CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210115Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

MICROBIOLOGY/IMMUNOLOGY REVIEW
DIVISION OF TRANSPLANT AND OPTHALMOLOGY PRODUCTS

NDA # 210115 (SDN-001 and -002)

Reviewer: Shukal Bala
Correspondence Date: 07/26/2017; 09/19/2017
CDER Receipt Date: 07/26/2017; 09/19/2017
Review Assign Date: 07/31/2017; 09/19/2017
Review Complete Date: 01/09/2018

APPLICANT: Astellas Pharma US INC
1 Astellas Way
Northbrook, Illinois 60062

DRUG CATEGORY: Immunosuppressive agent

INDICATION: Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants

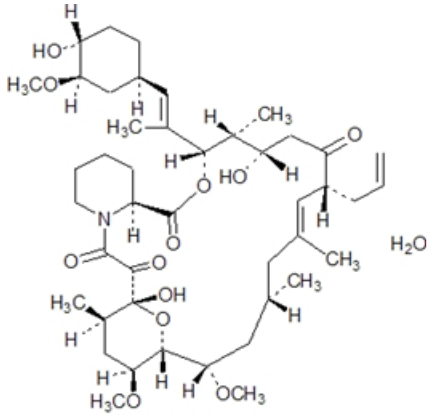
DOSAGE FORM: Oral suspension

PRODUCT NAMES:
a. PROPRIETARY: PROGRAF®

b. NONPROPRIETARY: Tacrolimus; FK506

c. CHEMICAL: [3*S* – [3*R**[*E*(1*S**, 3*S**, 4*S**)], 4*S**, 5*R**, 8*S**, 9*E*, 12*R**, 14*R**, 15*S**, 16*R**, 18*S**, 19*S**, 26a*R**]] – 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 – methoxycyclo – hexyl) – 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.

STRUCTURAL FORMULA:



Molecular Weight: 822.03
Molecular Formula: $C_{44}H_{69}NO_{12}\bullet H_2O$

SUPPORTING DOCUMENTS: NDAs 50708 (PROGRAF®), 50709 (PROGRAF®), 204096 (ASTAGRAF XL®)

1. Introduction and Background

The subject of this NDA is tacrolimus granules (PROGRAF®). Immediate-release oral (NDA 50708) and intravenous (NDA 50709) formulations of PROGRAF (tacrolimus) are FDA approved for the prophylaxis of organ rejection in patients receiving allogeneic heart, kidney, or liver transplants. PROGRAF® is to be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids (for details see labeling).

ASTAGRAF XL® [tacrolimus extended-release capsules (NDA 204096); Applicant's product] and ENVARSUS XR® [tacrolimus extended-release tablets (NDA 206406) Applicant - Veloxis Pharmaceuticals, Inc.] were approved in July 2013 and August 2015, respectively, for the prophylaxis of organ rejection in patients receiving a kidney transplant in combination with other immunosuppressants.

In this NDA, the Applicant has submitted clinical studies in pediatric patients to support inclusion of pediatric formulation (tacrolimus for oral suspension) in the PROGRAF® labeling. This is in accordance with 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. There are no changes proposed for the 'Indications' and 'Mechanism of Action' sections of the labeling.

Reviewer comments:
It is noted that the "Mechanism of Action" section 12.1 of the labeling was based on review of studies in 1993 – 1994 (for details see Pharmacology/Toxicology review dated December 1993; Medical Officer review dated June 1994) and reads as follows:

(b) (4)

Some of the publications supporting activity of tacrolimus in vitro and/or in vivo were reviewed previously for NDAs 50708, 50709 and 204096 (for more details see Immunology/Microbiology reviews, dated January 14, 2015) and for NDA 206406 (see review dated July 24, 2014). Based on the information reviewed, Section 12.1 'Mechanism of Action' of the ASTAGRAF XL®

labeling and Envarsus XR labeling was updated. These changes should also be made in Section 12.1 of the PROGRAF® labeling.

3. Recommendations

The NDA is approvable pending an accepted version of the labeling. Changes recommended in the Section 12.1 Mechanism of action should read as follows (additions are double-underlined and deletions striked out):

Tacrolimus (b) (4) (b) (4) binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (an ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition (b) (4) prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include (b) (4) (b) (4) interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor). Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

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CONCURRENCE:
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DTOP/PM/Wendy Streight

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/s/

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01/09/2018

RENATA ALBRECHT
01/09/2018