CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-117s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-117

COMPLETE RESPONSE

Organon USA Inc.
Attention: Todd Paporello, Pharm.D., MBA
Associate Director & Liaison, Global Regulatory Affairs
56 Livingston Ave.
Roseland, NJ 07068

Dear Dr. Paporello:

Please refer to your new drug application (NDA) dated August 30, 2007, received August 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asenapine Maleate 5 mg and 10 mg Sublingual Tablets.

We acknowledge receipt of your submissions dated –

September 28, 2007	October 24, 2007	November 20, 2007	June 23, 2008
November 30, 2007	December 3, 2007	December 7, 2007	July 25, 2008
December 10, 2007	December 21, 2007	December 27, 2007	July 28, 2008
December 28, 2007	January 11, 2008	January 17, 2008	September 4, 2008
January 30, 2007	February 21, 2008	March 11, 2008	September 11, 2008
March 27, 2008	April 7, 2008	April 8, 2008	September 15, 2008
April 10, 2008	April 11, 2008	April 18, 2008	September 18, 2008
April 29, 2008	April 30, 2008	May 9, 2008	September 23, 2008
May 14, 2008	May 21, 2008	June 13, 2008	
June 20, 2008	June 23, 2008	June 20, 2008	

We also acknowledge receipt of your amendment dated August 29, 2008, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Pharmacology/Toxicology (Deficiencies in Carcinogenicity Studies)

Your submission dated August 29 2008, included the previously requested information on the rat and mouse carcinogenicity studies. Our review and evaluation of these data will be completed within the next cycle of the NDA.

Office of New Drug Quality Assessment

1. Provide levels of amorphous material in all the clinical batches, including the batches used in BE studies (Batch #AN and AT).

2. Provide information about 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 for not including such control based on ICH Q6A.

5. You have proposed to use a site in Veersemeer, The Netherlands for API manufacture and particle size reduction. You have not submitted any data to support the (b) (4) operation at this site. Please provide appropriate (b) (4) data to support the use of this site.

Labeling

Please submit revised draft labeling for the drug. Please review and make changes according to the recommendations contained in the enclosed printed labeling. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Request for Additional Information Regarding Clinical Data in NDA

As part of your response to this complete response action, we ask that you provide greater clarity on the number of patients exposed to asenapine and the extent of exposure in your updated database (see Safety Update above). We found it difficult to determine extent of exposure in your 12-27-07 safety update. Therefore, in your safety update submitted in response to this action letter, please provide a detailed enumeration of subjects and patients exposed to asenapine, including not only the new data but also all previous data for the entire program. In addition to an overall enumeration, we ask that you provide information broken out by dose and duration of exposure, including estimates of person-years of exposure for various relevant subgroups. We recognize that this may require estimation for certain studies that are still ongoing and unblinded. Please provide a list of these studies. We would be happy to respond to a proposal for an approach to characterizing asenapine exposure.

You refer to 5 cases of anemia and 1 case of thrombocytopenia in your program. Please provide case numbers, narratives, and complete information on hematology parameters for these patients.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Keith Kiedrow, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1924.

Sincerely yours,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

[FDA edits to labeling sent by sponsor 10 MARCH 2008. We have made numerous changes, and we have included bracketed comments to request additional information and changes. Please replace "bid" with "twice daily" throughout labeling. Please ensure that references to other sections of labeling are accurate.]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Tradename (asenapine) safely and effectively. See full prescribing information for Tradename.

Tradename (asenapine) sublingual tablets
Initial U.S. Approval: 200x

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSES
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Tradename is not approved for the treatment of patients with dementia-related psychosis. (5.1)

----------**INDICATIONS AND USAGE**----------
Tradename is an atypical antipsychotic indicated for:
- Acute treatment of schizophrenia in adults(1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults as monotherapy (1.2)

----------**DOSAGE AND ADMINISTRATION**----------
Schizophrenia: The recommended starting and target dose of Tradename is 5 mg sublingually twice daily. (2.1)
Bipolar disorder: The recommended starting dose of Tradename is 10 mg sublingually twice daily. The dose can be decreased to 5 mg twice daily if there are adverse effects. (2.2)
Administration: Tradename sublingual tablets should be placed under the tongue and left to dissolve completely; tablets should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration. (2.1, 2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------
Sublingual Tablets: 5 mg and 10 mg (3)

----------**CONTRAINDICATIONS**----------
None (4)

----------**WARNINGS AND PRECAUTIONS**----------
- *Cerebrovascular Adverse Events:* An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs. (5.2)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring. (5.3)
- *Tardive Dyskinesia*: Discontinue if clinically appropriate (5.4
- *Hyperglycemia and Diabetes Mellitus*: Monitor glucose regularly in patients with, and at risk for, diabetes (5.5)
- *Orthostatic Hypotension and Syncope:* Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients. (5.6)
- *QT Prolongation*: increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval (5.7)
- *Hyperprolactinemia:* Causes increases in prolactin levels, both acutely and chronically (5.8)
- *Seizures/Convulsions*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery (5.10)
- *Suicide*: The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients (5.12)

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (≥ 5%and at least twice the rate on placebo) were: sedation, dizziness, akathisia, weight increase, and oral hypoesthesia. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Organon USA Inc. at 1-800-631-1253 x 4535 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------**DRUG INTERACTIONS**----------
- **Centrally-Acting Drugs:** Use caution in combination with other drugs with CNS effects. Avoid alcohol. (7.1)
- **Antihypertensive agents:** Asenapine may add to the hypotensive effects of these agents when co-administered. (7.1)
- **Fluvoxamine (strong CYP1A2 inhibitor):** Coadministration causes modest increases in asenapine concentrations. (7.3)

[Please elaborate on the paroxetine/asenapine interaction and describe your understanding of the mechanism of this interaction which does not seem to be explained by an interaction at CYP2D6.]

