CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-117

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Maternal Health Team Review

Date: July 6, 2009

From: Jeanine Best, MSN, RN, PNP
Regulatory/Labeling Reviewer
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Psychiatric Products (DPP)

Drug: Saphris (asenapine) sublingual tablets, NDA 22-117

Subject: Pregnancy, Labor and Delivery, and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Saphris (asenapine) sublingual tablets labeling

INTRODUCTION

Organon submitted a New Drug Application (NDA 22-117) for Saphris (asenapine) sublingual tablets on August 30, 2007, for the treatment of schizophrenia and for the treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder. FDA issued a Complete Response (CR) Letter on January 13, 2009, and Organon submitted a Class 1 resubmission in response to the CR Letter on February 12, 2009. Asenapine is a psychotropic agent (atypical antipsychotic) that belongs to the dibenzo-oxepino pyrroles class.

The Division of Division of Psychiatric Products (DPP) asked the Maternal Health Team (MHT) to review the Pregnancy, Labor and Delivery, and Nursing Mothers section of Saphris (asenapine) sublingual tablets labeling.

BACKGROUND

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides MHT's suggested revisions to the sponsors proposed Pregnancy, Labor and Delivery, and Nursing Mothers subsections of Saphris (asenapine) sublingual tablets labeling.

SUMBMITTED MATERIAL

Sponsors Proposed Pregnancy, Labor and Delivery, and Nursing Mothers Labeling submitted February 12, 2009, and edited by DPP.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy**: SAPHRIS should be used only if the potential benefit justifies the potential risk. (8.1)
- **Nursing Mothers**: Breast feeding is not recommended. (8.3)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Pregnancy Category C: Asenapine was not teratogenic in reproduction studies in rats and rabbits at intravenous doses up to 1.5 mg/kg in rats and 0.44 mg/kg in rabbits. These doses are 0.7 and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 10 mg twice daily given sublingually on a mg/m^2 basis. Plasma levels of asenapine were measured in the rabbit study, and the AUC at the highest dose tested was 2 times that in humans receiving the MRHD.

In a study in which rats were treated from day 6 of gestation through day 21 postpartum with intravenous doses of asenapine of 0.3, 0.9, and 1.5 mg/kg/day (0.15, 0.4, and 0.7 times the MRHD of 10 mg twice daily given sublingually on a mg/m2 basis), increases in post-implantation loss and early pup deaths were seen at all doses, and decreases in subsequent pup survival and weight gain were seen at the two higher doses. A cross-fostering study indicated that the decreases in pup survival were largely due to prenatal drug effects. Increases in post-implantation loss and decreases in pup weight and survival were also seen when pregnant rats were dosed orally with asenapine.

(b) (4)

8. 2 Labor and Delivery
The effect of SAPHRIS on labor and delivery in humans is unknown.

8. 3 Nursing Mothers
Asenapine was excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. It is recommended that women receiving SAPHRIS should not breast feed.

CONCLUSIONS
While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

LABELING RECOMMENDATIONS
Provided below are MHT's recommended revisions to the sponsors' proposed labeling (with DPP edits). Appendix A of this review provides a track changes version of labeling that highlights the MHT recommended revisions.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy**: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers**: Discontinue drug or nursing taking into consideration importance of drug to the mother. (8.3)

Reviewer Comment: Language revised to reflect appropriate regulatory language.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well controlled studies of SAPHRIS in pregnant women. In animal studies, asenapine increased the rates of pre-implantation and post-implantation loss, and decreased neonatal survival at exposures similar to or less than human exposures at recommended clinical doses. In these studies, there was no increase in the incidence of structural abnormalities clearly attributable to asenapine exposure. SAPHIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In embryo-fetal toxicity studies, pregnant rats and rabbits received intravenous asenapine at doses up to 1.5 mg/kg (rats) and 0.44 mg/kg (rabbits). These doses are 0.7 and 0.4 times, respectively, based on body surface area (mg/m^2), the maximum recommended human dose (MRHD) of twice daily sublingual doses of 10 mg. Plasma levels in rabbits at the 0.44 mg/kg i.v. dose showed asenapine exposures $\leq$ 2 times the human exposure at the MRHD (based on AUC); plasma levels were not obtained in rats. In rats, there were no adverse reproductive outcomes, but in rabbits, there was an increase in post-implantation loss at all doses compared to controls. There were no observed structural abnormalities clearly related to asenapine exposure.

In prenatal/postnatal development studies, pregnant rats received intravenous asenapine 0.3, 0.9, or 1.5 mg/kg/day from day 6 of gestation through day 21 postpartum (doses equivalent to 0.15, 0.4, and 0.7 times the MRHD of 10 mg twice daily given sublingually on a mg/m^2 basis). Increased post-implantation loss and early pup deaths occurred at all doses. Pup survival and weight gain were decreased at the two higher doses. A cross-fostering study indicated that the decrease in pup survival was largely due to prenatal drug effects.

Reviewer Comment: Subsection reorganized to place clinically relevant information first.

8. 2 Labor and Delivery

The effect of SAPHRIS on labor and delivery in humans is unknown.

8. 3 Nursing Mothers

It is not known whether asenapine or its metabolites are excreted in human milk. In rats, asenapine was excreted in milk during lactation. Because many drugs are excreted in human

milk and because of the potential for serious adverse reactions in nursing infants from SAPHRIS, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer Comment: Language revised to reflect appropriate regulatory language.

Appendix A – Track Changes Version of Labeling

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/s/

Jeanine Best
7/6/2009 07:48:48 AM
LABELING REVIEWER

Karen Feibus
7/6/2009 03:38:51 PM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review.

Lisa Mathis
7/7/2009 01:59:15 PM
MEDICAL OFFICER

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-117
APPLICANT	ORGANON USA INC
DRUG NAME	SAPHRIS (asenapine)
SUBMISSION DATE	February 13, 2009
SEALD REVIEW DATE	June 24, 2009
SEALD REVIEWER(S)	Abiola Olagundoye, PharmD
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

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/s/

Abiola Olagundoye
6/25/2009 12:22:25 PM
CSO
SEALD comments sent to review division 06/24/09

Laurie Burke
7/6/2009 02:27:06 PM
INTERDISCIPLINARY

MEMORANDUM

To: **Keith Kiedrow, PharmD**
Division of Psychiatry Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **May 26, 2008**

Re: **Comments on draft labeling for asenapine sublingual tablets**
NDA 22-117

We have reviewed the proposed label for asenapine (FDA version dated 5/14/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

GENERAL COMMENTS

(b) (4)

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/s/

Iris Masucci
5/27/2008 09:49:27 AM
DDMAC REVIEWER

Laurie Burke
6/6/2008 12:25:44 PM
INTERDISCIPLINARY