CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210115Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 22, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 210115
Product Name and Strength:	Prograf Granules (tacrolimus for oral suspension), 0.2 mg and 1 mg
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
FDA Received Date:	May 9, 2018 and May 11, 2018
OSE RCM #:	2017-1524-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised container label, carton labeling, Prescribing Information (PI), Instructions for Use (IFU), and Patient Information for tacrolimus for oral suspension (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Astellas implemented most of our recommendations. However, we recommended that Astellas revise the NDC numbers so that the carton labeling and container label (unit dose packets) NDC numbers are different. In response, Astellas stated that a different NDC number on the unit dose packets may lead to confusion (i.e., implying that each packet can be sold separately). However, we maintain our previous recommendation regarding the need for different package codes for the carton labeling and container label.

[a] Patel M. Label and Labeling Review for PROGRAF (NDA 210115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 19. RCM No.: 2017-1524.

Furthermore, at the May 1, 2018 teleconference with Astellas[b], FDA asked Astellas to propose label and labeling strategies to address medication error concerns regarding the inclusion of the modifier "Granules" in the proposed proprietary name, which may lead users to think that the product can be administered like granule dosage forms (e.g., sprinkling directly on the tongue or on food). To address this concern, Astellas proposes the following statement to be included on the carton labeling:

> "Mix Prograf Granules only with water. Do not sprinkle on food. Read the Instructions for Use for how to mix and prepare Prograf Granules as a liquid suspension."

They also state that, *"Astellas has added this text to the back panel instead of the principal display panel due to the lack of space. Reducing the size of this text to fit it on the principal display panel may compromise readability, which could drive selection errors at the pharmacy level."*

We find their proposal unacceptable from a medication error perspective. This does not address our concern of users possibly sprinkling directly on the tongue.

3 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Revise the statement on the back panel "Do not sprinkle on food." to read, "Do not sprinkle directly on tongue or on food." As currently presented the statement does not address our concern of users possibly sprinkling the contents directly on the tongue. Additionally, if space permits, we recommend increasing the prominence of this information (e.g. bold, highlight, increase font size, etc.) to minimize the risk of the information being overlooked.
B. As stated previously, the container label of one unit and the carton labeling of 50 units should have different NDC numbers. Revise the NDC numbers so that package codes for the carton labeling and container label are different.

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[b] Chaudhry A. Memorandum of Teleconference for Prograf (tacrolimus) (NDA 210115) on May 1, 2018. Silver Spring (MD): FDA, CDER, OSE (US); 09 MAY 2018.

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/s/

MADHURI R PATEL
05/22/2018

SARAH K VEE
05/22/2018

Division of Transplant and Ophthalmology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 210115

Name of Drug: Prograf Granules (tacrolimus for oral suspension)

Applicant: Astellas Pharma US, Inc.

Labeling Reviewed

Submission Date: 7/26/17

Receipt Date: 7/26/17

Background and Summary Description:

The Applicant submitted a new drug application (NDA) for a new granule formulation of 0.2 mg and 1 mg tacrolimus, a calcineurin-inhibitor immunosuppressant, for oral suspension for the prevention of rejection of pediatric heart, kidney or liver transplant recipients. This application was submitted in response to a Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA) for NDA 204096 (Astagraf XL) to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years. Orphan Drug Designation was granted for tacrolimus granules for oral suspension on October 4, 2016.

Review

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the Selected Requirements for Prescribing Information (SRPI) checklist.

Recommendations

Minor SRPI format deficiencies were identified in the review of this PI. All SRPI format deficiencies of the PI were conveyed to Astellas Pharma US, Inc., during labeling negotiations and were corrected, as noted, in the May 9, 2018, labeling submission.

Wendy Streight, PhD	See Stamp Date
Regulatory Project Manager	Date
Diana Willard	See Stamp Date
Chief, Project Management Staff	Date

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/s/

WENDY M STREIGHT
05/17/2018

DIANA M WILLARD
05/17/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 1, 2018
To:	Renata Albrecht, MD Director **Division of Transplant and Ophthalmology Products (DTOP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	PROGRAF (tacrolimus)
Dosage Form and Route:	for oral suspension
Application Type/Number:	NDA 210115
Applicant:	Astellas Pharma US, Inc.