----------**USE IN SPECIFIC POPULATIONS**----------
- **Pregnancy**: Tradename should be used only if the potential benefit justifies the potential risk. (8.1)
- **Nursing Mothers**: Breast feeding is not recommended. (8.3)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Renal Impairment**: No dose adjustment needed. (8.6)
- **Hepatic Impairment**: Asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C). (2.2, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: x/200x

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescr bing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Tradename (asenapine) is not approved for the treatment of patients with dementia-related psychosis [*see WARNINGS AND PRECAUTIONS* (5.1)].

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Tradename is indicated for the acute treatment of schizophrenia in adults. [*see CLINICAL STUDIES* (14.1)]. The physician who elects to use Tradename for extended periods in schizophrenia should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. [*see DOSAGE AND ADMINISTRATION* (2.1)]

1.2 Bipolar disorder

Tradename is indicated for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults. [*see CLINICAL STUDIES* (14.2)]. The physician who elects to use Tradename for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient [*see DOSAGE AND ADMINISTRATION* (2.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Usual Dose for Acute Treatment in Adults

The recommended starting and target dose of Tradename is 5 mg given twice daily. In controlled trials, there was no suggestion of added benefit with higher doses, but there was a clear increase in certain adverse reactions. The safety of doses above 10 mg twice daily has not been evaluated in clinical studies.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with Tradename should be maintained, it is generally recommended that responding patients be continued beyond the acute response.

2.2 Bipolar disorder

Usual Dose for Acute Treatment in Adults

The recommended starting dose of Tradename, and the dose received by 90% of the patients studied, is 10 mg given twice daily. In clinical trials, the starting dose for Tradename was 10 mg twice daily. On the second and subsequent days of the trials, the dose could be lowered to 5 mg twice daily, based on tolerability, but less than 10% of patients had their dose reduced. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long the bipolar patient treated with Tradename should be maintained, it is generally recommended that responding patients be continued beyond the acute response.

2.3 Dosage in Special Populations

[Please provide raw data for further review of risk factors referred to in your proposed labeling, (i.e., age, gender, race, or renal impairment status), before we reach a final judgment about this language.]

In a study of subjects with hepatic impairment who were treated with asenapine, there were increases in asenapine exposures, (compared to subjects with normal hepatic function), that correlated with the degree of hepatic impairment. In subjects with severe hepatic impairment, asenapine exposures, (on average), were 6-fold the concentrations of those in subjects with normal hepatic function, after a single dose of Tradename 5 mg. Thus, asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal impairment status. [*see USE IN SPECIFIC POPULATIONS* (8.4, 8.5, 8.6, 8.7) *and CLINICAL PHARMACOLOGY* (12.3)].

2.4 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia or bipolar mania from other antipsychotics to Tradename or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

3 DOSAGE FORMS AND STRENGTHS

- Tradename 5 mg tablets are round, white to off-white sublingual tablets, with “5” on one side.
- Tradename 10 mg tablets are round, white to off-white sublingual tablets, with “10” on one side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. Tradename is not approved for the treatment of patients with dementia-related psychosis [*see Boxed Warning*].

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Tradename was not marketed at the time these studies were performed. Tradename is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions (5.1)].

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS), has been reported in association with administration of antipsychotic drugs, including asenapine. Cases of NMS have been reported during asenapine treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia (TD)

A syndrome of potentially irreversible, involuntary, dyskinetic movements can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause TD is unknown.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, Tradename should be prescribed in a manner that is most likely to minimize the occurrence of TD. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the

smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of TD appear in a patient on Tradename**,** drug discontinuation should be considered. However, some patients may require treatment with Tradename despite the presence of the syndrome.

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including asenapine. In clinical trials of Tradename, the occurrence of any adverse event related to glucose metabolism was less than 1% in both the Tradename and placebo treatment groups**.** Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies, which did not include Tradename, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical

antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Orthostatic Hypotension, Syncope, and other Hemodynamic Effects

Tradename may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Syncope was reported in 0.2% and 0.3% (1/572, 1/379) of patients treated with therapeutic doses (5-10 mg twice daily) of Tradename, compared to 0.2% and 0% (1/503, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During clinical trials with Tradename, including long-term trials without comparison to placebo, syncope was reported in 0.5% (11/2251) of patients treated with Tradename.

Four normal volunteers in phase 1 studies treated with either intravenous or oral Tradename experienced hypotension, bradycardia, and sinus pauses. These spontaneously resolved in 3 cases, but the fourth subject received external cardiac massage. The risk of this sequence of hypotension, bradycardia, and sinus pause might be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. However, patients without a prior history of antipsychotic drug use might be at particular risk for these types of events.

Patients should be instructed about nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position. Tradename should be used with caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to

hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications); and (2) in the elderly. Tradename should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, respiratory or central nervous system depression (see Drug Interactions). Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.

