

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-117s000

SUMMARY REVIEW

**ADDENDUM TO
MEMORANDUM** DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 12, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
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Division of Psychiatry Products
HFD-130

SUBJECT: Recommendations for approvable action for asenapine maleate (sublingual tablets) in adults in two indications:
1. Schizophrenia
2. Bipolar disorder, acute manic or mixed episodes

TO: File NDA 22117
SN 000
Standard Priority Original NDA of an NME

Reviewers

Chemistry: Tele Chhagan, Ph.D.
Pharmacology/Toxicology: Elzbieta Chalecka-Franaszek, Ph.D.
Clinical: Robert Levin, M.D.
Biometrics: Yeh-Fong Chen, Ph.D. (Schizophrenia)
George Kordzakhia, Ph.D. (Bipolar Disorder)
QTIRT: Christine Garnett, Ph.D., Suchitra Balakrishnan, Ph.D.
DSI: Diane Tesch, John Lee, M.D.
DMEP: Felicia Duffy, R.N., B.S.N., M.S.Ed.
OSE Risk Management Plan Review: Jeanine Best, MSN, RN/Mary Dempsey
SEALD: Iris Masucci, Pharm.D., B.C.P.S.
Clinical Pharmacology: Ronald Kavanaugh, Ph.D.
Controlled Substances Staff: Katherine Bonson, Ph.D.

1.0 BACKGROUND

The purpose of this addendum to the first CDTL memorandum signed off on 14 May 2008 is to provide the additional information from the Office of Clinical Pharmacology (OCP) review to aid the Office Director and Division Director in the regulatory

processing of this pilot NME NDA. Asenapine has been developed as an atypical antipsychotic with effects mediated at least in part via 5HT₂, D₂ and α₁-adrenergic receptor antagonist properties. The OCP review was signed off on 15 May 2008 and the OCP TL memorandum was signed on 10 June 2008.

Asenapine (sublingual tablet) was developed under IND 51-641 (schizophrenia) and IND 70-329 (bipolar disorder). We held a number of meetings with the sponsors. At the End-of Phase 2 meeting held 20 November 2002, the sponsor stated that asenapine 5 mg BID was the minimum effective dose in the treatment of schizophrenia.

2.0 CHEMISTRY

Dr. Tele Chhagan clarified remaining CMC issues for the action letter.

1. Provide level of amorphous material in all the clinical batches including the batches used in BE studies (Batch #: AN and AT).
2. Provide information on the in-process controls and the manufacturing critical process parameters that control the amorphous material content in the final dosage form.
3. Provide information in tabular form about the physico-chemical properties of the amorphous material, ^{(b) (4)} (i.e., solubility, stability, etc.).
4. Include either a release and shelf-life control of the amorphous content in the drug product through specification or a justification from for not including such control based on ICH Q6A.

I am not aware of any CMC issues at this point that would preclude an approvable action for this NDA

3.0 PHARMACOLOGY

Pharmacology/Toxicology has determined that the rat and mouse carcinogenicity studies are inadequate to support approval until all histopathology slides from the low and medium dose groups of the rat study, and the low and medium dose female groups from the mouse study have been examined and the results submitted for review. We provided the rationale for this decision in our communication of 8 April 2008 to the sponsors.

Dr. Chalecka-Franaszek found that the degree of decreased weight gain in the rat study, particularly at the high dose, was of a magnitude which may have decreased the sensitivity of the animals to drug-induced tumors. In the mouse study, a large increase in malignant lymphomas compared to the vehicle control group, but not to an untreated control group, was seen in high dose females and therefore examination of the lower dose

groups is necessary to determine if this was a true drug effect and if so, if there is a no-effect dose.

The sponsors addressed these concerns in their submission of 29 April 2008; however we still believe that examination of the additional groups is necessary. As summarized by Dr. Rosloff, the primary arguments for the rat study were as follows:

1. The sponsors reply read that the literature indicates that in dietary restriction studies, it is the decrease in food consumption, and not the consequent decrease in bodyweight gain, which is responsible for the decrease in tumors seen, and that food consumption was only slightly decreased in the asenapine study. However, it is our opinion that the available evidence is not sufficient to rule out a significant (or even a primary) effect of decreased bodyweight gain. There is also evidence for a role of decreased weight gain in drug studies, e.g., methylphenidate. In fact a decrease in tumors was seen in the asenapine study, (e.g., benign mammary and pituitary tumors in females, and pheochromocytomas) were also decreased in this study.
2. The sponsors stated that the number of animals that remain to be examined in the lower dose groups is small, presumably since animals which died or were prematurely sacrificed in these groups were examined. The sponsors stated that “the number of animals that remain to be fully examined in these groups is... about 17% of the total number on study for both the rat and the female mouse”; however we find the number to be much greater for the low and medium dose groups in the rat study, e.g. the % alive at termination (and thus presumably not fully evaluated) ranged from 33 to 55%. Furthermore, some of the tissues from premature decedents could not be adequately evaluated due to autolysis. Additionally, animals dying or sacrificed prematurely are at lower risk for development of tumors than those which survived to termination (an effect which may be exaggerated in the face of dietary restriction/decreased weight gain—Keenan et. al., *Toxicologic Pathology* 24:6, 757-768, 1996).
3. The sponsors stated also that the use of doses which would have caused a smaller degree (10%) of weight gain reduction would result in drug exposures in high dose males which are less than those in humans. However, Pharmacology/Toxicology concluded that this is less crucial to an assessment of carcinogenic potential than is a decrease in the sensitivity of the assay due to an excessive decrease in weight gain.

