



NDA 22117/S-003/S-004

**SUPPLEMENT APPROVAL**

Organon USA Inc.  
Attention: Jill Kompa  
Liaison, Global Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

Dear Ms. Kompa:

Please refer to your Supplemental New Drug Applications (sNDA) dated November 6, 2009, received November 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Saphris (asenapine) 5 mg and 10 mg sublingual tablets.

We acknowledge receipt of your submissions dated December 17, 2009, January 11, 2010, February 12, 2010, February 25, 2010, March 3, 2010, March 5, 2010, March 22, 2010, March 29, 2010, April 13, 2010, April 27, 2010, April 29, 2010, May 19, 2010, May 24, 2010, May 25, 2010, July 1, 2010, July 8, 2010, July 16, 2010, July 22, 2010, August 4, 2010, August 11, 2010, and August 23, 2010.

These "Prior Approval" supplemental new drug applications provide for the maintenance treatment of schizophrenia in adults (S-003) and the indication of adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder (S-004).

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.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 for this NDA, including pending “Changes Being Effected” (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.

### **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.

**Schizophrenia:** The average age of onset for schizophrenia is 18 years for men and 25 years for women. Schizophrenia is much less common in children and adolescents than in adults, affecting only about 1 in 40,000 children under 18, with about 1 in 10,000 children developing the disease before the age of 12. Therefore, it is difficult to conduct large scale studies on children ages 1 to 12 years. In view of the oral and parenteral antipsychotic drug options available on the market, Saphris probably will not be used in a substantial number of patients under age 13 years after approval, and conducting pediatric studies under age 13 years would be impracticable.

**Bipolar Mania or Mixed episodes:** According to the DSM IV-TR, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the 10 to 17 year-old population is thought to be relatively common and symptomatically similar to bipolar disorder seen in adults. Thus, the study of Saphris in the treatment of bipolar disorder in 10 to 17 year-olds should be feasible and should yield useful information.

We are waiving the pediatric study requirement for 0 to 12 years in the treatment of schizophrenia and 0 to 9 years in the acute treatment of manic or mixed episodes associated with bipolar I disorder because the necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric studies for ages 13 to 17 years in the treatment of schizophrenia and 10 to 17 years in the acute treatment of manic or mixed episodes associated with bipolar I disorder because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act 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 Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

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

Final Report Submission: by December 1, 2016

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

Final Report Submission: by December 1, 2016

Submit all clinical protocols to your IND for this product. Submit all final reports to your NDA 22-117. Use the following designator to prominently label all submissions and refer to PMC set number **1496: "Required Pediatric Assessment(s)"**.

### **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  
Division of Drug Marketing, Advertising, and Communications  
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.(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

**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 Terry Harrison, Regulatory Project Manager, at (301) 796-2770 or email terry.harrison@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22117	SUPPL-4	ORGANON USA INC	Saphris
NDA-22117	SUPPL-3	ORGANON USA INC	Saphris

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

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/s/

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MITCHELL V Mathis  
09/03/2010  
For Dr. Laughren