Division Director Summary Review for Regulatory Action And Cross Disciplinary Team Leader Review

Date	(electronic stamp)
From	Ozlem Belen, MD, MPH, Deputy for Safety Renata Albrecht, MD, Division Director Division of Transplant and Ophthalmology Products (DTOP)
Subject	Cross Disciplinary Team Leader Review and Division Director Summary Review
NDA and Supplement #	NDA 204096/S-005
Applicant	Astellas
Date of Submission	November 1, 2017
PDUFA Goal Date	September 1, 2018
Major Amendment	August 8, 2018
PDUFA Goal Date	December 1, 2018
Proprietary Name	Astagraf XL
Established or Proper Name	tacrolimus extended-release capsules
Dosage Form	oral
Applicant Proposed Indication	Prevention of rejection in kidney transplantation
Action or Recommended Action:	*Approval*

Material Reviewed/Consulted	**Names of discipline reviewers, review dates**
Medical Officer Review	Marc Cavaille Coll 10/29/2018
Statistical Review	Hongling Zhou, Yan Wang 7/31/2018
Pharmacology Toxicology Review	Aaron Ruhland, Lori Kotch 7/23/2018
OPQ Review	Libaniel Rodriguez 12/15/2017
Clinical Pharmacology Review	Amit Somani, Phil Colangelo 6/21/2018, 10/23/2018
DPMH Consult	Lily (Yurek) Mulugeta, Hari Sachs 11/29/2018
OPDP	Carrie Newcomber 8/8/2018
DMPP	Sharon Williams, LaShawn Griffiths 8/14/2018
Project Manager	Jacquelyn Smith

OPQ=Office of Pharmaceutical Quality
DPMH=Division of Pediatric and Maternal Health
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Planning

1. Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Astellas submitted Study Report PMR-EC-1206: conversion from Prograf to ASTAGRAF XL in 81 stable pediatric transplant patients (including 48 kidney transplant patients), and Study Report PMR-EC-1207: Prograf vs ASTAGRAF XL-based immunosuppression in a randomized study of 44 de novo pediatric transplant patients, including 25 pediatric kidney transplant patients. In these studies, all pediatric transplant patients, including pediatric kidney transplant patients, were alive with functioning kidney allografts at the end of the 52-54 week follow up. Two kidney transplant patients treated with ASTAGRAF XL experienced acute rejection that responded to treatment.

The pediatric information was presented at the Pediatric Review Committee and subsequently labeling was discussed with the Division of Pediatric and Maternal Health (DPMH) during several meetings, and DPMH recommendations were followed, as documented in the DPMH consult review. The determination was made that: The safety and effectiveness of ASTAGRAF XL in de novo pediatric kidney transplant patients have been established. The efficacy of Astagraf XL can be extrapolated from adult to pediatric patients because the pathophysiology, diagnosis, and management of kidney transplant patients and allograft rejection are sufficiently similar between the two populations and there is sufficient pharmacokinetic and safety data to support dosing recommendations in pediatric patients. The safety and efficacy of Astagraf XL have been established in adults, based on randomized, controlled clinical trials in de novo adult kidney transplant patients, who received treatment for at least 12 months, therefore covering both the induction phase and the maintenance phase of treatment (when patients were stable). These data are supplemented by existing PK and safety data on Prograf (tacrolimus, Astellas) in de novo pediatric kidney transplant patients. This information is incorporated in Section 8.4 Pediatric Use of labeling.

The recommended starting dose of Astagraf XL in de novo pediatric kidney transplant patients was evaluated in Study 1207 and is supported by the Prograf starting dose. The starting dose of 0.3 mg/kg/day of Astagraf XL in de novo pediatric kidney transplant patients is included in Section 2.2 of labeling.