The sponsors’ primary argument regarding the mouse study is that there is a high and variable incidence of malignant lymphoma in this strain and that the incidence in the asenapine study is within the historical range. Furthermore, the incidence in the untreated control group was similar to that in the high dose females. However, Pharmacology/Toxicology remains concerned with the much higher incidence in the high dose female group compared to the vehicle control group, which Pharmacology/Toxicology finds to be the most appropriate comparator group.

Examination of the low and medium dose female groups would help determine if there was a true drug effect (e.g., if there were a dose-response in incidence) and if there is a no-effect dose; alternatively if the incidences in the low and medium dose female groups were similar to those in the high dose and untreated control groups, it might be concluded that the vehicle control group was an outlier and that there was no drug effect on the incidence of this tumor.

In order to accurately describe the carcinogenic potential of asenapine in the labeling, full histopathological examination of all animals in the low and medium doses in the rat carcinogenicity study, and of all low and medium dose females in the mouse carcinogenicity study, should be performed prior to NDA approval. As communicated to the sponsors on 8 April 2008, in order to validly compare results across groups, the originally examined slides from these studies should be re-examined in concert with the newly evaluated slides by a single pathologist, and subjected to peer review. These conclusions of Pharmacology/Toxicology were confirmed twice by the Executive CAC.

In addition, Pharmacology/Toxicology recommends that the sponsors perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity or (b) (4)

That the non-clinical carcinogenicity data filed to the NDA is considered by Pharmacology/Toxicology to be "unacceptable" precludes an approval action for this NDA.

4.0 BIOPHARMACEUTICS

At present, OCP has determined that the asenapine metabolic scheme is uncertain based on the data submitted by the sponsors to this application. Dr. Baweja summarized the critical outstanding pharmacology issues.

1. From a clinical pharmacology standpoint the sponsors have not adequately ascertained what moieties are circulating in plasma. In the mass balance study, the plasma concentrations of ¹⁴C asenapine (equivalents) greatly exceed that of asenapine (cold drug) as well as the metabolites measured. The moieties looked for are asenapine, desmethylenapine, and the N-oxide. The total AUC counts for total radioactivity (¹⁴C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. Therefore, there is a vast amount of circulating material in plasma that has not been ascertained. At least 96.6% of the circulating species have not been identified. This is a matter for concern and we require an explanation for this vast gap in plasma between circulating radioactivity and moieties circulating and identified.
2. Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose was recovered with 49 % in the urine and

39 % in the feces. This is a generalized presentation of assessing the elimination pathways of the radioactivity. Specifically, what is known is that direct glucuronidation accounts for 12-21% of the dose. Furthermore, 5-16 % of the dose is that of the unchanged drug, asenapine. When these two percentages of moieties are added, only 17–37 % of the dose is represented. Therefore, 63-83 % of the dose has not been adequately characterized for the primary elimination pathways.

3. The characterization of the metabolism moieties circulating in plasma and of the human elimination pathways must be clearly delineated and properly addressed by the sponsors.

OCP raised an additional concern in the review (page 481) that was emphasized at the meeting held by Dr. Temple (27 May 2008) followed by an email that referred to an association between 5HT2b agonism (associated with “Phen-fen cardiac valvulopathy”) that OCP attributed also to asenapine with a list of subjects that he thought had “Aes potentially consistent with 5HT2B agonism”. In response, Dr. Chalecka-Franaszek reviewed more extensively the receptor binding affinities of asenapine and Dr. Barry Rosloff sent an email dated 11 June 2008 reading that asenapine antagonizes D2, 5HT2a and 5HT2b receptors. Dr. Levin and I are reviewing the clinical data in depth regarding the list of subjects with Aes potentially consistent with 5HT2b agonism” to find all relevant clinical and laboratory data possible. Each case will be medically reviewed by Drs. Laughren, Mathis, Levin, and I for medical adjudication on 16 June 2008.

