DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22117/S-017, S-018, S-019

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENT

Forest Laboratories, Inc.
Attention: Patricia Pacificador, PharmD
Senior Manager, Regulatory Affairs
Harborside Financial Center, Plaza V
Suite 1900
Jersey City, NJ 07311

Dear Dr. Pacificador:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received August 28, 2014 (S-017), September 12, 2014 (S-019), and September 24, 2014 (S-018), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Saphris (asenapine) sublingual tablets 2.5 mg, 5 mg and 10 mg.

We acknowledge receipt of your amendments dated:

September 24, 2014	October 17, 2014	November 3, 2014	November 21,2014
December 3, 2014	January 8, 2015	January 21, 2015	January 23, 2015
January 30, 2015	February 3, 2015	February 6, 2015	February 26, 2015
March 4, 2015	March 6, 2015	March 10, 2015	March 12, 2015

These “Prior Approval” supplemental new drug applications propose the following changes:

S-017: labeling revisions to the **Dosage and Administration**, **Postmarketing Experience,** and **Patient Counseling Information** regarding choking associated with asenapine treatment, including cases with fatal outcomes, as requested in an Agency supplement request letter dated July 30, 2014

S-018: Updates to the labeling to reflect safety results from the following Pediatric Clinical Trials in Schizophrenia adolescent patients aged 12 to17 years:

- P05896: An 8-Week, Placebo-Controlled, Double-Blind, Randomized, Fixed-Dose Efficacy and Safety Trial of Asenapine in Adolescent Subjects with Schizophrenia
- P05897: A 26-Week, Multi-Center, Open Label, Flexible Dose, Long-Term Safety Trial of Asenapine in Adolescent Subjects With Schizophrenia

S-019: Updates to the labeling to reflect safety and efficacy results from the following Pediatric Clinical Trials in Bipolar I Disorder patients aged 10 to17 years:

- P06107: Efficacy and Safety of a 3-Week Fixed-Dose Asenapine Treatment in Pediatric Acute Manic or Mixed Episodes Associated with Bipolar I Disorder
- P05898: A 50-Week Open-Label, Flexible-Dose Trial of Asenapine Extension Treatment to P06107 in Pediatric Subjects with Acute Manic or Mixed Episodes Associated With Bipolar I Disorder

Additionally, we note that supplemental applications 22117/S-018 and 22117/S-019, containing a request for Pediatric Exclusivity determination, were submitted to fulfill the requirements of a Written Request to obtain information on asenapine in pediatric patients with schizophrenia and bipolar I disorder.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF 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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and

annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We remind you of your March 10, 2015 agreement to submit revised carton labeling to match the language in the Instructions for Use within 6 months of approval.

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 note that you have fulfilled the pediatric studies requirement for all relevant pediatric age groups for this application.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submissions dated September 12, 2014, and September 24, 2014, containing the final reports for the following postmarketing requirements listed in the August 13, 2009 approval letter.

1496-1 A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17 years. A study to obtain pharmacokinetic data and provide information pertinent to dosing of asenapine sublingual tablets in the relevant pediatric population.

1496-2 A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17 years. A study of the efficacy and safety of asenapine sublingual tablets in the relevant pediatric population.

1496-3 A deferred pediatric study under PREA for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder ages 10 to 17 years. A study to obtain pharmacokinetic data and provide information pertinent to dosing of asenapine sublingual tablets in the relevant pediatric population.

1496-4 A deferred pediatric study under PREA for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder ages 10 to 17 years. A study of the efficacy and safety of asenapine sublingual tablets in the relevant pediatric population.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that the following postmarketing commitments listed in the August 13, 2009 approval letter are still open.

1496-5 To conduct an adequate and well-controlled long-term maintenance study to evaluate the efficacy and safety of asenapine in the treatment of adults with acute manic or mixed episodes associated with bipolar I disorder. The maintenance study should be appropriately designed to assess the efficacy of asenapine in preventing all types of mood episodes associated with bipolar disorder (depression, mania, and mixed episodes).

1496-6 It is not apparent from the studies you have conducted in bipolar mania that the lowest effective dose of asenapine has been identified. We request that you further characterize the utilization of asenapine in the treatment of adults with acute manic or mixed episodes associated with bipolar I disorder with a dose lower than 10 mg twice daily (e.g. 5 mg twice daily) through an adequate and well controlled trial

1496-7 It is not apparent from the studies you have conducted in schizophrenia that the lowest effective dose of asenapine has been identified. We request that you further characterize the utilization of asenapine in the treatment of adults with schizophrenia with a dose lower than 5 mg twice daily (e.g. 2.5 mg twice daily) through an adequate and well controlled trial.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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, contact Shin-Ye Sandy Chang, Regulatory Project Manager, at shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MITCHELL V Mathis
03/12/2015