5.7 QT Interval Prolongation

The effects of Tradename on the QT/QTc interval were evaluated in a dedicated QT study. This trial involved Tradename doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily and placebo, and was conducted in 151 clinically stable patients with schizophrenia, with electrocardiographic assessments throughout the dosing interval at baseline and steady state. There were placebo-subtracted increases from baseline in the QTc interval ranging from 5 to 10 msec. No patients treated with Tradename experienced QTc increases ≥60 msec from baseline measurements, nor did any patient experience a QTc of ≥500 msec. There were no reports of torsades de pointes or any other adverse reactions associated with delayed ventricular repolarization. Electrocardiogram (ECG) measurements were taken at various time points during the Tradename clinical trial program (5-10 twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for Tradename and placebo in these short-term trials.

The use of Tradename should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). Tradename should also be avoided in patients with a history of cardiac arrhythmias and in certain other

circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; and (3) presence of congenital prolongation of the QT interval.

5.8 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, TRADENAME elevates prolactin levels and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. **[We request that you include a statement here about any relevant animal carcinogenicity findings, once these data become available.]** Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

5.9 Seizures

Seizures were reported in 0% and 0.3% (0/572, 1/379) of patients treated with doses of 5 and 10 twice daily of Tradename, respectively, compared to 0% (0/503, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During

clinical trials with Tradename, including long-term trials without comparison to placebo, seizures were reported in 0.3% (6/2251) of patients treated with Tradename. As with other antipsychotic drugs, Tradename should be used with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

[We request that you combine the terms 'somnolence,' 'sedation,' 'hypersomnia,' and any other relevant terms under 'Somnolence' and provide the appropriate data. In addition, please provide these data by dose (5 BID and 10 BID), for the Schizophrenia trials.]

5.10 Potential for Cognitive and Motor Impairment

Somnolence was reported in patients treated with Tradename [*see ADVERSE REACTIONS* (6.1)]. In short-term, placebo-controlled schizophrenia trials of therapeutic asenapine doses (5 mg and 10 mg twice daily, somnolence was reported in **[data to be determined]** of patients, respectively. In short-term, placebo-controlled bipolar mania trials of therapeutic doses (5-10 mg twice daily), somnolence was reported in **[data to be determined]** of patients on Tradename compared to **[TBD]** of placebo patients, respectively. During clinical trials with Tradename, including long-term trials without comparison to placebo, somnolence was reported in **[TBD]** of patients treated with Tradename.

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that Tradename therapy does not affect them adversely.

[We request that you specify the adverse events potentially related to body temperature dysregulation.]

5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. In the short-term placebo-controlled trials for both schizophrenia and acute bipolar disorder, the incidence of adverse reactions suggestive of body temperature increases was low (≤ 1%) and comparable to placebo. During clinical trial with Tradename, including long-term trials without comparison to placebo, the incidence of adverse reactions

suggestive of body temperature increases **[Please specify what these adverse reactions were]** was ≤ 1%. Appropriate care is advised when prescribing Tradename for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for Tradename should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia was reported in 0.2% and 0% (1/572, 0/379) of patients treated with therapeutic doses (5-10 mg twice daily of Tradename as compared to 0% (0/503, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During clinical trials with Tradename, including long-term trials without comparison to placebo, dysphagia was reported in 0.1% (2/2251) of patients treated with Tradename.

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Tradename is not approved for use in treating dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia [*see also WARNINGS AND PRECAUTIONS* (5.1)].

5.14 Use in Patients with Concomitant Illness

Clinical experience with Tradename in patients with certain concomitant systemic illnesses is limited [*see CLINICAL PHARMACOLOGY* (12.3)].

Tradename has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with Tradename, caution should be observed in cardiac patients [*see WARNINGS AND PRECAUTIONS* (5.6)].

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions profile

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis [See BOXED WARNING and WARNINGS and PRECAUTIONS (5.1 and 5.2)]
- Neuroleptic Malignant Syndrome (NMS) [see WARNINGS AND PRECATIONS (5.3)]
- Tardive Dyskinesia *[see WARNINGS AND PRECAUTIONS (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see WARNINGS AND PRECAUTIONS (5.5)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.6)]*
- *QT Prolongation [see WARNINGS AND PRECAUTIONS (5.7)]*
- *Hyperprolactinemia [see WARNINGS AND PRECAUTIONS (5.8)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.10)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.11)]*
- Suicide [see WARNINGS AND PRECAUTIONS (5.12)]
- Dysphagia [see WARNINGS AND PRECAUTIONS (5.13)]

- Use in Patients with Concomitant Illness [see WARNINGS AND PRECAUTIONS (5.14)]

The information below is derived from a clinical trial database for asenapine consisting of over 3350 patients and/or normal subjects exposed to one or more sublingual doses of asenapine. Of these subjects, 1953 (1480 in schizophrenia and 473 in acute bipolar mania) were patients who participated in multiple-dose effectiveness trials of therapeutic doses (5 to 10 mg twice daily, with a total experience of approximately 611 patient-years. A total of 486 asenapine-treated patients was treated for at least 24 weeks and 293 asenapine-treated patients had at least 52 weeks of exposure.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation. The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2 Clinical Studies Experience

Adult Patients with Schizophrenia

The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of three 6-week fixed-dose trials and one 6-week flexible-dose trial) in which sublingual asenapine was administered in doses ranging from 5 to 10 mg twice daily.

