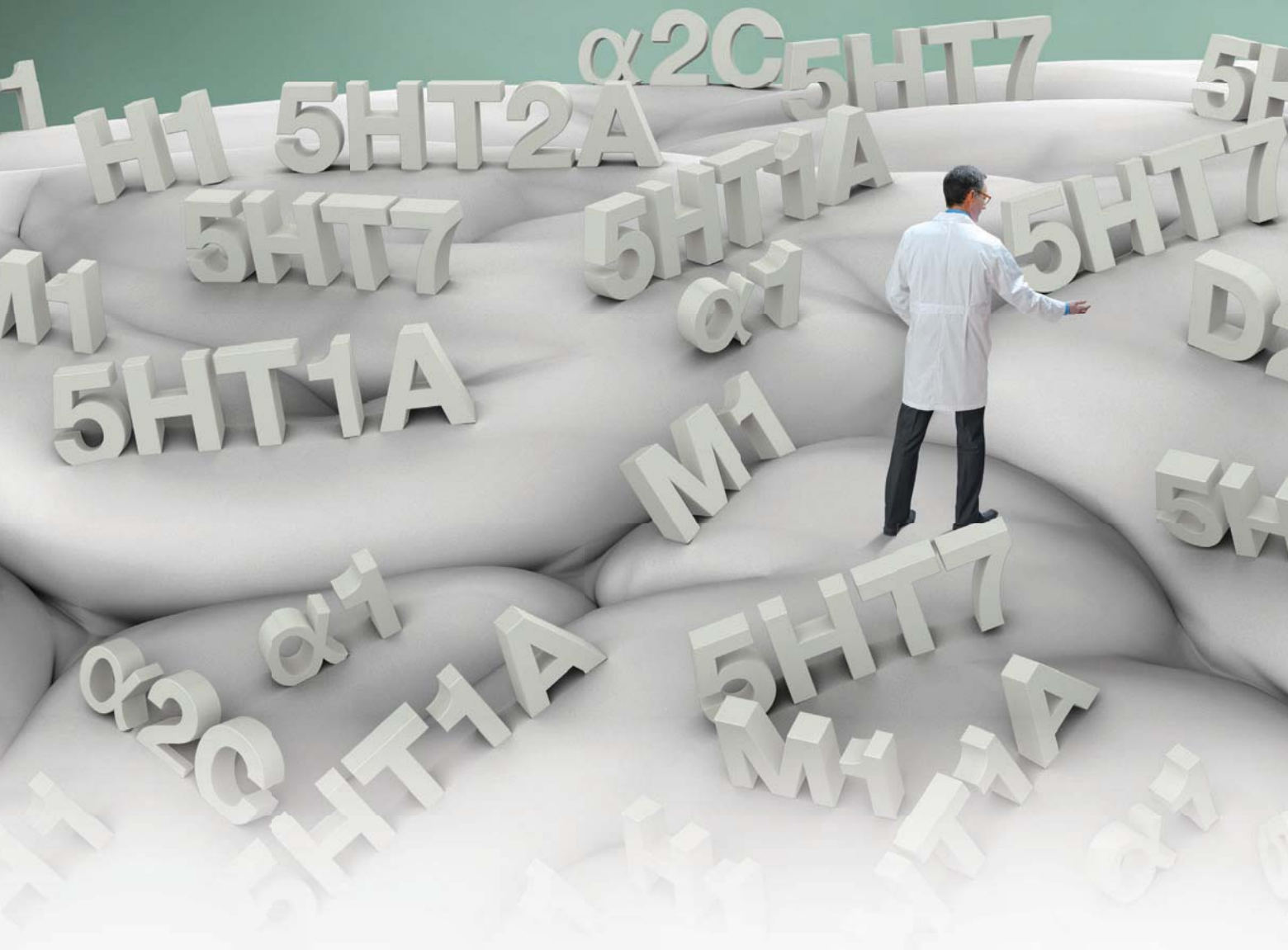
We are looking at D_2 and $5HT_{2A}$ receptor binding and beyond in the development of treatments for schizophrenia



Sepracor Inc., soon to become Sunovion Pharmaceuticals, Inc., is committed to ongoing research and development in schizophrenia. Sepracor is looking beyond receptor binding to learn more about this deeply complex disorder.