Safety information from both studies is included in Section 6.1 ADVERSE REACTIONS and consists of previously reported reactions; no unlabeled adverse reactions were reported. The pharmacokinetic (PK) information is included in Section 12.3 Pharmacokinetics of labeling, and shows that at steady state, PK parameters of Prograf and Astagraf XL are comparable. Based on the recently-published guidance, the Division was informed to include “adult and pediatric patients” in Section 1 of the labeling.

Astellas provided pediatric information in this efficacy supplement as well as their NDA 210115 for Prograf Granules (approved May 24, 2018), and thereby fulfilled the two Post-Marketing Requirements included in the Astagraf XL approval letter dated July 19, 2013. The availability of pediatric information in the labeling for ASTAGRAF XL (as well as the pediatric formulation, Prograf Granules) provides this therapeutic option for the pediatric population.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Kidney transplantation is a treatment for end stage renal disease (ESRD), and has better prognosis than dialysis, long term.	ESRD mainly affects adults, however about 500 pediatric patients receive kidney transplants annually.
Current Treatment Options	• There are a few products approved for pediatric kidney transplant patients including mycophenolate mofetil (suspension formulation) and Prograf Granules (approved in May 2018).	Astagraf XL (tacrolimus extended-release capsules) is a once daily formulation, which provides an option to patients who can swallow capsules intact.
Benefit	• Astagraf XL has been approved since 2013, and the efficacy reported in adults is reflected in labeling. • In the pediatric conversion study (1206), 2/48 patients reported acute rejection that was successfully treated, there were no deaths of graft losses in the 54-week duration of the study. • In the 13 de novo pediatric kidney transplant patients treated with Astagraf XL, there were no acute rejections, graft loss or death reported in the 52-week duration of the study (1207).	Approved products for immunosuppression are effective in preventing acute rejections, graft loss and death as measured during the first-year post-transplant. Over time, survival of the graft and patient declines.
Risk and Risk Management	• Labeling includes information on the range of adverse reactions reported in the adult clinical studies. • In the pediatric studies in this application, no deaths or graft losses were reported. Three patients discontinued treatment. • The most common adverse reactions reported in these pediatric transplant patients were diarrhea, headache, cough, elevated creatinine and upper respiratory tract infection.	Immunosuppressive therapy is association with off- target toxicity that can be seen at therapeutic doses. Therapeutic drug monitoring is used to titrate doses to target whole blood trough concentrations. Dose adjustment is used to minimize toxicity. Other drug therapy (antihypertensive, hypoglycemic, anti-infective) is used to manage adverse reactions.

2. Background

Astagraf XL[1] (tacrolimus extended-release capsules) is an extended-release formulation of tacrolimus, approved July 19, 2013, for the prevention of rejection in kidney transplant patients.

At the time of approval, the action letter included two Post-Marketing Requirements (PMR) under Pediatric Research Equity Act (PREA).

- PMR 1 was to develop an age appropriate formulation for patients 1 to < 5 years of age. This PMR was fulfilled with the submission of NDA 210115, Prograf Granules (tacrolimus for oral suspension). The application was approved May 24, 2018, and labeling includes use in pediatric liver, kidney and heart patients.

- PMR 2 was to evaluate Astagraf XL in stable pediatric patients 5 to 16 years in age, converted from a Prograf-based regimen. The current efficacy supplement submission, containing Study PMR-EC-1206, fulfills this PMR.

- At the time of approval, the pediatric study requirement for ages 0 to < 1 year was waived because there are too few pediatric patients, ages 0 to < 1 year, making studies in this age group impossible or highly impracticable.

Following the review of Study Report PMR-EC-1206 (Part A and B), DTOP consulted with DPMH regarding labeling for the application. Among the other recommendations included in the DPMH consult was the recommendation that efficacy of Astagraf XL could be extrapolated from adult to pediatric de novo kidney transplant patients and DPMH recommended a starting dose of Astagraf XL be identified, if data were available. (See Section 10. Pediatrics, of this review.)