Adverse Events Associated with Discontinuation of Treatment

A total of 9% of TRADENAME-treated subjects and 10% of placebo subjects discontinued due to adverse events. The most common and likely drug-related adverse events associated with discontinuation in subjects treated with TRADENAME (rates at least 1% and at least twice the placebo rate) were **[Please identify these events and include here, along with discontinuation rates.]**.

Adverse Reactions Occurring at an Incidence of 2% or More in Tradename-Treated Schizophrenic Patients

Adverse reactions associated with the use of Tradename (incidence of 2% or greater, rounded to the nearest percent, and Tradename incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 1.

[For the ≥ 2%Tables 1 and 2, we request that you combine the various EPS terms (refer to examples in the footnote below the table) under 'Extrapyramidal Symptoms.' Similarly, please combine 'sedation,' 'somnolence,' hypersomnia, and any other relevant term under the term 'Somnolence.' For Table 1, we request that you present adverse reactions data by fixed-dose groups.]

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of TRADENAME® in 6-Week Trials – SCHIZOPHRENIA

System Organ Class/ Preferred Term	**Placebo N= 503**	**Asenapine 5 mg BID N= TBD**	**Asenapine 10 mg BID N= TBD**
***Extrapyramidal symptoms** (excluding Akathisia)	TBD	TBD	TBD
Akathisia	3%	4%	12%
Somnolence: [combine sedation, somnolence, hypersomnia, etc.]	TBD	TBD	TBD
Weight gain	<1%	2%	2%
Dizziness	5%	7%	3%
Hypoesthesia, oral	1%	6%	7%
Hypersalivation	0	< 1%	4%

*Extrapyramidal symptoms should include the following (and any other relevant AE term): dystonia, dyskinesia, rigidity, 'Parkinsonism' (and all examples of parkinsonism), extrapyramidal disorder, movement disorder, (excluding akathisia)

Dose-Related Adverse Events

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from three trials in patients with schizophrenia comparing two fixed doses (5, 10 mg BID) of TRADENAME® to placebo. **[Please list the dose-related adverse events here.]**

Adult Patients with Bipolar Mania

The following findings are based on the short-term placebo-controlled premarketing trials for bipolar mania (a pool of two 3-week flexible-dose trials) in which sublingual asenapine was administered in doses ranging from 5 to 10 mg twice daily.

Adverse Events Associated with Discontinuation of Treatment

Approximately 10.0% (38/379) of TRADENAME®-treated patients in short-term, placebo-controlled trials discontinued treatment due to an adverse event, compared with about 6% (12/203) on placebo. The most common and likely drug-related adverse events associated with discontinuation in subjects treated with TRADENAME (rates at least 1% and at least twice the placebo rate) were **[Please identify these events and include here, along with discontinuation rates.]**.

Adverse Reactions Occurring at an Incidence of 2% or More Among Tradename-Treated Bipolar Patients

Adverse reactions associated with the use of Tradename (incidence of 2% or greater, and Tradename incidence greater than placebo) that occurred during acute therapy (up to 3-weeks in patients with bipolar mania) are shown in Table 2.

[We request that you present the AE data as outlined for table 1 above (with the exception that there will be a single asenapine flexible-dose group).]

Table 2: Common Treatment-Emergent Adverse Reactions Associated with the Use of Tradename in Bipolar Mania

Preferred Term	Tradename* (N=379)	Placebo (N=203)
Somnolence	(TBD)	(TBD)
Dizziness	11%	3%
**Extrapyramidal symptoms	(TBD)	(TBD)
Akathisia	4%	3%
Weight increased	5%	1%
Hypoesthesia oral	5%	1%
Hypersalivation	2%	1%

Asenapine 5-10 mg BID with flexible dosing.

** Extrapyramidal symptoms should include: dystonia, dyskinesia, 'Parkinsonism' (and all examples of parkinsonism), extrapyramidal disorder, movement disorder, and rigidity, (excluding akathisia

[We request that you include the class labeling language for dystonia below.]

Dystonia

Antipsychotic Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities

Glucose

The effects on fasting serum glucose levels in the short-term schizophrenia and bipolar mania trials revealed no clinically important changes. [*see also WARNINGS AND PRECAUTIONS* (5.5)].

Lipids

[Please provide data on outliers, e.g., "In controlled Schizophrenia trials, the proportions of patients with elevations of total cholesterol ≥240 mg/dL and triglycerides ≥200 mg/dL were [TBD]% and [TBD]% for TRADENAME-treated patients, respectively, compared to [TBD]% and [TBD]% for placebo-treated patients, respectively. In controlled Mania trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were [TBD]% and [TBD]% for TRADENAME-treated patients, respectively, compared to [TBD]% and [TBD]% for placebo-treated patients, respectively."]

During short-term clinical trials with Tradename, no mean changes from baseline on lipid metabolism were observed.

Transaminases

Transient elevations in serum transaminases (primarily ALT) were somewhat more common in treated patients. The proportions of patients with transaminase elevations (ALT) > 3 times the upper limit of the normal reference range in the short-term placebo-controlled trials of Tradename at therapeutic doses (5-10 mg twice daily in patients with schizophrenia or bipolar mania were 3.3% and 2.5% (18/539, 8/324), respectively, for patients treated with Tradename compared to 1.9% and 0.6% (9/469, 1/165), respectively, in the placebo patients. No cases of more severe liver injury were seen.