OCP conducted a post hoc evaluation employing the Bipolar Disorder data of changes in YMRS scores (pages 397 to 402) in a section entitled 5.6.2.2.1.2 Reviewer’s Exploratory Assessments of Exposure Response of Asenapine on Young Mania Rating Scale (YMRS). To summarize the general approach, OCP began by dividing the 3 treatment groups (placebo, olanzapine and asenapine) into quintiles based on YMRS score at any time before baseline (screening, baseline, “or other evaluations.” The lack of uniformity of timing for severity rating for allocation into quintile adds additional variability and confounding that would likely attenuate the power of the analysis. The sparse sampling in a number of the cells detracts from the power to detect differences between changes from some time before the first dose asenapine. Consequently, in my opinion, these post hoc analyses limited by confounding and reduced statistical power provide no additional regulatory information to the review of efficacy and I do not recommend consultation by Biometrics on these analyses.

I concur with the OCP conclusions and recommendations to the Division and Office Directors that the plasma metabolic exposure profiles, the metabolic scheme, mass balance study and enzymes responsible for various elimination pathways need to be further clarified. The absence of adequate basic pharmacology data to address all of these issues precludes approval of this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data Overview

5.1.1 Overview of Studies Pertinent to Efficacy (SZ)

Summary of Significance of Primary PANSS Endpoint: 3 Placebo-Controlled Trials

<u>Study #</u>	<u>Asenapine 5 mg BID</u>	<u>Asenapine 10 mg BID</u>	<u>RIS</u>	<u>HAL</u>	<u>OLZ</u>
041004	SS		NS		
041021	NS	NS			SS
041023	SS	NS*		SS	

* Post hoc MMRM analysis (p-value = 0.04)

I concur with Drs. Levin and Chen that only the asenapine 5 mg twice daily dose meets criteria for a claim in the acute treatment of schizophrenia. In my first memorandum CDTL memorandum, after review of Dr. Chen's FDA confirmation of primary efficacy and the sensitivity analyses, I had plumbed the secondary data beyond the analysis of the primary endpoint analyses to attempt to get a sense of the potential for efficaciousness of the asenapine 10 mg BID dose level in future trials. Metaphorically speaking, this is akin to tracing the path of a comet in the sky. There were only 2 randomized controlled trials that were informative for regulatory purposes. In one trial, the asenapine 10 mg BID dose was not statistically significant and only significant on a post hoc MMRM analysis in the other trial compared to placebo. No data was found to support a claim for the 10 mg BID dose in the acute treatment of schizophrenia, despite the highly significant separation from placebo in the asenapine 10 mg BID treated patients in the bipolar mania trials.

5.1.2 Overview of Studies Pertinent to Efficacy (BP, manic or mixed episodes)

There were two highly significant trials with concurrence between Drs. Kordzakhia and Levin and that the improvement from baseline to 3-week endpoint on the YMRS total score in these 2 positive, flexible-dose acute treatment trials compared to the placebo groups provide adequate evidence to support that asenapine flexibly dosed in the range of 5- 10 mg BID is satisfies regulatory criteria to support the claim that asenapine is efficacious in the acute treatment of bipolar I disorder, manic and mixed episodes. The limitation of the findings from the 2 randomized controlled trial evaluating asenapine in the treatment of bipolar disorder is that a small minority of patients had their dose reduced from the starting dose of asenapine 10 mg BID to 5 mg BID (approximately 10%) during the two trials, and this lower dose was the only dose supported for a claim in the schizophrenia program. The magnitude of the effect compared to placebo was less than that observed with olanzapine.

5.1.3 Conclusions Regarding Acute Efficacy of Asenapine in the Schizophrenia and Bipolar Disorder (manic or mixed episodes)

Taken together, the sponsors have, in my view as well as the views of Dr. Levin, Chen, and Kordzakhia, provided sufficient evidence for regulatory purposes in two positive short-term studies to support the claim of efficacy of asenapine 5 mg BID in the treatment of schizophrenia. The sponsors have provided sufficient evidence also in two positive trials to support the claim of short-term efficacy of asenapine in the treatment of bipolar disorder, manic or mixed episodes. Qualitative review in my prior memorandum suggests that the asenapine's magnitude of effect appears to be less than that of olanzapine, and usual for the class of atypical antipsychotic drugs on the market. One issue limiting the ability to clearly describe recommended dosing is the paucity of data in the optimal clinical dosing range in fixed dose studies in both indications. The greatest need is to study the acute efficacy of asenapine 5 mg BID in bipolar disorder, manic and mixed episodes to see if for similar efficaciousness, the adverse event profile can be improved compared to the 10 mg BID dose level. No clear predictors of response were identified in either the acute treatment of schizophrenia or bipolar disorder.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

In my memorandum dated 14 May 2008, I referred to Dr. Levin's thorough review of the safety data in the NDA. In addition, I reviewed data that I thought required additional analysis and confirmation. It is noteworthy that the rates of death in the placebo-controlled asenapine database were 1.7 per 100 patient-years in the asenapine group and 1.9 per 100 patient-years in the placebo group. In the asenapine group, there was one death associated with asenapine exposure with symptoms of dystonia and dyspnea associated with epiglottitis and laryngitis, raising the possibility of laryngeal dystonia. There was also one death in a patient diagnosed with pulmonary embolism coupled with hyperthermia associated with asenapine exposure. The placebo patient who died was diagnosed with malignant thymoma, which was highly unlikely to be related to treatment.