Therefore, DTOP requested information on de novo pediatric kidney transplant patients and Astellas submitted Study Report PMR-EC-1207 (Part A and B) as a major amendment on August 8, 2018. The submission provided ASTAGRAF XL dosing information and tacrolimus concentrations, including trough concentrations, in pediatric de novo kidney transplant patients.

[1] Astagraf XL is the trade name for tacrolimus extended-release capsules for the product marketed by Astellas in the United States. The same product is marketed in Europe under the trade name of Advagraf, in Japan under the trade name Graceptor, and elsewhere in the world under the trade name Prograf XL. Since these studies are submitted to support pediatric labeling for Astagraf XL, that name is used in this application, except in the actual titles of the two protocols, where the Advagraf trade name is retained for these two studies conducted in Europe.

This supplement application also includes the addition of the adverse reaction, calcineurin-inhibitor induced pain syndrome, to Section 6.2 of the labeling and provides updated labeling in Sections 8.1, 8.2, and 8.3 to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The Division was informed to add "adults and pediatric patients" to Section 1, based on a recently published guidance document.

3. Product Quality

Astagraf XL is a legally marketed product and there are no CMC issues in this supplement. The applicant requested and was granted Categorical Exclusion from submitting an Environmental Assessment. CMC recommends approval of the supplement.

4. Nonclinical Pharmacology/Toxicology

This submission includes revisions to the labeling in Sections 8.1, 8.2, and 8.3 to conform with PLLR. The information on tacrolimus exposure during pregnancy was recently reviewed by Pharmacology/Toxicology for NDA 210115, Prograf Granules (tacrolimus for oral suspension, Astellas). The same reviewer reviewed the Astagraf XL PLLR language. Some changes in the exposure margins were considered based on the recommended human doses and labeling revisions incorporated. We concur with these recommendations.

5. Clinical Pharmacology

The original submission of the efficacy supplement contained the results from study PMR-EC-1206 in stable patients and a second study, PMR-EC-1207, was submitted as a major amendment during this review cycle.

Study PMR-EC-1206 compared tacrolimus pharmacokinetics (PK) in stable pediatric kidney (n=48), liver (n=31) and heart patients (n=2) from 5 to 16 years of age who were converted 1:1 (mg:mg) from a Prograf based immunosuppressive regimen to Astagraf XL based immunosuppressive regimen.[2] The PK portion of the study was referred to as Part A. Patients had PK of Prograf measured, were converted to Astagraf XL and had PK measured on Day 7. [Part B of the protocol consisted of continued treatment and long-term follow up for 52 additional weeks and was reviewed by the clinical group.]

The mean (SD) duration of exposure to Prograf was 7.5 (1.3) days. The mean (SD) Prograf daily dose by subgroup was 8.67 (5.53) mg in kidney transplant, 6.68 (3.40) mg in liver transplant, and 9.00 (4.24) mg in heart transplant. When Prograf daily dose was normalized by body weight, the mean dose in liver and heart transplant groups was 0.15 and 0.14 mg/kg, respectively. The normalized daily dose in the kidney transplant group was 0.23 mg/kg.

[2] Prograf is dosed as mg/kg/day and the total dose is given in two divided doses, approximately 12 hours apart. ASTAGRAF XL is dosed as mg/kg/day and the total dose is administered once-daily.

The mean (SD) duration of exposure to Astagraf XL was 6.9 (0.3) days. The mean (SD) daily dose by subgroup was 8.63 (5.56) mg in kidney transplant, 6.86 (3.40) mg in liver transplant, and 9.00 (4.24) mg in heart transplant. When normalized by body weight, the mean (SD) Astagraf XL daily doses were 0.22 (0.11) mg/kg in kidney transplant, 0.15 (0.07) mg/kg in liver transplant, and 0.14 (0.07) mg/kg in heart transplant.