There is no one single cause for the many symptoms of schizophrenia, which is influenced by different genetic, environmental, developmental, and other factors. Research has shown that the pathology of schizophrenia is complex and may be associated with more than one receptor site and neurotransmitter in the brain.[1]

Researching the relationship between receptor binding and the pathophysiology of schizophrenia may help researchers better understand how patients are affected. At Sepracor, our goal is to gain new insights into this devastating illness to improve patient outcomes.

Reference: 1. Kim DH, Maneen MJ, Stahl SM. Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimension of schizophrenia. *Neurotherapeutics*. 2009;6:78-85.

Note: Sepracor Inc. is proud to announce that later this year we will be formally changing our name to Sunovion Pharmaceuticals, Inc. in the United States; this new name is a reflection of the combined vision resulting from Dainippon Sumitomo Pharma, Co., Ltd.'s acquisition of Sepracor in October 2009.

SUNOVION

PSYCHIATRY
BOARD REVIEW SERIES
THE KAUFMAN COURSES

NEW BOARD EXAM FORMAT FOR SEPTEMBER 2011

SPONSORED BY MONTEFIORE MEDICAL CENTER CREDIT DESIGNATED BY ALBERT EINSTEIN COLLEGE OF MEDICINE
Accreditation Statement: Albert Einstein College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

PART I AND CERTIFICATION COURSES

CLINICAL NEUROLOGY FOR PSYCHIATRISTS
David Myland Kaufman, MD

This intensive three-day weekend course, offered for the 39th year, is designed for psychiatrists in practice and in residency as an update and board preparation. Focusing on essential topics, the course uses lectures, an extensive syllabus, and the new edition of *Clinical Neurology for Psychiatrists*, David M. Kaufman (6th edition).

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 25 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

PART I COURSE
March 18-20, 2011 (NEW YORK)

CERTIFICATION COURSES
MAY 20-22, 2011 (NEW YORK)
or
July 22-24, 2011 (LOS ANGELES)

All Course Hours: 7:30 AM – 6:00 PM

PSYCHIATRY FOR PSYCHIATRISTS
Andrea J. Weiss, MD and David Myland Kaufman, MD

This two-day course will be a pre-test that complements standard psychiatry review courses and completes the review in *Clinical Neurology for Psychiatrists*. An expert group of faculty who are experienced and well-informed about modern psychiatry and test-taking strategies present essential information through a series of test-type questions utilizing an audience response system and using answers for discussions and explanations.

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 16 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

PART I COURSE
March 21-22, 2011 (NEW YORK)

CERTIFICATION COURSES
May 23-24, 2011 (NEW YORK)
or
July 25-26, 2011 (LOS ANGELES)

All Course Hours: 7:30 AM – 6:00 PM

MAINTENANCE OF CERTIFICATION COURSES

THE PSYCHIATRY RECERT COURSE
Andrea J. Weiss, MD and David Myland Kaufman, MD

This intensive two-day course designed for psychiatrists reviews the psychiatric information likely to appear on the recertification examination. It will cover current evidence-based treatments for psychiatric disorders, emphasizing clinical matters and advances in diagnosis and treatment. Presentation of the material will be in a mixed format, with both lecture and question-and-answer utilizing audience response system keypads.

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 14.5 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

NEW YORK
SUNY College of Optometry
Joseph and Roberta Schwarz Theater
33 West 42nd Street
(Between 5th and 6th Avenues)
New York, NY 10036
Friday, January 7 to Saturday, January 8, 2011
7:30 AM – 6:00 PM

THE CHILD AND ADOLESCENT PSYCHIATRY RECERT COURSE
Audrey Walker, MD, Andrea J. Weiss, MD and David Myland Kaufman, MD

This intensive one-day course designed for child and adolescent psychiatrists reviews material likely to be on the recertification examination and provides an update on the diagnosis and treatment of children and adolescents with psychiatric disorders. Presentations are given in a mixed format, with both lecture and question-and-answers utilizing an audience response system. Faculty discuss responses to questions and from there review the content.