1 INTRODUCTION

On July 26, 2017, Astellas Pharma US, Inc. submitted for the Agency's review an original New Drug Application (NDA) 210115 for PROGRAF (tacrolimus) for oral suspension. This NDA proposes the use of tacrolimus granules 0.2 mg and 1 mg for oral suspension for the prevention of rejection in pediatric heart, kidney, or liver transplant recipients. This submission seeks to fulfill the Postmarketing Requirement under the Pediatric Research Equity Act (PREA) for NDA 204096 (Astagraf XL) to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years. PROGRAF (tacrolimus) capsules, for oral use, PROGRAF (tacrolimus) injection, for intravenous use and PROGRAF (tacrolimus) for oral suspension will share Prescribing Information. PROGRAF (tacrolimus) capsules, for oral use and PROGRAF (tacrolimus) for oral suspension will share a Patient Package Insert.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Transplant and Ophthalmology Products (DTOP) on January 25, 2018 and July 28, 2017, respectively for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PROGRAF (tacrolimus) for oral suspension.

DMPP conferred with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 19, 2018.

2 MATERIAL REVIEWED

- Draft PROGRAF (tacrolimus) for oral suspension PPI and IFU received on December 5, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2018.
- Draft PROGRAF (tacrolimus) for oral suspension Prescribing Information (PI) received on December 5, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU documents using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
05/01/2018

CARRIE A NEWCOMER
05/02/2018

SHARON W WILLIAMS
05/02/2018

LASHAWN M GRIFFITHS
05/02/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs—ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Lily (Yeruk) Mulugeta, PharmD, Clinical Reviewer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Team Leader
John Alexander, MD, MPH, Deputy Director, DPMH

To: Division of Transplant and Ophthalmology Products (DTOP)

Drug: Prograf for suspension (tacrolimus for suspension)

NDA: 210115

Proposed Indication: Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants, in combination with other immunosuppressants.

Dosage form and route of administration: Immediate-release granules for oral suspension

Sponsor: Astellas Pharma US

Consult Request: DTOP requested input from DPMH regarding section 8.4 of the Prograf (tacrolimus) labeling for this new dosage form and the rationale for extrapolation of efficacy from existing data in adults and pediatric liver transplant patients to pediatric kidney and heart transplants.

Background

Tacrolimus is a calcineurin inhibitor immunosuppressant originally approved in the United States (US) as Prograf (NDA 050708) in 1994 for use in adult liver transplants. The oral (immediate-release capsules) and intravenous formulations of tacrolimus of Prograf are currently approved for the prophylaxis of organ rejection in patients receiving kidney, liver and heart transplants. Labeling is shared between the two formulations. Of

note, the current Prograf labeling does not include an age restriction in the indication statement. The Warnings and Precautions section of labeling for Prograf includes lymphomas and other malignancies, infections, new onset diabetes, nephrotoxicity, neurotoxicity, hyperkalemia, QT prolongation, myocardial hypertrophy, pure red cell aplasia, etc. The dosing section of labeling does not include dosing information in pediatric patients. Oral Astragraf XL (extended-release capsules) is approved in the US in adult patients receiving kidney transplants.

An immediate-release granule for oral suspension formulation of tacrolimus has been developed by Astellas. The granules are packaged in packets (b) (4) of 0.2 mg and 1 mg. The sponsor is seeking use of tacrolimus oral suspension in the treatment of pediatric liver, kidney or heart transplant patients. The clinical development for tacrolimus granules included a pharmacokinetic (PK) study in adult healthy volunteers (Study 95-0-001), and two safety and efficacy studies in pediatric liver transplant patients (Study FG-506-01-08 [including a pharmacokinetic sub-study] and Study FG-506-01-13). In addition, the sponsor conducted an open-label study (Study F506-CL-0403) to determine the pharmacokinetics of tacrolimus after the first oral dose and at steady state in 52 pediatric patients 12 years of age or younger undergoing de novo allograft transplantation (heart, liver and kidney). This study was followed by a 12-month open-label extension study (Study F506-CL-0404A).