OCP stated in the section on "Comments Previously Provided to the Medical Review Team" on page 42 of their review that on 1 May 2008 "this reviewer went to the medical division to discuss a death in the ongoing studies. Due to workload the medical review team requested followup midweek the following week. On Thursday May 8th, 2008 a followup email was sent to the medical review team informing them of a possible case of aplastic anemia." In the data, Dr. Levin found no evidence of pancytopenia. If this were the case, as CDTL working with Drs. Levin, Laughren and Mathis and Lieutenant Commander Kiedrow, we would have used one of our reserved meeting times to review the action plan.

5.2.2 Common Adverse Event Profile for Asenapine

Schizophrenia

The common AEs that are associated with asenapine use in the acute treatment of schizophrenia ($\geq 5\%$ and at least twice that of placebo) are consistent with the usual safety profile atypical antipsychotic drugs such as sedation, akathisia, and oral hypoesthesia (particular to the sublingual formulation) along with extra-pyramidal symptoms if all terms are combined.

Bipolar Disorder

The common AEs that are associated with asenapine use in the acute treatment of bipolar disorder, manic or mixed episodes, ($\geq 5\%$ and at least twice that of placebo) are consistent with the usual safety profile atypical antipsychotic drugs such as sedation, dizziness, weight gain, and oral hypoesthesia along with extra-pyramidal symptoms if all terms are combined.

Almost all of the AEs associated with discontinuation occurred in less than one percent of the patients in the placebo-controlled trials. In the absence of complete data employing standard AEs terms that we think are reasonable to categorize adverse drug reactions, the sponsor should submit revised complete tables of AEs with percentages greater than 1% and at least twice placebo stratified by diagnostic category.

5.2.3 Adverse Reactions of Particular Interest

Cardiac Sinus Arrest and Other Arrhythmias

During the review process, one of the clinical concerns that emerged were some of the cardiac adverse events reported in the database. In view of the complexity that the data posed to the medical reviewers, an objective review by cardiologists was welcomed. Drs. Suchitra Balakrishnan and Dr. Norman Stockbridge of the Division of Cardio-Renal Products (DCRP) reviewed thoroughly the totality of the relevant cardiac clinical data summarized in their review dated 23 April 2008 that included data from the bioequivalence study identified by OCP. They noted that the sponsors attribute to Neurally Mediated Reflex Bradycardia (NMRB) the 9 episodes of sinus arrest and 4 reports of nodal rhythm in healthy volunteers who received asenapine < 5 mg. Dr. Stockbridge reviewed the explanations provided by the sponsor and found the explanation of NMRB secondary to α -receptor blockade to be "reasonable." In terms of other dysrhythmias, the incidence of tachycardia, sinus bradycardia, heart block and ventricular extra-systoles were higher than in the placebo group and comparable to the frequencies observed in olanzapine-treated patients. The consultation by Drs. Stockbridge and Balakrishnan concludes: "It appears that the arrhythmia related AEs associated with asenapine are similar to those of olanzapine and consistent with class effects based on our review of the summary of clinical safety, non-clinical summary and additional analysis of ECG intervals in Study INT 0036960. Over all, the data are suggestive of risk of cardiac conduction abnormalities similar to those reported with olanzapine."

In the 15 May 2008 as well as in the 10 June 2008 OCP reviews, despite Dr. Stockbridge's conclusions in the DCRP review of 23 April 2008, OCP continued to conclude that the data supported a severe risk of cardiac toxicity associated with asenapine. On page 22 of the OCP review, in section 2.2.2, Summary of Major Conclusion), OCP opined that "There appears to be no margin of safety with regards to cardiac toxicity." This contradicts the conclusions of Drs. Stockbridge's and Balakrishnan's interpretations of the data and conclusions in their review.

I defer to the expertise of DCRP in the evaluation of the clinical cardiological risk profile of asenapine.

QTIRT evaluation of Risk of QT Prolongation and Other Cardiovascular AEs

The QTIRT consultants found that there was an asenapine concentration-dependent increase in the QTc interval that was mild and of little material clinical significance in the QT study review dated 29 February 2008. The greatest prolongation with a mean ($\Delta\Delta\text{QT}_c\text{F}$) of 10.5 msec with an upper bound of the 90% CI of 16.5 msec was found in the e10 mg BID asenapine group. In discussion with the QTIRT team, the inverted U-shape was most likely due to the variability stemming from small sample sizes (11 April 2008). As a result, one suggestion from the QTIRT was to consider employing the exposure-response data in labeling.

