ASCEND

June 24, 2013

2013 JUL 29 A 11:20

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

Amendment

Docket Number FDA-2013-P-0767/CP1 – Tacrolimus Suspension

The undersigned submits this amendment under 21 CFR 10.25(a) and 21 CFR 10.30 to supplement the petition submitted (06/18/2013) to 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 grant a waiver for Pediatric Research Equity Act (PREA) requirements for the proposed dosage, Tacrolimus Oral Suspension.

B. Statement of Grounds

Data from clinical study of Modigraf Granules for Oral Suspension in pediatric population suggests that in pediatric liver transplant patients the mean oral bioavailability of is 26%± 23% (individual range in pediatric liver transplant patients 4 - 80%) (**Attachment I**).[1] Data on oral bioavailability of Modigraf in other indications is not available.

After oral administration (0.30 mg/kg/day) to pediatric liver transplant patients in the said study[1], steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. In pediatric liver and kidney transplant patients, values for total body clearance of 2.3 ± 1.2 ml/min/kg and 2.1 ± 0.6 ml/min/kg, respectively, have been observed. Highly variable age dependent total body clearance and half-life were observed in limited pediatric clinical investigations, especially in early childhood. The half-life in pediatric transplant patients averages approximately 12 hours.

A second study involved 185 children who were given either Modigraf with corticosteroids (a group of immunosuppressant medicine) or a combination of other immunosuppressant medicines (cicosporin, azathioprine and corticosteroids) for one year. The main measure of effectiveness in this study was based on the number of patients who did not have organ rejection. It also looked at the number of organ rejections in patients that did not respond to corticosteroids (**Attachment I**).

[1]European Medicines Agency, Evaluation of Medicines for Human Use. Doc. Ref.: EMEA/306253/2009 ASSESSMENT REPORT FOR Modigraf. Pages 14 – 23.

Modigraf is oral granule formulation of tacrolimus for suspension, as 0.2 mg and 1 mg sachets. The granule is used for preparation of water dispersion, for swallowing or for administration via a (non-polyethylene) nasogastric tube. The composition of the granule formulation is based on the composition of the intermediate granule formulation which is used in the manufacture of the established immediate release capsule formulation of Prograf capsules 0.5, 1 and 5 mg. The proposed drug product composition will be similar to Modigraf.

NDA 050708 PROGRAF (tacrolimus) capsule, gelatin coated and PROGRAF (tacrolimus) injection, approved Pack Insert states

> "Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5±3.8 hours, 2.6±2.1 L/kg and 0.138±0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean AUC and C_{max} were 337±167 ng•hr/mL and 48.4±27.9 ng/mL, respectively. The absolute bioavailability was 31±24%.
>
> Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations [see Dosage and Administration (2.2)].
>
> Pharmacokinetics of tacrolimus have also been studied in kidney transplantation patients, 8.2±2.4 years of age. Following IV infusion of a 0.06 (range 0.06 – 0.09) mg/kg/day to 12 pediatric patients (8 male and 4 female), mean terminal half-life and clearance were 10.2±5.0 (range 3.4-25) hours and 0.12±0.04 (range 0.06-0.17) L/hr/kg, respectively. Following oral administration to the same patients, mean AUC and C_{max} were 181±65 (range 81-300) ng•hr/mL and 30±11 (range 14-49) ng/mL, respectively. The absolute bioavailability was 19±14 (range 5.2-56) %."

Furthermore, there is evidence in the scientific literature to sufficiently inform use of tacrolimus in pediatric patients (**Attachment I**). Ascend believes that there is enough evidence in the literature to indicate that the bioequivalence/bioavailability of tacrolimus in pediatric population may not be affected due to dosage forms differences. Hence, ASC requests a waiver for Pediatric Research Equity Act (PREA) requirements for its proposed dosage form.

ASC herein also encloses a draft labeling for the proposed drug product (**Attachment II**).

The undersigned respectfully requests FDA to direct any correspondence relating to this petition to me at the above address or phone number 201-326-9004 and facsimile number 201-47601987or email afrimpong@ascendlaboratories.com

Sincerely,

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

From: (201) 326-9004
Augustine Frimpong
Ascend Laboratories
180 Summit Avenue
Suite 200
Montvale, NJ 07645

Origin ID: UMMA

FedEx Express

J13111302120326

Ship Date: 25JUL13
ActWgt: 2.5 LB
CAD: 100461312/INET3370

Delivery Address Bar Code

Ref # Tacrolimus Suspension
Invoice #
PO #
Dept #

SHIP TO: (888) 463-6332 BILL SENDER

Office of Generic Drugs
Food & Drug Administration
Department of Health & Human Svcs.
5360 Fishers Lane, Room 1061
Rockville, MD 20852

MON - 29 JUL AA
** 2DAY **

TRK# 0201 7963 1904 6195

20852
MD-US
IAD

SA NSFA

518G1/AA04/83AB

After printing this label:
1. Use the 'Print' button on this page to print your label to your laser or inkjet printer.
2. Fold the printed page along the horizontal line.
3. Place label in shipping pouch and affix it to your shipment so that the barcode portion of the label can be read and scanned.

Warning: Use only the printed original label for shipping. Using a photocopy of this label for shipping purposes is fraudulent and could result in additional billing charges, along with the cancellation of your FedEx account number.
Use of this system constitutes your agreement to the service conditions in the current FedEx Service Guide, available on fedex.com.FedEx will not be responsible for any claim in excess of $100 per package, whether the result of loss, damage, delay, non-delivery,misdelivery,or misinformation, unless you declare a higher value, pay an additional charge, document your actual loss and file a timely claim.Limitations found in the current FedEx Service Guide apply. Your right to recover from FedEx for any loss, including intrinsic value of the package, loss of sales, income interest, profit, attorney's fees, costs, and other forms of damage whether direct, incidental,consequential, or special is limited to the greater of $100 or the authorized declared value. Recovery cannot exceed actual documented loss.Maximum for items of extraordinary value is $1,000, e.g. jewelry, precious metals, negotiable instruments and other items listed in our ServiceGuide. Written claims must be filed within strict time limits, see current FedEx Service Guide.