CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204096Orig1s000

Trade Name: Astagraf XL

Generic Name: tacrolimus extended-release capsules

Sponsor: Astellas Pharma US, Inc.

Approval Date: July 19, 2013

Indications: ASTAGRAF XL is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction.

Limitations of use:
Not interchangeable with tacrolimus immediate-release capsules.
Do not use simultaneously with cyclosporine.

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APPLICATION NUMBER:

204096Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

NDA APPROVAL

Astellas Pharma US, Inc.
Attention: Glen Spears, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 21, 2012, received September 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Astagraf XL (tacrolimus extended-release capsules).

We acknowledge receipt of your amendments dated:

October 2, 2012	February 13, 2013	March 21, 1013	June 7, 2013 (2)
October 25, 2012	February 14, 2013	March 22, 2013	June 20, 2013
November 15, 2012	February 15, 2013	April 2, 2013	June 25, 2013
November 20, 2012	February 19, 2013	April 9, 2013	June 28, 2013
January 3, 2013	February 28, 2013	April 17, 2013	July 2, 2013 (2)
January 7, 2013	March 4, 2013	April 18, 2013	July 3, 2013
January 9, 2013	March 6, 2013	April119, 2013	July 9, 2013
January 14, 2013	March 8, 2012	April 24, 2013	July 15, 2013
January 17, 2013	March 13, 2013	April 30, 2013	July 17, 2013 (2)
February 6, 2013	March 18, 2013	May 23, 2013	
February 11, 2013	March 20, 2013	June 4, 2013 (2)	

This new drug application provides for the use of Astagraf XL (tacrolimus extended-release capsules) for prophylaxis of organ rejection in adult patients receiving kidney transplants.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204096**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to < 1 year because necessary studies are impossible or highly impracticable because there are too few pediatric patients, ages 0 to < 1 year, with disease/condition to study.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually

according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

We are deferring submission of your pediatric study for ages 1 to < 5 years because this product is ready for approval for use in adults and the pediatric study has not been completed.

2061-1 Deferred requirement for development of an age appropriate formulation: Develop an age appropriate formulation to allow for dosing for ages 1 to <5 years.

Final Report Submission: 12/2020

We are deferring submission of your pediatric study for ages 5 to 16 years because this product is ready for approval for use in adults and the pediatric study has not been completed.

2061-2 PMR-EC-1206 A Phase II, Open-Label, Multi-Center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from a Prograf® Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf® Based Immunosuppressive Regimen, Including a Long-Term Follow-Up

Final Protocol Submission:	Completed
Study Completion:	12/2016
Final Report Submission:	12/2017

Submit the protocol(s) to your IND 64148, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2061-3 Optimize the dissolution method with respect to detection of (b) (4) by evaluating the dissolution profiles of 0.5 mg and 5 mg capsules containing (b) (4) under different test conditions (medium with 0.0%, 0.05% and 0.1 % added sodium lauryl sulfate (SLS), at paddle speeds of 50, 75 and 100 rpm).

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	03/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

2061-4 Optimize the acceptance criteria for the regulatory dissolution test method by analyzing the dissolution profile data of all the strength of your product at release and on stability, obtained by collecting data at two-hour intervals until a minimum of (b) (4) of tacrolimus is released, as well as at the 24 hour time point. Based on these results, propose the revised acceptance criteria for the dissolution test of your product.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	03/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

2061-5 Evaluate the relationship between (b) (4) and dissolution rate under stressed conditions and under long term stability.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	01/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

2061-6 Characterize the (b) (4) of tacrolimus in (b) (4) in order to confirm the proposed shelf life of the (b) (4) using a validated and appropriately discriminating direct measurement (e.g., ss-NMR, NIR) of (b) (4) and using the optimized discriminating dissolution test. Evaluate stressed and aged samples. Compare the (b) (4) prior to introduction into manufacture of capsules, to the (b) (4) of the resulting capsules.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	01/2014

Study Completion: 09/2014
Final Report Submission: 11/2014

Submit clinical protocols to your IND 64148 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacquelyn Smith, M.A., Senior Regulatory Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Medication Guide
Carton and Container Labeling

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

/s/

RENATA ALBRECHT
07/19/2013