Table 1. Completed Studies with Tacrolimus Immediate-release Granules

Study ISN	Type of Study	Treatment	Population	Age Range (Years)	Transplant Organ
95-0-001	P1, randomized, single-dose, open-label, 4-period, 4-sequence, crossover, replicate design, 8-week, BE study with iv extension study	5 x 1 mg tacrolimus capsules; 5 x 1 mg tacrolimus granule packets 0.025 mg/kg tacrolimus 4-h iv infusion	32 adult healthy volunteers	19 - 50	NA
FG-506-01-08	P2, open-label, noncomparative, PK, pilot, safety and efficacy 12-month study conducted at 2 European centers	Tacrolimus iv: 0.025 mg/kg/h as 24-h iv infusion for 12 h to 4 days; Tacrolimus granules: 0.3 mg/kg/day po in 2 divided doses + AZA and CS maintenance therapy	28 pediatric liver transplant recipients	< 1 - 13	Liver
FG-506-01-13	P3, randomized, open-label, parallel-group, multicenter, 12-month, efficacy and safety study	Tacrolimus granule: 0.3 mg/kg/day po in 2 divided doses + CS	91 treated patients	< 5: n = 70 ≥ 5: n = 21	Liver
		CyA-ME/AZA + CS	90 treated patients	< 5: n = 70 ≥ 5: n = 20	
F506-CL-0403 (OPTION)	P4, open-label, noncomparative, multicenter, PK, 14-day study	Tacrolimus granule: 0.3 mg/kg/day po in 2 divided doses	52 treated patients 20 liver, 15 kidney, 17 heart	≤ 12	Liver, Kidney, Heart
F506-CL-0404A (PROGRESSION)	P4, long-term, open-label, noncomparative, multicenter, efficacy and safety extension study of Study F506-CL-0403	Tacrolimus granule, po dose equal to the final daily dose at the end of Study F506-CL-0403	47 treated patients 18 liver, 8 kidney, 17 heart	≤ 12 at enrolment into Study F506-CL-0403	Liver, Kidney, Heart

AZA: azathioprine; BE: bioequivalence; CS: corticosteroid; CyA-ME: ciclosporin A microemulsion; NA: not applicable; P1: phase 1; P2: phase 2; P3: phase 3; P4: phase 4; PK: pharmacokinetics

Source Sponsor's submission June 2017; NDA 210115 Clinical Overview page 6 of 27.

Pediatric Liver transplant

The efficacy of tacrolimus oral suspension plus corticosteroids was compared with a triple regimen of cyclosporine/corticosteroids/azathioprine in a randomized, open-label study, in de novo pediatric liver transplant patients. The distribution of pediatric patients by age was similar in both treatment groups, with a majority less than 5 years of age. Patients were randomized to either tacrolimus for oral suspension 0.3 mg/kg/day (N = 91) or cyclosporine 10 mg/kg/day orally (N = 90) initiated 6 hours after completion of transplant surgery. Doses throughout the 1-year study period were adjusted to maintain target whole blood trough levels within 5-20 ng/mL. Based on trough levels, doses of tacrolimus were adjusted to 0.17 mg/kg/day and 0.14 mg/kg/day by days 2 and 3,

respectively. At 12 months, the incidence rate of biopsy-proven acute rejection, graft loss, death, or lost to follow-up was 52.7% in the tacrolimus group and 61.1% in the cyclosporine group. In Study F506-CL-0404A, a long-term extension study in children with either kidney, liver, or heart transplant, the most common AEs were diarrhea, hypomagnesemia, and hypertension. No new safety signal was identified and DTOP has determined the data are sufficient to support approval in adults as well as pediatric liver transplants.

Pediatric Heart and Kidney transplant

DPMH agrees with DTOP that the efficacy of tacrolimus can be extrapolated from adult to pediatric patients because the pathophysiology, diagnosis, and management of allograft rejection are sufficiently similar between the two populations and there is sufficient pharmacokinetic and safety data (see table 1) to support dosing recommendations.