OCP (page 415) in his review of the QTIRT consultation review of the Thorough QT study stated "that some of these serious cardiac toxicities were noted in the QT study but that they hadn't been highlighted and had been explained largely as vasovagal in origin."

Dr. Stockbridge stated in discussion with regarding the QTIRT review on 11 April 2008 (with Dr. Garnett) that he found the QT interval prolongation to be relatively comparable to that seen with olanzapine and to be of little clinical significance.

Hypotension and Syncope

In the actual text from the study report of Study 25509 (Initial Sublingual Single Dose Rising Study), the sponsor summarized: "Org SL94 appears to be safe in endocrinological, biochemical and haematological terms. However single high doses of Org SL93 may induce cardiovascular adverse experiences in animal and humans.... Results from cardiotoxicity studies suggested that Org SL94 may cause postural hypotension at high doses."

In my opinion, hypotension with attendant risk of syncope remains from the initiation of phase I research a safety concern with asenapine administration in a clinical setting. Consistent with α_1 -receptor blockade, the data support the conclusion that healthy volunteers are likely to be more susceptible to orthostatic hypotension associated with dizziness and tachycardia associated with asenapine exposure than psychiatric patients. Nonetheless, hypotension and the risk of syncope were observed in the psychiatric

patients especially when starting treatment. In Phase II/III studies, the frequency observed of syncope was 0.5% in the asenapine 10-20 mg daily groups, 0.4% in the olanzapine group and 0.1% in the placebo group. The risk of orthostatic hypotension, particularly early in the acute treatment of schizophrenia and bipolar disorder may be greater with asenapine than olanzapine exposure and therefore will remain a particular concern in asenapine treated patients to be monitored in clinical settings.

Elevations of Hepatic Transaminases

The potential for asenapine-induced hepatotoxicity was one of the first areas of concern identified upon first review of the asenapine NDA. Dr. Levin particularly scrutinized the data for related adverse events and liver enzymes levels and cases of any hepatic impairment in preparation for the 18 October 2007 filing meeting in order to obtain an early consultation by Dr. John Senior to evaluate for Drug-Induced Liver Injury (DILI). Dr. Levin emailed me a summary of his review of all of the DILI-related data in the NDA (in an email date 15 November 2007) of the liver-related adverse events and abnormal laboratories. By the time of the 1 February 2008 mid-cycle meeting, Dr. Levin remained unable to identify any cases consistent with Hy's Law (reflecting impaired hepatocyte function)¹ associated with asenapine exposure and he documented in his review that the percentages of elevated transaminases were higher in the olanzapine-treated patients than in the asenapine for placebo treated patients: "In the acute, controlled trials, the proportion of subjects with transaminase (ALT) elevations > 3 times ULN in the asenapine, placebo, and olanzapine groups were 3.6% (76/2128); 1.6% (10/634); and 7.8% (66/840), respectively."

On the basis of formation of the N-oxide metabolite of asenapine, OCP informed us to evaluate for hepatotoxicity. And we did so very thoroughly. Of concern regarding accuracy of documentation, however, is the following paragraph by OCP (page 317 of the 15 May 2008 OCP review):

"The totality of the information suggests that a dose and treatment duration hepatotoxicity is of real concern with asenapine and there may be greater risk if the drug is swallowed or if children should take an adult dose. Due to these concerns this reviewer requested that the sponsor be asked to provide complete laboratory information and informed the medical reviewer so that this concern could be fully evaluated. A meeting was held with the medical division where the medical division dismissed the concern of hepatotoxicity [sic]. However, this reviewer has been unable to find where the information request for laboratory information was ever forwarded to the sponsor or where it was ever received."

In my role as Cross Discipline Team Leader and Lieutenant Commander Keith Kiedrow in the role of Regulatory Project Manager on this NDA pilot project, we are to be notified of any issue that is not minor and to be copied on emails of any importance. I never heard of an additional request for data and I never discussed a request to the sponsor for more data. Dr. Levin confirmed with me today that he never discussed with OCP a

¹ Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006 Feb 16; 354(7):731-9.

request for additional data, so it is unclear what OCP is referring to in the sentence above cited again: “However, this reviewer has been unable to find where the information request for laboratory information was ever forwarded to the sponsor or where it was ever received.”

OCP noted in their review on page 24 “the dose and time dependent hepatotoxicity observed with oral administration.” Based on OCP’s review of the pharmacological data, On page 37, OCP noted: “The TQT study employed higher doses than would be used clinically 15 mg - 20 mg BID and the medical reviewer was informed of the possible increased bilirubins.” It is not clear what OCP means by “possible increased bilirubins.” Dr. Levin meticulously reviewed the relevant liver function tests in the entire clinical database and uncovered no evidence for DILI.