Steady state parameters in the kidney transplant patients for Prograf (Day 7 of study) and Astagraf XL (Day 14 of study) are presented in the table below.

Organ Transplant Population	**Mean ± SD Pharmacokinetic Parameters and Range for Prograf Capsules and Astagraf XL**		
	PK Parameters	**Prograf Capsule**	**Astagraf XL**
Pediatric Kidney (n=45)	$AUC_{(0-24)}$ (ng·h/mL)	188.8 ± 53.5	173.2 ± 44.6
	$AUC_{(0-24)}$ range (ng·h/mL)	102.3-406.8	80.9-262.5
	C_{max} (ng/mL)	14.9 ± 5.8	12.5 ± 4.5
	C_{max} range (ng/mL)	4.9-34.4	5.4-24.4
	C_{24} (ng/mL)	5.6 ± 1.9	5.1 ± 1.4
	C_{24} range (ng/mL)	2.9-13.8	2.0-8.4

Study PMR-EC-1207 enrolled 44 de novo pediatric transplant patients. This included 25 pediatric kidney transplant patients, 4 to 15 years of age (mean age of 10.6 years), who were randomized to Prograf (n=12) or Astagraf XL (n=13). Patients received a starting daily dose of 0.3 mg/kg/day of Prograf Capsules divided into two daily doses or 0.3 mg/kg/day of Astagraf XL given once-daily. Serial blood samples were collected on Days 1, 7, and 28 of the Study. The PK analysis included 20 of the 25 pediatric de novo kidney transplant patients [i.e., Prograf capsules (n=10) and Astagraf XL (n=10)].

Study Visit[a]	**Mean ± SD Pharmacokinetic Parameters and Range for Prograf Capsules and ASTAGRAF XL**		
	PK Parameters	**Prograf Capsules[b]**	**ASTAGRAF XL**
Day 1	$AUC_{(0-24)}$ (ng·h/mL)	280.4 ± 164.4	211.4 ± 128.2
	$AUC_{(0-24)}$ range (ng·h/mL)	145.0 – 688.4	76.9 – 459.8
	C_{max} (ng/mL)	23.1 ± 14.4	17.7 ± 11.1
	C_{max} range (ng/mL)	8.2 – 55.7	5.0 – 44.9
	C_{24} (ng/mL)[c]	8.5 ± 5.4	6.7 ± 4.3
	C_{24} range (ng/mL)	3.2 – 16.7	2.0 – 16.5
	T_{max} (h)[d]	2.0	2.0
	T_{max} range (h)	0.9 – 4.0	1.0 – 12.0

Day 7	$AUC_{(0-24)}$ (ng·h/mL)	347.2 ± 124.2	350.6 ± 92.7
	$AUC_{(0-24)}$ range (ng·h/mL)	153.7 – 561.8	149.0 – 493.0
	C_{max} (ng/mL)	28.7 ± 14.6	37.7 ± 13.9
	C_{max} range (ng/mL)	10.5 – 49.0	15.1 – 62.6
	C_{24} (ng/mL)	9.6 ± 2.8	8.4 ± 2.7
	C_{24} range (ng/mL)	5.9 – 16.0	4.3 – 14.4
	T_{max} (h)	1.0	1.0
	T_{max} range (h)	1.0 – 2.3	1.0 – 2.0
Day 28	$AUC_{(0-24)}$ (ng·h/mL)	323.6 ± 114.5	322.4 ± 78.1
	$AUC_{(0-24)}$ range (ng·h/mL)	234.5 – 614.0	240.3 – 516.4
	C_{max} (ng/mL)	28.5 ± 17.1	24.7 ± 4.8
	C_{max} range (ng/mL)	17.5 – 70.1	14.2 – 32.5
	C_{24} (ng/mL)	9.8 ± 3.1	9.2 ± 3.0
	C_{24} range (ng/mL)	5.4 – 16.0	5.1 – 15.9
	T_{max} (h)	1.0	1.5
	T_{max} range (h)	1.0 – 4.0	1.0 – 4.0

[a] Study Visit Day on which PK profile were collected following administration of Prograf Capsules or ASTAGRAF XL.
[b] PK estimates following the morning Prograf capsule dose are reported for T_{max} and C_{max}.
[c] Observed whole blood tacrolimus trough levels at 24 hours following the dose of Prograf capsules or ASTAGRAF XL.
[d] T_{max} - Reported as median.