The use of tacrolimus as an immunosuppressant to prevent allograft rejection in solid organ transplant pediatric recipients has been well established in clinical practice.[1,2,3,4,5] As in adults, tacrolimus dosing in pediatric patients is individualized to achieve a range of systemic tacrolimus concentrations (target drug monitoring) depending on the organ type, time after transplantation and other patient specific factors. [4,5]

In addition, in response to an information request sent on 05/02/2018, the sponsor submitted data from additional clinical studies evaluating tacrolimus in pediatric kidney and heart transplant patients to support initial starting dose recommendations. Given that target tacrolimus concentration in heart and kidney transplant patients are similar to target concentrations in pediatric liver transplant patients, the safety data collected in pediatric liver transplant patients can support the safety of tacrolimus in pediatric heart and kidney transplant patients.

Therefore, DPMH recommends updating the product labeling for Prograf to include dosing for pediatric heart and kidney transplant patients. We defer to clinical pharmacology regarding the specific recommendations for the starting dose for each indication.

Discussion:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population.

[1] Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus. A further update of its use in the management of organ transplantation. Drugs. 2003;63(12):1247-97.
[2] Ellis D, Shapiro R, Jordan ML, et al. Comparison of FK-506 and cyclosporine regimens in pediatric renal transplantation. Pediatr Nephrol 1994; 8: 193.
[3] Mathew A, Talbot D, Minford EJ et al. Reversal of steroid-resistant rejection in renal allograft recipients using FK506. Transplantation 1995.
[4] Tacrolimus rescue therapy for renal allograft rejection – five-year experience. Transplantation 1997; 63: 223–228
[5] Webber SA. 15 years of pediatric heart transplantation at the University of Pittsburgh: lessons learned and future prospects. Pediatr Transplant 1997; 1: 8–21.

For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c) (9) (iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Since the product will be indicated for use in pediatric patients, the information should be distributed throughout labeling as appropriate and summarized in 8.4 Pediatric Use.

DPMH Recommendations: Sponsor proposed labeling of section 8.4 with DPMH recommended edits (~~strikethroughs~~ represent deletions and underlining represents additions):

As per the DTOP consult request, this review will only address sections 8 (Use in Specific Populations, subsection 8.4).

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric liver, kidney, and heart transplant patients.

(b) (4)

Safety and efficacy using PROGRAF for oral suspension in a pediatric de novo liver transplant patients less than 16 years of age have been established based on evidence from studies conducted in adults and supported by a safety, efficacy and pharmacokinetic study conducted in children. Two randomized active-controlled adult trials of PROGRAF capsules in primary liver transplantation included 56 pediatric patients. Thirty-one (31) patients were randomized to PROGRAF-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of PROGRAF to maintain blood trough concentrations of tacrolimus similar to adult patients [see Dosage and Administration (2.4)].

In an open-label, safety and efficacy comparator study, over a 12-month period a total of 181 randomized pediatric patients were treated with either a PROGRAF for oral suspension (N = 91) or a cyclosporine-based regimen (N = 90). Efficacy was also demonstrated in a second single-arm, non-comparative, open-label, 12-month, safety, efficacy and pharmacokinetic study (N = 28) in pediatric de novo liver transplant patients. Dose adjustments were made in both studies based on clinical status and whole

blood concentrations [see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)].

Use of PROGRAF capsules and PROGRAF for oral suspension in pediatric kidney and heart transplant patients is supported by adequate and well controlled studies in adult kidney and heart transplant patients with additional pharmacokinetic data from adult and pediatric patients and safety data in pediatric liver transplant patients [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Reviewer's comment: Given that the details of the clinical studies are appropriately summarized in the relevant sections of the label, DPMH recommends a very briefsummary under 8.4 cross-referencing to the other sections of the label and a brief discussion of the data used to support safety, effectiveness, and dosing in heart and kidney transplant.

Conclusions:
DPMH forwarded the above draft comments to DTOP on 05/11/2018 and participated in a labeling meeting on 05/16/2018. The reader is directed to final negotiated labeling which may reflect changes not discussed in this review.

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/s/

YERUK A MULUGETA
05/18/2018
Hari C Sachs, MD, DPMH Team Leader has reviewed this document and agrees with the content and recommendations.