In contrast to the data that we reviewed of sublingual asenapine in generally healthy adult psychiatric patients, based on OCP’s review, I concur with the conclusions of Drs. Kavanaugh and Baweja (page 226 of the OCP review) that exposure in patients with any degree of hepatic impairment should be avoided. These safety precautions are addressed in draft labeling including advising that asenapine should be avoided in patients with any impairment of hepatic function. OCP found that there appears to be a narrow safety margin between therapeutic and potential hepatotoxic doses of asenapine in adolescents, as well as for elders. I concur and agree with OCP’s labeling language.

While OCP has continued to express concern regarding the risk of elevated transaminases and there were several outliers with enzymes greater than or equal to 3XULN coupled with Bilirubin levels greater than or equal to 2XULN, in the controlled trials and in open label extensions. Some of these enzyme elevations were associated with discontinuation from the studies. I do not think, however, that the data supports raising elevated transaminases to the levels of the “Warnings and Precautions” section of labeling as proposed by the sponsor unless there is data to support this.

Hematological

In the Clinical and OCP reviews, no confirmed actual cases of agranulocytosis had been identified. On page 437 of the OCP review, no actual lab values were provided, however, extrapolations to possible ANC values below 500 were indicated with dotted lines. In a letter dated 14 May 2008, however, the sponsors stated that 3 patients exposed to asenapine had been found with serum ANC < 500. The sponsors proposed that at least two of these cases may have been laboratory errors. Based on the uncertainty of these findings, I am inclined to recommend that we wait until we receive more definitive data on the risk of agranulocytosis before this be added into the Warnings and precautions section of proposed labeling.

In *Harrison’s Textbook of Medicine*, Drs. Rapoport and Bunn state: “The term *aplastic anemia* should be restricted to conditions in which a markedly hypocellular bone marrow results in pancytopenia (anemia, neutropenia, and thrombocytopenia). At the 12 May

2008 “OCP Office Level Briefing for the Drug Asenapine, NDA 22117”, Dr. Kavanaugh presented a slide that he thought identified the occurrence of aplastic anemia. Two subjects were identified (page 437). The data for subject 1 demonstrated a hematocrit above 25%, a White Blood Cell count (WBC) above 3 times and platelet counts at least 350,000/mL are not consistent with aplastic anemia. Nor are the laboratory values of hematocrit 34%, WBC at least $3.5 \times 10^3/\text{mm}^3$ and platelet counts greater than 200,000/mL.

Weight gain

Approximately 5% of asenapine treated subjects gained clinically significant weight (> 7% of body weight) compared to 2% of placebo treated subjects over 3 to 6 weeks of short-term treatment. Weight gain with a potential risk of potentially medically serious metabolic syndrome is an adverse event of clinical significance for asenapine.

Seizure

The risk of seizure associated with asenapine use was below 1% in the safety database. In the 6-week schizophrenia trials, there were no seizures reported in the asenapine 5 mg BID or 10 mg BID groups. Two seizures were reported in the application, one in the < 5 mg BID asenapine group and one seizure was reported in the olanzapine group. In the bipolar trials, over 3 weeks at high doses, one seizure occurred in the asenapine treated and 1 occurred in the olanzapine treated patients. I have no objection to the sponsors’ proposed language.

Hyperprolactinemia

Dr. Levin in his review reported that mean change from baseline in prolactin levels (ug/L) were similar in placebo (-3.4) and asenapine treated patients (-3.2) compared to elevations in the other treatment groups: risperidone (21.2) haloperidol (2.5) and olanzapine (0.4). Mean serum prolactin levels were more reduced in the asenapine treatment groups than in the placebo group. In comparison, the levels were highly elevated in the risperidone and less elevated in the haloperidol and olanzapine groups. As expected, however, asenapine elevates prolactin in many subjects, though less than is seen with risperidone. There were 19.3% of placebo and 44.4% of asenapine treated patients who changed from low baseline to high at endpoint levels. As a result, the sponsor sent us draft labeling with hyperprolactinemia in the “Warnings and Precautions” section.

EPS

Symptoms of EPS appeared generally similar to the frequencies observed with other atypical antipsychotic drugs and less than seen with first generation antipsychotic drugs and will be in labeling accordingly.

5.2.4 Use in Elderly Patients

Hepatic function tends to become less robust with age. In view of the clinical pharmacological risk of reduced metabolism with hepatic impairment of any degree and the seriousness of syncope, dizziness and the potential for accidental injury, I concur with OCP that asenapine should be used with caution, if at all, in elderly patients in addition to avoidance in patients with any degree of hepatic dysfunction.

5.2.5 Controlled Substances Consultation

Dr. Katherine Bonson noted in her CSS consult that the proposed language for the Abuse and Dependence section is not adequately supported scientifically to justify its inclusion.

There is no issue pertaining to abuse identified by CSS that would preclude an approvable action.