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 7.5 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

NEW YORK
SUNY College of Optometry
Joseph and Roberta Schwarz Theater
33 West 42nd Street
(Between 5th and 6th Avenues)
New York, NY 10036
Sunday, January 9, 2011
7:30 AM – 6:00 PM

FOR MORE INFORMATION
• **Web site** Course Information or To Register: **www.cnfp.org**
• **Write:** CCME, 3301 Bainbridge Avenue, Bronx, NY 10467
• **E-mail:** cme@montefiore.org
• **Call:** 718-920-6674 • **Fax:** 718-798-2336

Symptoms of major depressive disorder (MDD) adapted from DSM-IV-TR[1]

DEPRESSED MOOD

CHANGE IN SLEEP

FEELINGS OF GUILT

LACK OF ENERGY

LOSS OF INTEREST

SADNESS

When depression takes over

NEW FOR MDD

Introducing Once-daily OLEPTRO™

Treat Her Depression With

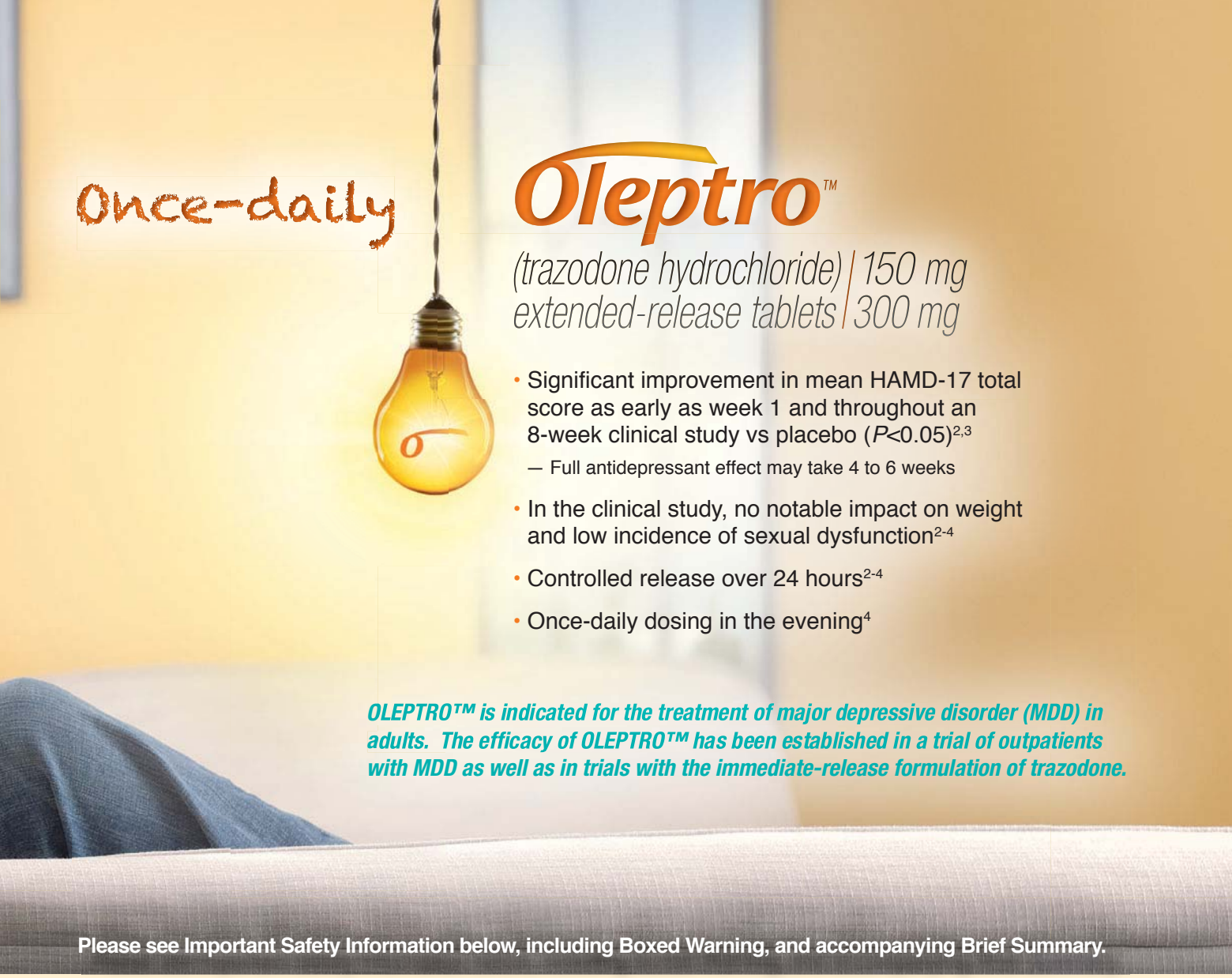
WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Oleptro or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Oleptro is not approved for use in pediatric patients.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Clinical worsening and suicide risk: All patients, whether adult or pediatric, being treated with antidepressants for both psychiatric and non-psychiatric disorders, should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**
- **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathesia (psychomotor restlessness), hypomania and mania, unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observations by families and caregivers.**
- **Serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions:** The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions has been reported with antidepressants, and may occur with OLEPTRO™, particularly with concomitant use of other serotoninergic drugs including SSRIs, SNRIs and triptans.
- Treatment with OLEPTRO™ and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately and supportive treatment should be initiated. OLEPTRO™ should not be used within 14 days of an MAOI.
- **Screening patients for bipolar disorder and monitoring for mania/hypomania:** A major depressive episode may be the initial presentation of bipolar disorder. Prior to initiating treatment, patients should be adequately screened to determine if they are at risk for bipolar disorder and monitored for mania/hypomania. OLEPTRO™ is not approved for use in treating bipolar depression.
- **QT prolongation and risk of sudden death:** Trazodone is known to prolong QT/QTc interval. Some drugs that cause QT prolongation may lead to Torsades de Pointes and even death especially in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or a genetic predisposition to prolonged QT/QTc. There have been post-marketing reports of Torsades de Pointes with immediate release trazodone even at doses of 100 mg per day or less.
- **Use in patients with heart disease:** Caution should be used when administering OLEPTRO™ to patients with cardiac disease and such patients should be closely monitored, since antidepressant drugs (including trazodone hydrochloride) may cause cardiac arrhythmias. Concomitant administration of drugs that prolong the QT interval or that are inhibitors of CYP3A4 may increase the risk of cardiac arrhythmia in these patients. Trazodone is not recommended for use during the initial recovery phase of myocardial infarction.