JOHN J ALEXANDER
05/18/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 25, 2018

To: Wendy Streight, PhD
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 210115**
. **PROGRAF (tacrolimus) for oral suspension**

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on July 28, 2017, for PROGRAF (tacrolimus) for oral suspension. OPDP's comments are provided directly below on the attached draft copy of the proposed PI. Our comments are based on the version of the proposed labeling that was emailed to OPDP by Wendy Streight on April 24, 2018.

OPDP comments on the proposed Carton and Container Labeling will be provided under separate cover. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the Patient Package Insert (PPI) and Instructions for Use (IFU) in a joint review under separate cover.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
04/25/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 19, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 210115
Product Name and Strength:	Prograf (tacrolimus) for oral suspension, 0.2 mg and 1 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
Submission Date:	July 26, 2017 and January 24, 2018
OSE RCM #:	2017-1524
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed container label, carton labeling, Prescribing Information (PI), Instructions for Use (IFU), and Patient Information for Prograf (tacrolimus) for oral suspension (NDA 210115), submitted by Astellas Pharma US, Inc. on July 26, 2017 and January 24, 2018, to determine if it is acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Astagraf XL (tacrolimus extended-release capsules) (NDA 204096) was approved on July 13, 2013 for the prophylaxis of organ rejection in patients receiving a kidney transplant in combination with other immunosuppressants. At the time of approval, Astellas committed to a Post Marketing Requirement (PMR) under the Pediatric Research Equity Act (PREA), to develop an age-appropriate formulation of Astagraf XL, to allow for dosing of tacrolimus in patients ages 1 to less than 5 years.[a] Hence, this NDA 210115 proposes the use of *immediate-release* tacrolimus for oral suspension for the prevention of rejection in pediatric heart, kidney, or liver transplant recipients.

Astellas Pharma US, Inc, submitted container label, carton labeling, Prescribing Information (PI), Instructions for Use (IFU), and Patient Information for Prograf (tacrolimus) for oral suspension

[a] Germain J. Annual Status Report Review Form: Postmarketing Requirements and Commitments Summary for Astagraf XL (tacrolimus extended release) NDA 204096 on 17 SEP 2014. Silver Spring (MD): FDA, CDER, OND, DTOP (US); 2014 SEP 24.

(NDA 210115) on July 26, 2017 and a revised PI, IFU, and Patient Information on January 24, 2018. DMEPA finds the Patient Information acceptable from a medication error perspective. However, we note that the container label and carton labeling can be improved to facilitate identification of the product. Additionally, we note that the IFU can be improved to provide clarity on the two ways to prepare the product and the supplies needed. The PI can also be improved to remove trailing zeros from dosing to mitigate dose confusion.

4 CONCLUSION & RECOMMENDATIONS

The Patient Information is acceptable from a medication error perspective. We note that the container label, carton labeling, and IFU can be improved to enhance important information and facilitate identification of the product. We also note that the IFU can be improved to provide clarity in the supplies needed and how the product should be administered. The PI can be improved to mitigate dose confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. For the Instructions for Use (IFU), we note that the product can be administered by using a glass cup or by using an oral syringe.
   1. To ensure that the two methods of preparations are clearly labeled, we recommend revisions to the heading of each method to indicate which method is indicated (i.e., glass cup or oral syringe).
   2. Under supplies needed for each dose for both methods, the instructions state (b) (4) (b) (4) (b) (4). Hence, we recommend removing the (b) (4) and revising "packets" to "unit-dose packets".
   3. We recommend using only metric measurements [e.g., "15 to 30 milliliters" instead of "1 to 2 tablespoons (15 to 30 milliliters)] throughout the IFU where appropriate to prevent medication errors.

B. Prescribing Information (PI)
   1. There are trailing zeros following a decimal point in the dose presentations (e.g. 0.10-0.15 mg/kg/day and 0.15-0.20 mg/kg/day) that may lead to errors. We recommend eliminating the trailing zero, an error prone dose designation, which may be misinterpreted if the decimal point is not seen.[b]
   2. We recommend using only metric measurements [e.g., "15 to 30 milliliters" instead of "1 to 2 tablespoons (15 to 30 milliliters)] throughout the PI where appropriate to prevent medication errors.
   3. We recommend revising the Route of Administration statements to spell out "intravenous" instead of using the abbreviation "IV" where it appears in the PI.