5.2.6 Risk: Benefit Evaluation

The morbidity and mortality of such a serious disorder of the major psychoses, schizophrenia and bipolar disorder, is well established. Drugs that provide advantages over those on the market are needed. Overall, the safety profile is typical generally for the olanzapine-like atypical antipsychotic drugs with out the greater efficacy of olanzapine. I concur with Dr. Levin (page 5) that the serious AEs that were most likely related to asenapine were syncope, akathisia, somnolence, rhabdomyolysis, bradycardia, and dystonia. In terms of the risk: benefit analysis, there are numerous atypical drugs on the U.S. market. Given the serious issues raised by Pharmacology/Toxicology and OCP that have emerged without resolution since the GRMP deadline of 14 May 2008 for the CDTL memorandum (filed to meet the GRMP deadline while waiting for the OCP review to be completed necessitating this addendum), asenapine does not appear to offer unique advantages over numerous other atypical antipsychotic drugs on the market. I think that adverse drug reactions such as syncope, hypotension, akathisia and weight gain detract from the risk-benefit profile compared to other drugs on the market. While the efficacy compares adequately with some representative antipsychotic drugs, the efficacy of asenapine is not clearly superior to olanzapine, which has demonstrated superior efficacy to other antipsychotic drugs in research such as the CATIE study².

5.2.7 Conclusions Regarding the Safety of Asenapine

Based on Dr. Levin's detailed clinical review, the short-term clinical adverse drug reaction profile for the sublingual formulation of asenapine in the treatment of schizophrenia and the manic or mixed episodes of bipolar disorder appears to be similar generally to that observed with similar atypical antipsychotic drugs used in the treatment of schizophrenia and bipolar disorder. Orthostatic hypotension and dizziness (particularly with initiation of exposure), as well as sedation, akathisia, weight gain with

² Lieberman JA et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New Engl J Med* 2005 Sep 22;353(12):1209-23.

potential for elevations of serum glucose and lipids, appear to be a clinically germane risk with chronic use. Further data will be needed from the sponsors on adverse drug reactions with a dose-response.

At present, while additional clinical safety data will be requested from the sponsors, there appears to be no major clinical safety issues precluding an approvable action. Nonetheless, there are grave safety issues that must be addressed in terms of metabolism and elimination as outlined by clinical pharmacology. Moreover, the risk of carcinogenicity and reproductive toxicology needs also to be adequately addressed to ensure that asenapine would be safe for clinical use.

5.3 Clinical Sections of Labeling

The first draft of labeling has been achieved by Dr. Laughren.

6.0 WORLD LITERATURE

The sponsor provided certification that they reviewed the literature and found no relevant articles that would adversely affect conclusions about the safety of asenapine in the treatment of schizophrenia or bipolar disorder. Dr. Levin reviewed the literature and confirmed the sponsor's findings.

7.0 POST-MARKETING RISK MANAGEMENT PLAN

The sponsors submitted a usual plan for pharmacovigilance activities. Mary Dempsey, of Office of Surveillance and Epidemiology, in her review (dated 25 February 2008) concluded that although "the sponsor's submission does not constitute a formal Risk Minimization Action Plan (RiskMAP), the potential risks of asenapine use are "consistent and comparable" with those of already approved atypical antipsychotic drugs and that no additional safety concerns were identified. It is premature to explore a post-marketing plan further.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC)

It was decided by Dr. Laughren that there was no need to take this application to the PDAC in terms of the clinical data, which are consistent with a typical second generation antipsychotic drug.

9.0 DSI INSPECTIONS

As summarized by Dr. John Lee (4 June 2008), inspections were conducted at two US and three non-US sites. The inspectors found that the sites adhered generally to the applicable statutory requirement and FDA regulations governing the conduct of clinical investigations and the protection of human subjects as documented to be acceptable to support the validity of the data.

10.0 FOREIGN REGULATORY ACTIONS

To the best of my knowledge, asenapine is not approved anywhere at this time for the acute treatment of schizophrenia or bipolar disorder.

11.0 PHASE 4 COMMITMENTS

It is premature to discuss Phase IV commitments, including long-term data, in view of the outstanding Pharm/Tox and OCP requirements to be considered for approval.

12.0 LABELING AND APPROVABLE LETTER

We will include labeling in the PLR version of labeling with the approvable action letter, unless Dr. Temple finds that a nonapproval action is indicated given the outstanding requirements. Dr. Laughren completed draft asenapine labeling.