Upon review of the PK portion of Study PMR-EC-1207, the Clinical Pharmacology review team has concluded that following an initial dose of 0.3 mg/kg/day of Astagraf XL once daily (i.e., 0.3 mg/kg QD) or Prograf capsules twice daily (i.e., 0.15 mg/kg BID) in de novo pediatric kidney transplant patients aged 4 to 15 years, whole blood tacrolimus AUC24 and C24 (i.e., trough) were comparable on Days 7 and 28 post-transplant. Also, the correlation between AUC24 and C24 appeared to be strong for both Prograf capsules and Astagraf XL in the pediatric de novo kidney transplant patients.

Clinical Pharmacology made initial labeling recommendations and modification based on DPMH recommendations; we concur with these recommendations.

6. Clinical Microbiology

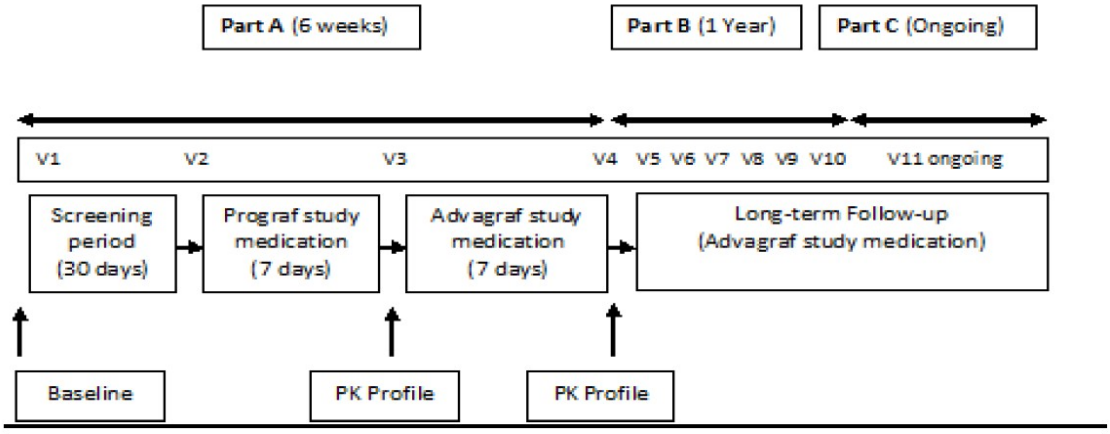
Not applicable

7. Clinical/Statistical-Efficacy

Two clinical studies were submitted with this application and were reviewed by the Clinical Pharmacology (Part A, covered in Section 5 of this review) and Clinical (Part B) disciplines. A summary of the clinical findings is provided below.

Study PMR-EC-1206 is titled, A Phase II, Open-Label, Multi-Center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Patients Converted from a Prograf Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf [3] Based Immunosuppressive Regimen (Part A), Including a Long-Term Follow-Up (Part B).

In the flow diagram below, Part A of the study lasted 6 weeks and Part B lasted 52 weeks, and visits occurred at 6, 10, 14, 28, 42 and 54 weeks after day 1, during which safety and efficacy data were collected, and tacrolimus trough levels were monitored. Tacrolimus dose adjustments were made if necessary to maintain trough levels.



PK: pharmacokinetic; v: visit

Efficacy failure was defined as the composite of death, graft loss, BPAR (biopsy proven acute rejection) and unknown outcome.