Prolactin

Increases in the number of reports of markedly abnormal (4 times the upper limit of normal) prolactin levels (4.5% (24/537) and 2.2% (7/313), respectively, were seen for asenapine-treated patients compared to placebo (1.1% (5/469) and 0.6% (1/158)) in the short-

term schizophrenia and bipolar mania trials. During clinical trials with Tradename, including long-term trials without comparison to placebo, increases in the number of reports of markedly abnormal (4 times the upper limit of normal) prolactin levels (5.4% (115/2116)) were seen [*see also WARNINGS AND PRECAUTIONS* (5.8)].

[Move the weight gain statement to warnings next to hyperglycemia.]

Weight Gain

In 6-week trials in schizophrenia, the mean weight gain for Tradename and placebo patients was 1.1 kg vs. 0.1 kg, respectively. The proportion of patients with a weight gain of ≥7% was 4.9% for Tradename compared to 2.0% for placebo. In 3-week trials in mania, the mean weight gain for Tradename and placebo patients was 1.3 kg vs. 0.2 kg, respectively, and the proportion of patients with a weight gain of ≥7% was 5.8% for Tradename compared to 0.5% for placebo. During clinical trials with Tradename, including long-term trials without comparison to placebo, the mean weight gain for Tradename-treated patients was 1.0 kg. The proportion of patients with a weight gain of ≥7% of body weight was 10.4% for Tradename.

Other Adverse Reactions Observed During the Premarketing Evaluation of Asenapine

[Please prepare a list of plausibly drug-related adverse reactions and other findings (laboratory, etc.) that were reported but not described elsewhere in labeling, and organize by body system for this section. You may include the 4 events you have already identified for this section, i.e., rhabdomyolysis, idiosyncratic drug reaction (this would need to be described), cardiac failure, and hyponatremia. Do not include implausible events, trivial events, and events common in any population.]

Following is a list of MedDRA terms that reflect adverse reactions as defined in *ADVERSE REACTIONS (6.1)* reported by patients treated with sublingual asenapine at multiple doses ≥5 mg/twice daily during any phase of a trial within the database of adult patients. The events listed are those that could be of clinical importance, as well as events that are plausibly

drug-related on pharmacologic or other grounds. Events already listed in other parts of *ADVERSE REACTIONS (6)*, or those considered in *WARNINGS AND PRECAUTIONS (5)* or *OVERDOSAGE (10) are not in*cluded. Although the reactions reported occurred during treatment with asenapine, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

7 DRUG INTERACTIONS

The risks of using Tradename in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of Tradename, caution should be used when it is taken in combination with other centrally acting drugs or alcohol. Patients should be advised to avoid alcohol while taking Tradename.

Because of its alpha adrenergic antagonism with potential for inducing hypotension, Tradename can [enhance] the effects of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect Tradename

Asenapine is cleared predominantly through direct glucuronidation and the CYP1A2 isoenzyme system. The potential effects of inhibitors of several enzyme pathways on asenapine clearance were studied.

Paroxetine

The effect of 20 mg once daily dosing of paroxetine (a CYP2D6 inhibitor) on asenapine concentration(5 mg twice daily) was studied in 26 healthy subjects. The exposure of asenapine

was decreased by 10%. Thus, asenapine does not appear to be cleared by CYP2D6. [*see DRUG INTERACTIONS* (7.2)].

Fluvoxamine

In vitro studies suggest that CYP1A2 is the most important CYP450 enzyme in the metabolism of asenapine. Co-administration of a low dose (25 mg twice daily) of fluvoxamine (a strong CYP1A2 inhibitor) in a cross-over study in 26 healthy male subjects resulted in a 29% increase in asenapine exposure; the full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations: such co-administration should be done cautiously.

Imipramine

Co-administration of a single 75 mg dose of imipramine (a CYP1A2/2C19/3A4 inhibitor) and a single 5 mg dose of asenapine in a cross-over study in 24 healthy subjects resulted in modestly increased maximum plasma concentrations of asenapine (17%). This interaction does not require a dosage adjustment.

Cimetidine

Co-administration of 800 mg twice daily of cimetidine (a CYP3A4/2D6/1A2 inhibitor) in a cross-over study in 12 healthy male subjects had no effect on the plasma concentrations of asenapine after a single dose of 5 mg.

Carbamazepine

Co-administration of a single dose of asenapine 5 mg after treatment with carbamazepine 200 mg twice daily (a CYP 3A4 inducer) in 24 healthy male subjects resulted in

a 16% decrease in asenapine exposure. The induction effect could be more pronounced if higher doses of carbamazepine were used.

Valproic acid

Direct glucuronidation is a primary metabolic pathway for asenapine. Co-administration of 500 mg twice daily of valproic acid (a glucuronyl transferase inhibitor) in 24 healthy male subjects did not have an effect on asenapine plasma concentrations when asenapine was administered as a single 5 mg dose. Valproic acid decreased both the AUC and C_{max} of asenapine glucuronide by 85%.

7.2 Potential for Tradename to Affect Other Drugs

[Please include data on drug interactions with ethanol and other CNS-active drugs.]

Coadministration with CYP2D6 Substrates

[Please elaborate on the paroxetine/asenapine interaction and describe your understanding of the mechanism since it does not seem to be explained by an interaction at CYP2D6.]