13.0 CONCLUSIONS AND RECOMMENDATIONS

As an OND NME NDA pilot project, we have attempted to provide a complete review package with issues that arose during review as fully addressed as possible to the Division Director by 14 May 2008. By GRMP the entire package was due to the Office Director his package by 7 June 2008. Issues particular to this application stemming from a paucity of information with respect to critical OCP and Pharm/Tox review areas arose that prevented the ability to meet the deadline and engage in labeling discussions. The GRMP deadline of June 7th target was intended to provide our Office Director adequate time for regulatory processing by the PDUFA action date of 30 June 2008. In terms of correction of errata in my review dated 14 May 2008, I had erroneously written that 7 June 2008 was the GRMP action date. That was incorrect. 7 June 2008 was the GRMP deadline to complete the full package for the Office Director in the absence of the unusual obstacles that arose. The action date is 30 June 2008.

In order to be eligible for approval, the Office of Clinical Pharmacology requires from the sponsors the following. From a clinical pharmacology standpoint the sponsors have not adequately ascertained what moieties are circulating in plasma. In the mass balance study, the plasma concentrations of ¹⁴C asenapine (equivalents) greatly exceed that of asenapine (cold drug) as well as the metabolites measured. The moieties looked for are asenapine, desmethyiasenapine, and the N-oxide. The total AUC counts for total radioactivity (¹⁴C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. Therefore, there is a vast amount of circulating material in plasma that has not been ascertained. At least 96.6% of the circulating species have not been identified. This is a matter for concern and we require an explanation for this vast gap in plasma between circulating radioactivity and moieties circulating and identified. Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose was recovered with 49 % in the urine and 39 % in the feces. This is a generalized presentation of assessing the elimination pathways of the radioactivity. Specifically, what is known is that direct glucuronidation accounts for 12-21% of the dose. Furthermore, 5-16 % of the dose is that of the unchanged drug, asenapine. When these two percentages of moieties are added, only 17–37 % of the dose is represented. Therefore, 63-83 % of the dose has not been adequately characterized for the primary elimination pathways. The characterization of the metabolism moieties circulating in plasma and of the human elimination pathways must be clearly delineated and properly addressed by the sponsors.

Pharmacology/Toxicology requires the following from the sponsors before approval can be considered. In order to accurately describe the carcinogenic potential of asenapine in the labeling, full histopathological examination of all animals in the low and medium doses in the rat carcinogenicity study, and of all low and medium dose females in the mouse carcinogenicity study, should be performed prior to NDA approval. As communicated to the sponsors on 8 April 2008, in order to validly compare results across groups, the originally examined slides from these studies should be re-examined in concert with the newly evaluated slides by a single pathologist, and subjected to peer review. These conclusions of Pharmacology/Toxicology were confirmed twice by the Executive CAC. In addition, Pharmacology/Toxicology recommends that the sponsors perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity or reduce the specifications for (b) (4) to the ICHQ3A9R) qualification limit (b) (4)

While an approvable has not been precluded by CMC issues, the following need to be submitted. The sponsors must provide the levels of amorphous material in all the clinical batches including the batches used in BE studies (Batch #: AN and AT). The sponsors provide information on the in-process controls and the manufacturing critical process parameters that control the amorphous material content in the final dosage form. The sponsors provide information in tabular form about the physico-chemical properties of the amorphous material, (b) (4) (i.e., solubility, stability, etc.). Include either a release and shelf-life control of the amorphous content in the drug product

through specification or a justification from for not including such control based on ICH Q6A.

In terms of clinical safety, major concerns stem from the risk of hypotension, syncope, dizziness, sedation (combining all related terms into one term), including sequelae such as accidental injury, as well as for akathisia and weight gain with potential for the development of metabolic syndrome with asenapine use. We will also request in the absence of complete data on terms that we think are reasonable to categorize adverse drug reactions, the sponsor should submit complete lists of AEs with percentages greater than 1% and at least twice placebo stratified by diagnostic category.

In terms of evaluation for risk of agranulocytosis, I would recommend that the sponsor submit more information regarding the three patients identified in their letter dated 14 May 2008, where the Absolute Neutrophil Count (ANC) was reported to be less than 500 cells per microliter. Please provide all clinical information on these three patients including the full sequence of laboratory and medical evaluations with time course of all hematological laboratory values, concomitant medication and co-morbid medical illnesses.

Dr. Levin is providing medical review of the clinical data in depth on the list of subjects with sent by OCP on 27 May 2008. Each case will be medically adjudicated by Drs. Laughren, Mathis, Levin, and I in a meeting on 16 June 2008.

The Division agreed to a deferral on pediatric studies in meeting minutes from the EOP2 27 April 2004.

Dr. Temple may decide to submit draft PLR labeling to the applicants when the action letter is issued if the action to be taken is an approvable. Consequently, Dr. Laughren has prepared draft labeling.

cc:

Orig NDA 22-117

ODE-I/R Temple

HFD-130

HFD-130/TLaughren/MMathis/GZornberg/RLevin/KKiedrow/BRosloff/

EChaleckaFranaszek/CTele/TOliver/SHardeman/PDavid

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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.**

/s/

Gwen Zornberg
6/12/2008 09:41:41 PM
MEDICAL OFFICER