Of the 113 patients screened for the study, 81 patients were enrolled in the study, including 48 kidney transplant patients, 31 liver transplant patients, and 2 heart transplant patients.

The majority of patients in the mFAS were male (57.0%), white (93.0%) and adolescent (58.2%). Ages ranged from 5 to 16 years. The overall mean age was 11.6 years. The mean for liver transplant patients was 12.4 years and kidney transplant patients 11.0 years. The heart patients was 13.5 years old.

Patients were followed for a period of 54 weeks in the study. No patient died or had a graft loss. Two kidney transplant patients developed acute rejection which was successfully treated. The clinical reviewer notes that compliance with target whole blood concentrations was reasonable. Over the course of the study, dose adjustments were made in two-thirds of the patients, including increasing or decreasing the dose.

[3] See Footnote 1.

Study PMR-EC-1207 (Part A and B) titled, A Phase 2, Parallel Group, Randomized, Multicenter, Open-label Study to Compare the Pharmacokinetics of Tacrolimus in De Novo Pediatric Allograft Patients Treated with an Advagraf [4] or Prograf-based immunosuppressive regimen, Including a Long-term Follow-up, was a randomized open-label comparison of tacrolimus pharmacokinetics in de novo pediatric kidney, liver, and heart transplant patients, conducted in Europe at the request of the European authorities. The study reports were submitted by Astellas at FDA's request to determine a starting dose in de novo pediatric kidney transplant patients.

Forty-four pediatric transplant patients were enrolled, including 25 kidney transplant patients who were randomized to Prograf (n=12) or Astagraf XL (n=13). Patients were 4-15 year of age and followed for at least 52 weeks after transplantation. The pharmacokinetic information from Part A of the study is summarized under Section 5 of this document. At the end of Part B or the study, no patients died or experienced graft loss. There were no episodes of biopsy-proven acute rejection (BPAR) in the Astagraf XL treated patients and one steroid responsive acute rejection in a Prograf patient.

Based on review of the study, Clinical Pharmacology concurred with the Applicant's proposed Astagraf XL starting dose of 0.3 mg/kg once daily, as well as target trough concentrations, provided in the table below:

Pediatric Use	Starting dose	Whole Blood Trough Concentration Range
With basiliximab, MMF and steroids	0.3 mg/kg once daily, administered within 24 hours following reperfusion.	• Month 1: 10- 20 ng/mL • > Month 1: 5- 15 ng/mL

Clinical and statistical reviewers recommend approval and we concur.

8. Safety

Safety information for pediatric patients was provided from the same two clinical studies (1206 and 1207) and included pediatric transplant patients 4 to 16 years of age.

Study PMC-ER-1206 was conducted in 81 stable pediatric allograft patients (including 48 kidney transplant patients) 5 to 16 years of age converted 1:1 (mg:mg) from Prograf to Astagraf XL. Seventy-nine patients completed Part A if the study. Three patients discontinued before completing part B (i.e., acute rejection, diarrhea, withdrawal of consent) Seventy-six pediatric patients completed at least one year of Astagraf-XL-based treatment. Treatment related adverse events were reported in 35%, including 13% serious adverse reactions. The most frequent adverse reactions were infections (55.7%), followed by gastrointestinal disorders (27.8%), skin and subcutaneous tissue disorders (21.5%), respiratory, thoracic and mediastinal disorders (20.3% each) The most common adverse reactions by preferred term were diarrhea (13.9%), headache (13.9%) and cough (11.4%).

[4] See Footnote 1.

Study PMR-EC-1207 was conducted in 44 de novo pediatric transplant patients, (including 25 kidney transplant patients; 13 randomized to Astagraf XL and 12 randomized to Prograf), who were started on 0.3 mg/kg of tacrolimus product, given once daily for Astagraf XL and divided into two doses for Prograf. Two kidney transplant patients on Prograf discontinued the study (withdrawn consent, sapovirus enteritis). Thirteen pediatric kidney transplant patients completed 52 weeks on Astagraf XL. The most common adverse reactions were diarrhea (7/13 [54%]), increased blood creatinine (6/13 [46%]), hypertension (3/13 [23%]), and upper respiratory tract infection (4/13[31%]).