In vitro studies indicate that asenapine weakly inhibits CYP2D6.

Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg BID decreased the DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg QD decreased the DX/DM ratio to 0.032. Thus, Tradename appears to be a weak inhibitor of CYP2D6. Nevertheless, co-administration of Tradename with drugs that are predominantly metabolized by CYP2D6 should be done cautiously.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Asenapine was not teratogenic in reproduction studies in rats and rabbits at i.v. 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 b.i.d. 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 i.v. 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 BID given sublingually on a mg/m^2 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.

There are no adequate and well-controlled studies in pregnant women and asenapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 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 Tradename should not breast feed.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

Of the approximately 2250 patients in premarketing clinical studies of Tradename, 1.1% (25) were 65 years of age or over. Multiple factors that might increase the pharmacodynamic response to Tradename, causing poorer tolerance or orthostasis, could be present in elderly patients, and these patients should be monitored carefully.

Elderly patients with dementia-related psychosis treated with Tradename are at an increased risk of death compared to placebo. Tradename is not approved for the treatment of patients with dementia-related psychosis. [*see Boxed Warning*].

8.5 Renal Impairment

The exposure of asenapine following a single dose of 5 mg was similar among subjects with varying degrees of renal impairment and subjects with normal renal function. [*see CLINICAL PHARMACOLOGY* (12.3)].

8.6 Hepatic Impairment

In a study of subjects with hepatic impairment who were treated with asenapine, there were increases in asenapine exposures, compared to subjects with normal hepatic function, that correlated with the degree of hepatic impairment. After a single dose of Tradename 5 mg in subjects with severe hepatic impairment, asenapine exposures were on average 6 times the concentrations of those in subjects with normal hepatic function. Thus, asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C). [*see DOSAGE AND ADMINISTRATION* (2.3) and *CLINICAL PHARMACOLOGY* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Tradename is not a controlled substance.

[We have edited the language regarding abuse and dependence. The rodent ICSS study does not directly evaluate the abuse potential of asenapine. Thus, the study does not support the proposed statement in the label concerning the lack of abuse potential of asenapine in rats. The statement in the label concerning the lack of drug-seeking behavior in clinical trials has not been adequately evaluated to support its inclusion.]

9.2 Abuse and Dependence

Asenapine has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance or physical dependence. Thus, it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs that they are misusing or abusing asenapine (e.g., drug-seeking behavior, increases in dose).

10 OVERDOSAGE

Human Experience

In premarketing clinical studies, involving more than 3350 patients and/or healthy subjects, accidental or intentional acute overdosage of Tradename was identified in 3 patients. Among these few reported cases of overdose, the highest estimated ingestion of Tradename was 400 mg. Reported adverse reactions at the highest dosage included agitation and confusion.

Management of Overdosage

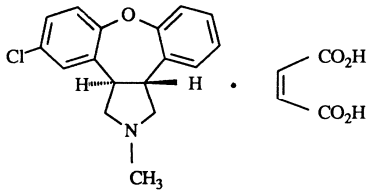
No specific information is available on the treatment of overdose with Tradename. There is no specific antidote to Tradename. The possibility of multiple drug involvement should be considered. An electrocardiogram should be obtained and management of overdose should

concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of Tradename-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

Tradename is a psychotropic (psychopharmacologic) agent that is available for sublingual administration. Asenapine belongs to the class dibenzo-oxepino pyrroles. The chemical designation is (3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1). Its molecular formula is $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ and its molecular weight is 401.84 (free base: 285.8). The chemical structure is:



Asenapine is a white to off-white powder.

Tradename is supplied for sublingual administration in fast dissolving tablets containing 5 or 10 mg asenapine; excipients include gelatin and mannitol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of asenapine is unknown. It has been suggested that the efficacy of asenapine is mediated through a combination of antagonist activity at D_2 and 5-HT_{2A} receptors. Actions at other receptors e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_6, 5-HT_7, D_3, and α_2-adrenergic receptors, may contribute to the clinical effects of asenapine.

12.2 Pharmacodynamics

Asenapine exhibits high affinity for dopamine D_2, D_3, D_4, and D_1 receptors (Ki values of 1.3, 0.42, 1.1, and 1.4 nM), serotonin 5-HT_{1A}, 5-HT_{1B} , 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6 and 5-HT_7 receptors (Ki values of 2.5, 4.0, 0.06, 0.16, 0.03, 1.6, 0.25, and 0.13 nM), α_1 and α_2-adrenergic receptors (Ki values of 1.2 and 1.2 nM), and H_1 receptors (Ki value 1.0 nM), and moderate affinity for H_2 receptors (Ki value of 6.2 nM). In *in vitro* assays asenapine acts as an antagonist at these receptors. Asenapine has no appreciable affinity for muscarinic cholinergic receptors (e.g., Ki value of 8128 nM for M_1).

12.3 Pharmacokinetics

Following a single 5 mg dose of Tradename, the mean Cmax was approximately 4 ng/ml, which was observed at a mean tmax of 1 hr. The mean half-life was 21 hrs. The primary route for metabolism is direct glucuronidation. Asenapine is also metabolized significantly through the CYP1A2 system. With multiple-dose twice daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Absorption

Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35%. Increasing the dose from 5 to 10 mg BID (a two-fold increase) results in nonlinear (1.7 times) increases in both the extent of exposure and maximum concentration.