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2017[cited 2018 APR 12]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4.2 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling, Container Label, and Instructions for Use
   1. Remove “granules” from the dosage form to read “Prograf (tacrolimus) for oral suspension”.

B. Carton Labeling and Container Label
   1. The container label of one unit and the carton labeling of 50 units should have different NDC numbers. Revise the NDC numbers so that the carton labeling and container label NDC numbers are different for these two package configurations.

C. Carton Labeling
   1. Ensure that the lot number and expiration date are presented on the carton labeling in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and ensure that they are clearly differentiated from one another.
   2. Revise the statement (b) (4) to read “50 unit-dose packets”

D. Container Label
   1. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, add the product linear barcode to the container label as required per 21CFR 201.25(c)(2). The barcode should be surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i). The barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g. perforation).
   2. Revise the statement (b) (4) to read “per unit-dose packet”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Prograf that Astellas Pharma US, Inc. submitted on July 26, 2017 and January 24, 2018.

Table 2. Relevant Product Information for Prograf

Product Name	**Prograf (NDA 210115) (proposed)**	**Prograf (NDA 050708 and NDA 050709)**
Initial Approval Date	N/A	April 8, 1994
Active Ingredient	tacrolimus	tacrolimus
Indication	Prograf is a calcineurin-inhibitor immunosuppressant indicated for: Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants	Prograf is a calcineurin-inhibitor immunosuppressant indicated for: Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants
Route of Administration	Oral	Oral (NDA 050708) Intravenous (NDA 050709)
Dosage Form	for oral suspension	Capsules (NDA 050708) Injection (NDA 050709)
Strength	0.2 mg, 1 mg	0.5 mg, 1 mg, and 5 mg (NDA 050708) 5 mg/mL (NDA 050709)
Dose and Frequency	**Patient Population** / **Recommended Initial Oral Dosage (two divided doses every 12 hours)** / **Observed Whole Blood Trough Concentrations** Pediatric Liver transplant / 0.15-0.2 mg/kg/day (capsule or for oral suspension) / month 1-12: 5-20 ng/mL	Oral capsules- **Patient Population** / **Recommended Initial Oral Dosage (two divided doses every 12 hours)** / **Observed Whole Blood Trough Concentrations** Adult Kidney transplant In combination with azathioprine / 0.2 mg/kg/day (capsules) / month 1-3: 7-20 ng/mL; month 4-12: 5-15 ng/mL

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>In combination with MMF/IL-2 receptor antagonist</td><td>0.1 mg/kg/day (capsules)</td><td>month 1-12: 4-11 ng/mL</td></tr>
<tr><td>Adult Liver transplant</td><td>0.10-0.15 mg/kg/day (capsules)</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td>Pediatric Liver transplant</td><td>0.15-0.2 mg/kg/day (capsule)</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td>Adult Heart transplant</td><td>0.075 mg/kg/day (capsules)</td><td>month 1-3: 10-20 ng/mL
month ≥ 4: 5-15 ng/mL</td></tr>
</table>
Injection-
The recommended starting dose of Prograf injection is 0.03-0.05 mg/kg/day in kidney and liver transplant and 0.01 mg/kg/day in heart transplant given as a continuous intravenous infusion. Adult patients should receive doses at the lower end of the dosing range.
</td></tr>
<tr><td>How Supplied</td><td>Carton containing 50 unit-dose packets</td><td>Capsules (NDA 050708)
Bottle – 100 count
10 blister cards of 10 capsules
Injection (NDA 050708)
Sterile solution in a 1 mL ampule, in boxes of 10 ampules</td></tr>
<tr><td>Storage</td><td>Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).</td><td>Capsules (NDA 050708)
Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F)
Injection (NDA 050708)
Store between 5°C and 25°C (41°F and 77°F).</td></tr>
<tr><td>Container Closure</td><td>n/a</td><td>n/a</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 24, 2018, we searched DMEPA's previous reviews using the terms, prograf. Our search did not identify any relevant previous reviews.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