Calcineurin-Inhibitor Induced Pain Syndrome

In addition, this submission has provided adequate information to support the addition of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS) under Musculoskeletal and Connective Tissue Disorders, in section 6.2 Postmarketing Experience. The event is based on an analysis of 181 reports, which were analyzed and show 10 index cases and 30 informative cases, reported while on tacrolimus therapy. The characteristic pattern is summarized in the clinical review and includes, among other symptoms and signs:

- Symmetrical pain starting in the lower extremities, ascending from feet to ankles and knees. Cases of pain ascending to hips and spine have also been described.
- In a later stage pain in hands, wrists, elbows and shoulders have also been reported.
- Pain is severe and may require the use of crutches or a wheelchair. Mean pain was reported as 71% on a 100% scale.
- Pain can be preceded or accompanied by (severe) pruritus.
- Onset is usually after weeks to months. In case of increased tacrolimus levels, time to onset tends to be shorter including cases of overdose.
- Animal studies were able to induce long-lasting nociceptive and mechanical hypersensitivity in rats treated with high doses of tacrolimus, providing a plausible mechanism of action.

In summary, CIPS appears to be a rare, severe complication that is associated with benign but severe disabling pain and is described in the transplant literature among patients receiving cyclosporine and tacrolimus. CIPS affects patient quality of life and in some cases, patients are in what is described as excruciating pain. The Applicant's analysis of their safety database has identified 10 index cases and 30 informative cases, while an additional 93 cases appear to fit the definition of CIPS but have been classified by the Applicant as inadequate due to lack of complete information. The clinical reviewer agrees with the Applicant's conclusion that the evidence from the literature and the case series analysis support a causal relationship between systemic tacrolimus exposure and CIPS and we concur.

9. Advisory Committee Meeting

This application did not raise any scientific issues that would benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

This application was discussed at the Pediatric Review Committee (PeRC) meeting on May 2, 2018, and after the meeting, a consult was sent to the Division of Pediatric and Maternal Health (DPMH) for assistance with the labeling of the pediatric information submitted. The minutes from the PeRC meeting include:

- This product is in response to PREA PMR 2061-2 issued on July 19, 2013 in the approval letter for NDA 204096 (Astagraf XL):
  - 2061-2: PMR-EC-1206 A Phase II, Open-Label, Multi-Center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Patients Converted from a Prograf Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf[5] Based Immunosuppressive Regimen, Including a Long-Term Follow-Up.
  - Final Report Submission 12/2017
- The division notes that the conversion study conducted in patients >5-16 years of age provides PK data, efficacy data and safety data for Astagraf XL. There were no unexpected safety findings. The PeRC agreed that Astagraf XL could be labeled based on these data.
- *PeRC Recommendations:*
  - The PeRC agrees with the division that the PREA PMR 2061-2 has been fulfilled and the product is fully assessed for the pediatric ages down to 5 years of age.
  - The PERC recommends the division consider consultation with DPMH for any labeling guidance.

DTOP and DPMH discussed the options for labeling and DPMH made recommendations, summarized in their consult review, which were incorporated in labeling. The consult furthermore includes the rationale supporting the labeling recommendations (See Section 12 of this document). DPMH recommended that a starting dose of Astagraf XL for pediatric kidney transplant patients be included in labeling, if available.

11. Other Relevant Regulatory Issues

The submission of the efficacy supplement fulfills one of two PMRs included in the approval letter of the original application, NDA 204096, Astagraf XL.

