90)

¹Unless otherwise stated, FK506 was administered by oral gavage to animals used in all toxicity studies in a dispersed suspension, stirred continuously during dosing. The formulation for the vehicle was TC-5R, lactose, and Ac-Di-Sol at proportions of 1:2:1, stirred with distilled water. The formulation used for i.v. dosing in nonclinical toxicity studies was HCO-60, polyoxyethylene hydrogenated castor oil.

B13. Preliminary 2-week oral toxicity study of FK506 in dogs. (Fujisawa; GLR 910395; Lot no. FR011050L; 4/86; non-GLP)

C. Genotoxicity

C1. Evaluation of FK506 in a chromosomal aberration test with chinese hamster lung cell line V79. (Fujisawa; GLR 930182; Japan GLP; lot no. 0541YL; 4/93)

C2. Evaluation of the potential of FK506 to induce unscheduled DNA synthesis in the in vitro hepatocyte DNA repair assay using the male F-344 rat. (GLR 910559; GLP; 5/20/91-8/8/91; lot no. 038008L).

C3. FK506 effects on in vitro non-mammalian cell systems: I. (Reversion or Ames tests). (GLR 880249; Fujisawa; 9/87; lot no. 011050L; Japan GLP)

C4. FK506 effects on in vitro non-mammalian cell systems: II. (Reversion or Ames tests). (GLR 910396; Fujisawa; 10/90; lot no. 036005L; Japan GLP)

C5. Mutagenicity study of FK506- chromosomal aberration test with chinese hamster lung cells in culture. (GLR 880250; Fujisawa; 9/87; lot no. 011050L; Japan GLP)

C6. Evaluation of FK506 in the chinese hamster ovary cell/HGPRT gene mutation assay. (GLR 910560; 4/91; lot no. 038008L; GLP)

C7. Mutagenicity study of FK506- micronucleus test in mice following single oral dosing. (GLR 910320; Fujisawa; 8/90; lot no. 018178L; Japan GLP)

C8. Mutagenicity study of FK506- micronucleus test in male and female mice. (GLR 930076; Fujisawa; 11/92; lot no. 207781K; Japan GLP and OECD)

D. Reproductive toxicity

D1. Study of FK506 on fertility and general reproductive performance in rats (Segment I) (GLR890455; GLP; lot no. 018178L and 014071L, 5/11/88-9/7/88)

D2. Developmental toxicity study in rats of p.o. FK506 (Segment II) (GLR910516; GLP; lot no. 018270L; 4/17/90-9/29/90)

D3. Perinatal and lactation study of FK506 in rats (Segment III) (GLR91059; GLP; lot 034103L; 11/2/90; I)

D4. Segment II reproductive toxicity study in New Zealand white rabbits. (GLR 890389; GLP; 8/1/88; lot no. 018178L)

E. Vehicle toxicity

E1. Reactions to HCO-60 (GLR920256; non-GLP;

E2. Single dose toxicity study of HCO-60 in rats by i.v. dosing. (Fujisawa; GLR930079; non-GLP; 11/92; lot no. FF1853)

E3. HCO-60 toxicity to rats by repeated administration for 4 weeks. (GLR910360; non-GLP;

E4. (34,654/151) Four week i.v. toxicity study of HCO-60 in rats. (Fujisawa; GLR 930211; Japan GLP; lot no. FF-2198; 1/93)

E5. (34,654/151) Mutagenicity of HCO-60 (micronucleus test) in mice. (Fujisawa; GLR 930173; Japan GLP; lot no. FF-2918; 2/93)

E6. (34,654/151) Evaluation of HCO-60 in chromosomal aberration test with chinese hamster lung cells line V79. (Fujisawa; GLR 930167; Japan GLP; lot no. FF-2918; 2/93)

E7. Antigenicity study of HCO-60 and cremophor in guinea pigs. (Fujisawa; GLR920248; Japan-GLP; lots FF0733 and MOE1381; 8/3/90)

E8. Correlation between plasma histamine levels and infusion time of HCO-60 in dogs. (Fujisawa; non-GLP; lot no. FF0733; 7/92; GLR 920324)

**E9. HCO-60 toxicity to baboons by repeated i.v. administration for 4 weeks.
Study no. 910404; non-GLP; lot no. 111585K; 6/28/88)**

E. Special toxicity

**F1. Morphological and functional changes in islet of Langerhans in FK506 treated rats.
(GLR910177; non-GLP; Fujisawa)**

**F2. Effects of FK506 and cyclosporin A on exocrine function of the rat pancreas. (GLR910616;
non-GLP; Fujisawa)**

**F3. Antigenicity study of FK506 in mice. (Fujisawa; Japan-GLP; GLR910600; lot no. 109003K; ..
8/91)**

**F4. Antigenicity study of FK506 in guinea pigs. (Fujisawa; Japan-GLP; GLR910318; 10/88; lot no.
019186L)**

**F5. Local irritation test of FK506 injectable formulation in rabbits by i.m. injection. (Fujisawa; GLR
890179; Japan-GLP; lot no. 111685K; 11/89)**

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/s/

AARON M RUHLAND
06/12/2013

LORI E KOTCH
06/12/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204096	Applicant: Astellas Pharma US Inc	Stamp Date: 9-21-2012
Drug Name: Advagraf (Tacrolimus extended -release capsules)	NDA/BLA Type: 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?	✓		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	✓		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	✓		
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)?	✓		
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).	✓		
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?	✓		
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?	✓		

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
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓		
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?	✓		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Deferred to CMC for identification of impurity issues. Should issues be identified during the review cycle, nonclinical qualification of impurities will be a review issue.
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

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

/s/

AARON M RUHLAND
11/16/2012

LORI E KOTCH
11/16/2012