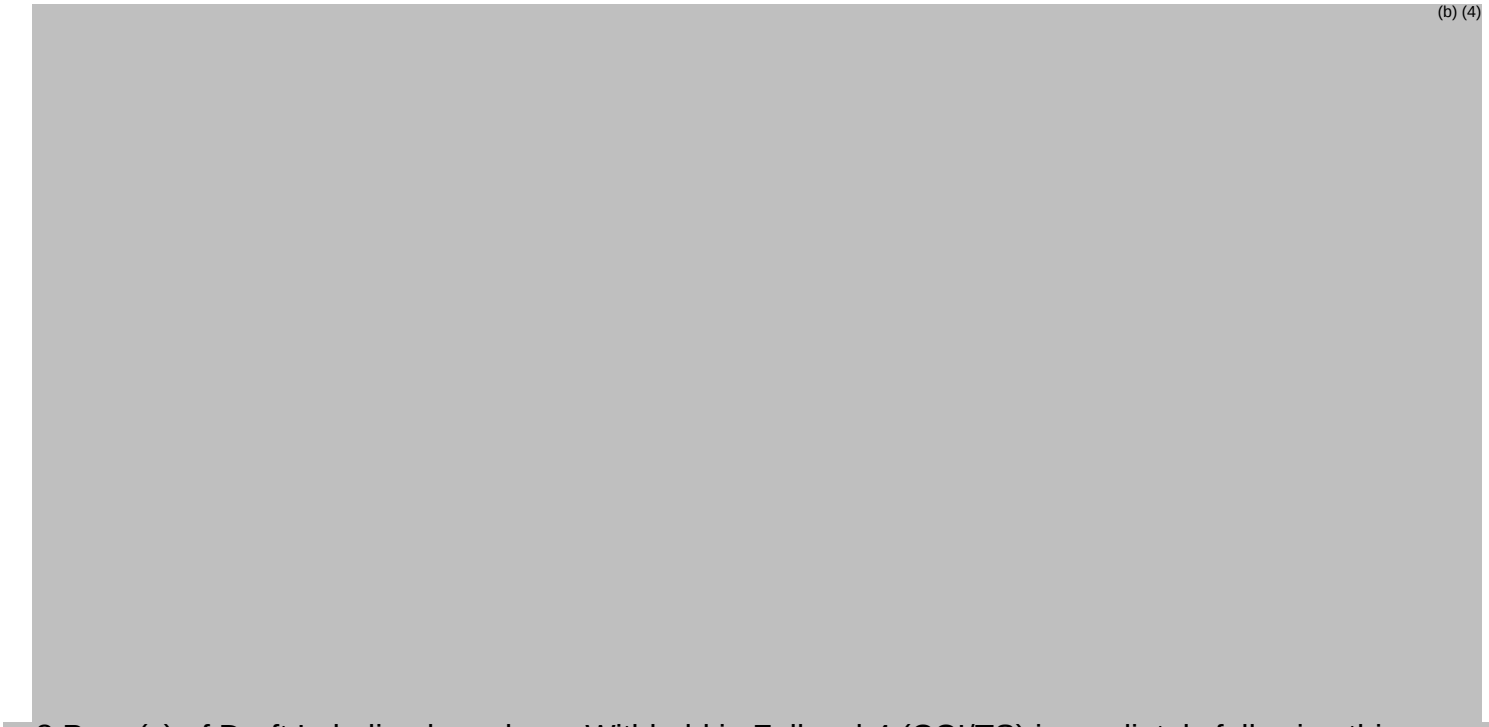
Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Prograf (tacrolimus) for oral suspension labels and labeling submitted by Astellas Pharma US, Inc. on July 26, 2017 and January 24, 2018.