Eating and drinking should be avoided for 10 minutes after administration.

Distribution

Asenapine is rapidly distributed and has a large volume of distribution (approximately 150 – 200 L/Kg), indicating extensive extravascular distribution. Asenapine is highly bound (95%) to plasma proteins, including albumin and α1-acid glycoprotein.

Metabolism and Elimination

Direct glucuronidation and metabolism by the CYP1A2 isoenzyme system are the primary metabolic pathways for asenapine.

Asenapine is a high clearance drug with a clearance after intravenous administration of 52 L/h. In this circumstance, hepatic clearance is influenced primarily by changes in liver blood flow rather than by changes in the intrinsic clearance, i.e., the metabolizing enzymatic activity. Following an initial more rapid distribution phase, the terminal half life of asenapine is approximately 24 to 36 hours. Steady-state concentrations of asenapine are reached within 3 days of twice daily dosing.

After administration of a radioactive dose, about 88% of the dose was recovered; approximately 50% was recovered in urine, and 40% recovered in feces.

In a mass balance study, about 50 % of the circulating species in plasma have been identified. The predominant species was asenapine-N-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Unchanged asenapine appears to be the only active species. There are other non-identified metabolites which account for 32% of the circulating species.

Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Asenapine metabolites were not assessed for induction. Coadministration of asenapine with known inhibitors/substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies [*see DRUG INTERACTIONS* (7.0)].

Smoking

[Please provide clarifying data on the effect of smoking on asenapine clearance from the population pk analysis.]

A population pharmacokinetic analysis revealed that smoking, an inducer of CYP1A2, had no effect on the clearance of asenapine in smokers. In a cross-over study in 24 healthy male subjects who were smokers administered a single 5 mg sublingual dose, concomitant smoking had no effect on the pharmacokinetics of asenapine. The effect of smoking on asenapine clearance in non-smokers is unknown.

Food

A cross-over study in 26 healthy male subjects was performed to evaluate the effect of food on the pharmacokinetics of a single 5 mg dose of asenapine. Consumption of food one hour prior to sublingual administration decreased asenapine exposure by 20%; consumption of food 4 hours after sublingual administration decreased asenapine exposure by about 10%. This effect is probably due to increased hepatic blood flow. The food study was not conducted under true fasted conditions as the 'fasted' individuals were administered a 'liquid breakfast' and an 'isotonic sports drink' one hour prior to taking asenapine. Thus, the magnitude of the decrease in bioavailability may be larger when fed and truly fasted regimens are compared.

In clinical trials establishing the efficacy and safety of Tradename, patients were instructed to avoid eating for 10 minutes following sublingual dosing. There were no other restrictions with regard to the timing of meals in these trials [*see DOSAGE AND ADMINISTRATION* (2.1, 2.2)].

Water

In clinical trials establishing the efficacy and safety of Tradename, patients were instructed to avoid drinking for 10 minutes following sublingual dosing. The effect of water administration following 10 mg sublingual asenapine dosing was studied at different time points of 2, 5, 10, and 30 minutes in 16 healthy male subjects. The exposure of asenapine following administration of water 10 minutes after sublingual dosing was equivalent to that when water was administered 30 minutes after dosing. Reduced exposure to asenapine was observed following water administration at 2 minutes (19% decrease) and 5 minutes (10% decrease) [*see DOSAGE AND ADMINISTRATION* (2.1, 2.2)].

Special Populations

Hepatically Impaired Patients: The effect of decreased hepatic function on the pharmacokinetics of asenapine, administered as a single 5 mg sublingual dose, was studied in 30 subjects (8 each in those with normal hepatic function and Child-Pugh A and B groups, and 6 in the Child Pugh C group). There were increases in asenapine exposures, compared to subjects with normal hepatic function, that correlated with the degree of hepatic impairment. In subjects with severe hepatic impairment, asenapine exposures were on average 6 times the concentrations of those in subjects with normal hepatic function. Thus, asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C). [*see USE IN SPECIFIC POPULATIONS* (8.7) and *WARNINGS AND PRECAUTIONS* (5.14)*]*.

Renally Impaired Patients: The effect of decreased renal function on the pharmacokinetics of asenapine was studied in subjects with mildly (CLcr 51 to 80 mL/min; N=8), moderately (CLcr 30 to 50; N=8), and severely (CLcr less than 30 mL/min but not on dialysis; N=8) impaired renal function and compared to normal subjects (CLcr greater than 80 mL/min; N=8). The exposure of asenapine following a single dose of 5 mg was similar among subjects with varying degrees of

renal impairment and subjects with normal renal function. The exposure of desmethylasenapine is about 20 % lower in moderate and severe renally insufficient groups compared to normal subjects. Dosage adjustment based upon degree of renal impairment is not required. The effect of renal function on the excretion of other metabolites and the effect of dialysis on the pharmacokinetics of asenapine has not been studied [*see USE IN SPECIFIC POPULATIONS* (8.6)].

Geriatric patients:

[Please provide the pharmacokinetic data and metrics employed in the geriatric population analysis, as only an abbreviated study report, with no raw data, was submitted.]

On average, Cmax and AUC in the elderly (65-85 years of age) were 30-40% higher for asenapine compared to younger adults. When the range of exposures in the elderly was examined, the highest exposure for asenapine was 3-fold higher than the highest exposure in younger subjects.

