ASCEND

2013 JUN 18 A 11:23

June 13, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm 1061
Rockville, MD 20852

Citizen Petition

The undersigned submits this petition under 21 CFR 10.25(a) and 21 CFR 10.30 to request the Commissioner of the Food and Drug Administration to determine the suitability of Tacrolimus Oral Suspension as additional dosage form to the approved dosage forms (capsules and injection solution).

A. Action Requested

The petitioner (Ascend Laboratories, LLC) requests that the Commissioner of the Food and Drug Administration to determine suitability Tacrolimus Oral Suspension as an additional dosage form to NDA 050708 PROGRAF (tacrolimus) capsule, gelatin coated and PROGRAF (tacrolimus) injection, solution held by Astellas Pharma US, Inc (**Attachment I**).

B. Statement of Grounds

NDA 050708 PROGRAF (tacrolimus) capsule, gelatin coated and PROGRAF (tacrolimus) injection, solution is approved for the following indications (**Attachment II** – Pack Insert of PROGRAF):

1. ***Prophylaxis of Organ Rejection in Kidney Transplant***
Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. It is recommended that Prograf be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids [see Clinical Studies (14.1)]. Therapeutic drug monitoring is recommended for all patients receiving Prograf [see Dosage and Administration (2.6)].

2. ***Prophylaxis of Organ Rejection in Liver Transplant***
Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids [see Clinical Studies (14.2)]. Therapeutic drug monitoring is recommended for all patients receiving Prograf [see Dosage and Administration (2.6)].

3. ***Prophylaxis of Organ Rejection in Heart Transplant***

FDA-2013-P-0767

2013-4695

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Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic heart transplants. It is recommended that Prograf be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids [see Clinical Studies (14.3)]. Therapeutic drug monitoring is recommended for all patients receiving Prograf [see Dosage and Administration (2.6)].

4. ***Limitations of Use***

Prograf should not be used simultaneously with cyclosporine [see Dosage and Administration (2.5)].

Prograf injection should be reserved for patients unable to take Prograf capsules orally [see Dosage and Administration (2.1) and Warnings and Precautions (5.11)].

The recommended oral dosage for both adults and children are presented in the tables below.

Table 1. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Adults

Patient Population	**Recommended Prograf Initial Oral Dosage** Note: daily doses should be administered as two divided doses, every 12 hours	**Observed Tacrolimus Whole Blood Trough Concentrations**
Adult kidney transplant patients		
In combination with azathioprine	0.2 mg/kg/day	month 1-3: 7-20 ng/mL month 4-12: 5-15 ng/mL
In combination with MMF/IL-2 receptor antagonist*	0.1 mg/kg/day	month 1-12: 4-11 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/mL
Adult heart transplant patients	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥4: 5-15 ng/mL

Table 2. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Children

Patient Population	**Recommended Prograf Initial Oral Dosage** Note: daily doses should be administered as two divided doses, every 12 hours	**Observed Tacrolimus Whole Blood Trough Concentrations**
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	Month 1-12: 5-20 ng/mL

The capsules formulation is not suitable for Pediatric patients who are often unable to swallow the capsules, and/or adult patients with swallowing difficulties or patients who need other than 0.5 mg incremental dose adjusted to optimize therapeutic drug levels. To assure dosage compliance, the health professionals prepare extemporaneous oral suspensions for the above patient population (**Attachment III**). The extemporaneous oral suspensions are not prepared under Current Good Manufacturing Practice (CGMP).

Tacrolimus is a high potency immunosuppressive agent with narrow therapeutic index (NTI). It is recommended that this potent drug is to be handled in a "contained" area with limited exposure to the healthy human while compounding, and care should be taken not to compromise its safety and efficacy. Ascend Laboratories, LLC (ASC) believes, a FDA approved suspension dosage form would add value to the above mentioned patient population dosing regimen and safety of the compounding pharmacist.

There is evidence in the literature to support a long term stability of suspension tacrolimus for accurate maintenance of stable therapeutic levels (**Attachment IV**).

Ascend Laboratories; LLC petitions FDA to grant ASC permission to submit application for the suspension dosage form.

C. Environmental Impact

A claim for categorical exclusion of the requirement for submission of an environmental assessment or environmental impact statement is made pursuant to 21 CFR 25.31

D. Economic Impact

In accordance with 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. ASC hereby commits to promptly provide this information, if so requested.

E. Certification

The undersigned certifies, that, to the best knowledge and belief: this petition includes all information and views upon which the petition relies; and this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition.

Sincerely,

Augustine Frimpong, M.Sc.
Vice President, Regulatory Affairs / Compliance

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