12. Labeling

Given that the efficacy supplement proposed to add information from pediatric studies in labeling, including results from a study submitted in response to a PMR, DPMH was consulted and participated in several labeling meetings and discussions. DPMH has provided their recommendations in their consult review dated 11/29/2018.

[5] See Footnote 1.

The following information is proposed for inclusion in Section 8.4 Pediatric Use, based on the rationale provided in the DPMH review.

8.4 Pediatric Use

The safety and effectiveness of ASTAGRAF XL in de novo pediatric kidney transplant patients have been established. Use of ASTAGRAF XL in pediatric kidney transplant patients is based on adequate and well controlled studies of ASTAGRAF XL in adult kidney transplant patients [see *Clinical Studies (14.1, 14.2)*] and supported by pharmacokinetic and safety data of ASTAGRAF XL in pediatric transplant patients 4 years of age and older who are able to swallow capsules intact and Prograf (tacrolimus) capsules in adult and pediatric transplant patients [see *Clinical Pharmacology (12.3)*].

De Novo Pediatric Kidney Transplant Patients

A pharmacokinetic and safety study included 25 de novo pediatric kidney transplant patients, 4 to 15 years of age, randomized to Prograf (N=12) or Astagraf XL (N=13). Tacrolimus exposures for the two drug products were comparable on Days 7 and 28 *[see Clinical Pharmacology (12.3)]*. Among the 13 pediatric kidney transplant patients who completed 52 weeks on ASTAGRAF XL, there were no graft loss, deaths or episodes of biopsy-proven acute rejection *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Stable Pediatric Kidney Transplant Patients

Another pharmacokinetic and safety study included 48 stable pediatric kidney transplant patients, 5 to 16 years of age, who were converted from a Prograf-based regimen to ASTAGRAF XL. Tacrolimus systemic exposures for the two drug products were comparable *[see Clinical Pharmacology (12.3)]*. Acute rejections were reported in 2/48 kidney pediatric patients that responded to subsequent treatment. There were no graft failures or deaths following use of ASTAGRAF XL during the 54-week follow up *[see Adverse Reactions (6.1)]*.

DPMH and DTOP discussed whether the information from studies PMR-EC-1206 and PMR-EC-1207 should be included in section 14; however, it was determined that because these clinical trials were not powered to detect a difference in clinical response between the two arms and the sample size was small thereby relying on extrapolation of efficacy from the adult kidney studies and pharmacokinetic information, the pediatric information should be included in section 8.4, and not section 14.

DPMH and DTOP agreed that information on the safety in pediatric patients should be appropriate to include in Section 6.1, ADVERSE REACTIONS. In addition, a brief summary of each pharmacokinetic portion of the study and pharmacokinetic data on pediatric kidney transplant patients was included in Section 12.3 Pharmacokinetics of labeling. Information on the starting dose in de novo pediatric kidney transplant patients was included in Section 2.2 DOSING AND ADMINISTRATION, and Section 1 INDICATIONS AND USAGE was updated with the phrase “in adult and pediatric patients” per recently-issued guidance. For all labeling updates, see Astagraf XL Labeling, appended to this Summary Review.

In summary, DPMH recommended that based on the pediatric PK and clinical information provided by Astellas for both Prograf and Astagraf XL, as well as the safety and efficacy provided from adults clinical and PK studies, the efficacy of Astragraf XL in pediatric kidney transplant patients who can swallow a capsule intact can be extrapolated from the adult kidney transplant patient studies of Prograf and Astagraf XL (both owned by Astellas).

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None

- Other Postmarketing Requirements and Commitments

None. However, this submission fulfills one of the two PREA PMRs for Astagraf XL, that was included in the original NDA approval letter dated July 19, 2013. Acknowledgement that this PMR has been fulfilled, and well as acknowledgement that Astellas has fulfilled the pediatric study requirements (PMRs) for all relevant pediatric age groups for this NDA will be included in the action letter for this application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RENATA ALBRECHT
11/29/2018
and OZLEM BELEN