Pediatric patients:

[Please provide the pharmacokinetic data and metrics employed in adolescents 12-17 years of age, as only an abbreviated report, with no raw, was submitted.]

Gender:

[Please provide the raw data for the population pharmacokinetic analysis.]

The potential difference in asenapine pharmacokinetics between males and females was not studied in a dedicated trial. In a population pharmacokinetic analysis, no significant differences between genders were observed..

Race:

[Please provide the raw data for the population pharmacokinetic analysis.]

In a dedicated study, the pharmacokinetics of Tradename were similar in Caucasian and Japanese subjects. In a population pharmacokinetic analysis, a small (about 14%) decrease in

clearance was observed in black patients compared to other patients. This difference requires no dose adjustments.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

[We acknowledge receipt of your submission dated August 29 2008 which included the previously requested information on the rat and mouse carcinogenicity studies. Complete review and evaluation of the data will be conducted in the next cycle of the NDA.]

Mutagenesis

The genotoxic potential of asenapine was tested in the *in vitro* bacterial reverse mutation assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assays in human lymphocytes, the *in vitro* sister chromatid exchange assay in rabbit lymphocytes and the *in vivo* micronucleus assay in rats. Asenapine was negative in these assays, except for an equivocal response in the chromosomal aberration assay. The weight of evidence suggests that asenapine lacks genotoxic potential.

Impairment of Fertility

Asenapine did not impair fertility in rats when tested at doses up to 11 mg/kg B.I.D. given orally. This dose is 10 times the maximum recommended human dose of 10 mg B.I.D. given sublingually.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of Tradename in the treatment of schizophrenia in adults was evaluated in three fixed-dose, short-term (6 week), randomized, double-blind, placebo-controlled trials of adult patients who met DSM-IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. In two of the three trials Tradename demonstrated superior efficacy to placebo. In a third trial, Tradename could not be distinguished from placebo, however, an active control in that trial was superior to placebo. Thus, this was a negative trial for Tradename.

In the two positive trials for Tradename**, t**he primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS), which assesses the symptoms of schizophrenia. The primary endpoint was change from baseline to endpoint on the PANSS total score. Effects on the Clinical Global Impression Improvement scale (CGI-I) were also examined. In both trials, Tradename 5 mg twice daily was superior to placebo on the PANSS total score and also on the CGI-I. In the trial that also included a 10 mg twice daily dose, the higher dose showed no added benefit compared to 5 mg twice daily and was, in fact, not significantly different from placebo. These data provide no basis for using a dose higher than 5 mg twice daily in schizophrenia. An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender or race.

14.2 Bipolar disorder

The efficacy of Tradename in the treatment of acute mania was established in two similarly designed 3-week, randomized, double-blind, placebo-controlled trials of adult patients who met DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS). Patients were also assessed on the Clinical Global Impression – Bipolar (CGI-BP) scale. In both trials, all patients randomized to Tradename were

initially administered 10 mg twice daily and the dose could be adjusted within the dose range of 5 to 10 mg twice daily from Day 2 onward based on efficacy and tolerability. Ninety percent of patients remained on the 10 mg twice daily dose. Tradename was superior to placebo on the change from baseline to Day 21 in YMRS total score and the CGI-BP Severity of Illness score (mania) in both studies. An examination of subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender or race.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tradename (asenapine) sublingual tablets are supplied as:

5 mg Tablets

Round, white to off-white sublingual tablets, with “5” on one side.

Child-resistant packaging		
Box of 60	6 blisters with 10 tablets	NDC 0052-0118-06
Hospital Unit Dose		
Box of 100	10 blisters with 10 tablets	NDC 0052-0118-90

10 mg Tablets

Round, white to off-white sublingual tablets, with “10” on one side.

Child-resistant packaging		
Box of 60	6 blisters with 10 tablets	NDC 0052-0119-06
Hospital Unit Dose		
Box of 100	10 blisters with 10 tablets	NDC 0052-0119-90

Storage

Store at 15° - 30° C (59° - 86° F) [*see* USP Controlled Room Temperature].

17.0 PATIENT COUNSELING INFORMATION

17.1 Tablet Administration

Firmly press and hold thumb button while pulling out tablet pack. Do not push tablet through tablet pack. Do not cut or tear tablet pack. Peel back colored tab. Gently remove tablet. Do not crush tablet.

To ensure optimal absorption, place the Tradename sublingual tablet under the tongue and allow it to dissolve completely. The tablet will dissolve in saliva within seconds. Do not swallow tablet. Do not eat or drink for 10 minutes after administration [*see DRUG INTERACTIONS* (7.10) and *CLINICAL PHARMACOLOGY* (12.3)]. Slide tablet pack into case until it clicks.

17.2 Interference with Cognitive and Motor Performance

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that Tradename therapy does not affect them adversely.

17.3 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially early in treatment, and also at times of re-initiating treatment or increases in dose.

17.4 Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Tradename. Patients should be advised not to breast feed if they are taking Tradename.

17.5 Concomitant Medication and Alcohol

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications since there is a potential for interactions. Patients should be advised to avoid alcohol while taking Tradename.

17.6 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Manufactured for Organon USA Inc.
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by Cardinal Health Ltd.
Swindon Wiltshire, SN5 8RU, UK

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/s/

Robert Temple

1/13/2009 10:00:10 AM