- Container label received on July 26, 2017
- Carton labeling received on July 26, 2017
- Instructions for Use received on January 24, 2018
- Prescribing Information (Image not shown) received on January 24, 2018
- Patient Information (Image not shown) received on January 24, 2018

G.2 Label and Labeling Images

Container Label

(b) (4)



8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MADHURI R PATEL
04/19/2018

SARAH K VEE
04/19/2018

M E M O R A N D U M

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

DATE: March 23, 2018

TO: Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products (DTOP)
Office of Antimicrobial Products
Office of New Drugs

FROM: Mohsen Rajabi Abhari, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

and

Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
DNDBE/OSIS

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDBE/OSIS

SUBJECT: Surveillance inspection (b) (4) (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies F506-CL-0403 (b) (4) (NDA 210115/S1), PMR-EC-1206 (b) (4) (NDA 204096/S005) and QCL117852 (b) (4) conducted at (b) (4) (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable. Thus, I recommend that the data from studies F506-CL-0403, PMR-EC-1206, and QCL117852

and other studies using similar methods be accepted for further Agency review.

Inspected Studies:

NDA 210115/S1

Study Number: **F506-CL-0403** (b) (4)
Study Title: "A Multicentre, Open-label, Pharmacokinetic Study of Modigraf®(Tacrolimus Granules) in de Novo Paediatric Allograft Recipients.
Dates of Bioanalytical study conduct: 08/02/2012 – 03/03/2015

204096/S005

Study Number: **PMR-EC-1206** (b) (4)
Study Title: "Compare the steady state AUC24 of tacrolimus for Advagraf with that of Prograf in stable pediatric allograft recipients after 1:1 (mg:mg) conversion from Prograf to Advagraf. To observe the safety and efficacy profile of tacrolimus, and to evaluate the relationship between AUC24 and C24 for Advagraf and Prograf at each pharmacokinetic profile."
Dates of Bioanalytical study conduct: 03/22/2013 – 01/26/2016

Studies not yet associated with an application

Study Number: **QCL117852** (b) (4)
Study Title: "Determination of Arbaclofen Placarbil and R-Baclofen in Plasma Samples from Sponsor Clinical Protocol Number QCL117852."
Dates of Bioanalytical study conduct: 02/09/2017 – 07/17/2017

Analytical site: (b) (4)

OSIS scientists Mohsen Rajabi Abhari and Arindam Dasgupta audited the analytical portion of the above studies at (b) (4) (b) (4) from 03/19/2018 to 03/21/2018.

The inspection included a thorough examination of study records,

facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the conclusion of the inspection, we did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site.

Conclusion:

After reviewing the inspectional findings, we conclude the data from the audited studies are reliable. Therefore, I recommend that the data from studies F506-CL-0403 (b) (4) (NDA 210115/S1), PMR-EC-1206 (b) (4) (NDA 204096/S005) and QCL117852 (b) (4) be accepted for further review. In addition, the data from studies using similar methods submitted to pending applications (Attachment 1) should be accepted for further Agency review.

Based on the inspectional findings, studies using similar methods conducted between the previous inspection (August 2006) and the end of the current Surveillance Interval should be accepted for review by the Agency without an inspection

Mohsen Rajabi Abhari, Ph.D.
Pharmacologist, DNDBE/OSIS

Arindam Dasgupta, Ph.D.
Deputy Director, DNDBE/OSIS

Final Classification:

NAI- (b) (4)

FEI#: (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Rajabi
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: MR 03/22/2018, AD 03/23/2018
Edit: CB 03/23/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES (b) (4) (b) (4) /NDA 210115 S-001_NDA 204096 S-005

OSIS File #: BE 7787, 7800
FACTS: (b) (4)

Attachment 1
Studies in support of Pending Applications

Application #	Study #	Study Type	Drug Name	Dates of conduct
NDA 210115 S-001	F506-CL-0403 (b) (4)	In vivo	Tacrolimus	May 25, 2011 to October 28, 2015
NDA 204096-S005	PMR-EC-1206	In vivo	Tacrolimus	June 9, 2001 to February 3, 2015
Not Applicable	QCL117852	In vivo	Arbaclofen Placarbil and R-Baclofen	February 9-July 17, 2017

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/s/

MOHSEN RAJABI ABHARI
03/24/2018

ARINDAM DASGUPTA
03/26/2018

CHARLES R BONAPACE
03/26/2018