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APPLICATION NUMBER:

22-117

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 22117	**Sponsor : Organon USA**
Drug: Asenapine (ORG5222)	
Formulation:	**Sublingual Tablets**
Proposed Indication:	**Schizophrenia** **Acute Mania Associated w/Bipolar Disorder**
Correspondence Date:	July 25, 2008 September 4, 2008 September 23, 2008
Reviewer:	Andre Jackson

Review History of Additional Plasma Metabolic Profile Data Submitted by the Firm

HISTORY

The firm submitted a letter on July 25th 2008 making the following points related to the clarification of the metabolite profile for Asenapine (see Appendix I).

- Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS.
- The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile.
- A significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS.

The FDA responded to that July 25th correspondence with comments in the format of a review (see Appendix II).

The amount of information presented by the firm related to metabolite analysis required an in depth re-analysis of all submitted data which was completed and is presented in Appendix III.

Questions were sent to the firm on September 3, 2008 seeking further clarification (see Appendix IV).

The firm's response is presented in Appendix V.

The firm's response response to FDA questions is presented in Appendix VI.

Information presented at the internal meeting on September 15, 2008 (see Appendix VII).

The firm's final response and data summary are presented in Appendix VIII.

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OVERALL COMMENT:

The metabolite data presented by the firm is acceptable to OCP and has been included in the label text.

OCP LABEL

Metabolism and Elimination

In a mass balance study about 50% of the circulating species in plasma have been identified and they are asenapine-N-glucuronide (34%), N-desmethylasenapine (5%), N-desmethylasenapine N-carbamoyl glucuronide (7%) and unchanged asenapine (4%). There are other non-identified metabolites which account for 32% of the plasma circulating species.

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raymond Baweja, Ph.D.

Team Leader_____

Cc-NDA 22117, HFD-860(Jackson, Baweja,Mehta), Central Documents Room(Biopharm-CDR)
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APPENDIX 1 July 25th 2008 LETTER FROM FIRM

Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS. The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile. Metabolites eluting in this region have been characterized by LC-MS and correspond mostly to Phase II (sulfate, glucuronide and methylated) products. Overall more than 70% of circulating radioactivity is associated with conjugated metabolites. In addition, it should be noted that a significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS. Given the well-characterized biotransformation pathways for asenapine in the mouse, rat, rabbit, and dog, we believe that we have adequately exposed non-clinical safety species to all relevant human metabolites. A more detailed discussion of these points can be found below.

Metabolite profiling was studied in human volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques. All samples were derived from four healthy male subjects who had received a single radiocarbon dose (10 mg) after having been previously administered unlabeled drug for 10 days.

- The most representative profile which illustrates total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. Referring to the radiochromatogram (**Figure 1**), we can see that asenapine (PC20) is extensively metabolized. While >9% the circulating radioactivity can be accounted for by asenapine and the desmethyl metabolite (PC19), an additional 40.5% is associated with asenapine N^+-glucuronide (PC12/13; 33.6%) and N-desmethylasenapine N-carbamoyl glucuronide (PC16; 6.9%). The N+-glucuronide, N-desmethylasenapine and asenapine-11-hydroxysulfate metabolites have also been quantified by validated bioanalytical assays in clinical PK trial 25546 (included in the dossier). These results reproduced the ratios found in the human ^{14}C-AME study. With the exception of the N-carbamoyl glucuronide, these metabolites have also been tested pharmacologically and showed decreased activity and/or no entrance into the brain.

- The remaining radioactivity which elutes between 13 and 25 min (**Figure 1**) corresponds to at least 15 different peaks, none of which represent more than 6% of the plasma radioprofile. As determined in urine by LC-MS, most peaks eluting before PC12/13 consisted of more than 3 metabolites, resulting in the characterization of greater than 40 metabolites. It is important to note that the majority (**Table 1**) of these metabolites correspond to phenolic sulfate and/or glucuronide conjugates and as per FDA guidance most likely pose little safety concern. The remaining unconjugated metabolites result from 10- and/or 11-hydroxylation and N-oxidation and represent no obvious structural alert. Each of these minor metabolites in turn have been detected in at least one preclinical safety species.

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