Oleptro™

(trazodone hydrochloride) 150 mg / 300 mg extended-release tablets

- Significant improvement in mean HAMD-17 total score as early as week 1 and throughout an 8-week clinical study vs placebo ($P<0.05$)[2,3]
  - Full antidepressant effect may take 4 to 6 weeks
- In the clinical study, no notable impact on weight and low incidence of sexual dysfunction[2-4]
- Controlled release over 24 hours[2-4]
- Once-daily dosing in the evening[4]

OLEPTRO™ is indicated for the treatment of major depressive disorder (MDD) in adults. The efficacy of OLEPTRO™ has been established in a trial of outpatients with MDD as well as in trials with the immediate-release formulation of trazodone.

Please see Important Safety Information below, including Boxed Warning, and accompanying Brief Summary.

- **Orthostatic hypotension and syncope:** Orthostatic hypotension and syncope have been reported in patients receiving trazodone hydrochloride. Concomitant use with an antidepressant drug may require a reduction in the dose of the antihypertensive drug.
- **Abnormal bleeding:** Drugs that interfere with serotonin reuptake, including trazodone hydrochloride, may increase the risk of bleeding events. Concomitant use with NSAIDs, aspirin, or other drugs that affect coagulation may compound this risk.
- **Interaction with MAOIs:** Serious, sometimes fatal, reactions have been reported when serotonergic drugs are used in combination with monoamine oxidase inhibitor(s). Therefore, OLEPTRO™ should not be used concomitantly or within 14 days of monoamine oxidase inhibitors.
- **Priapism:** Rarely, cases of priapism (painful erections lasting more than 6 hours) can occur in men receiving trazodone. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Trazodone should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease). Men who have an erection lasting greater than 6 hours, whether painful or not, should immediately discontinue the drug and seek medical attention. OLEPTRO™ should be used with caution in men who have predisposing conditions.
- **Hyponatremia:** There is a risk of hyponatremia when taking antidepressants. Elderly patients may be at greater risk, as well as patients taking diuretics or who are volume-depleted. Discontinuation of OLEPTRO™ should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be initiated.
- **Potential for cognitive and motor impairment:** OLEPTRO™ may cause somnolence or sedation and may impair the mental and/or physical ability required for the performance of potentially hazardous tasks. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain the drug treatment does not affect them adversely.
- **Discontinuation Symptoms:** Withdrawal symptoms including anxiety, agitation and sleep disturbances, have been reported with trazodone. Clinical experience suggests that the dose should be gradually reduced before complete discontinuation of the treatment.
- **Pregnancy Category C:** OLEPTRO™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

The most common adverse reactions (incidence greater than or equal to five percent and twice that of placebo) are: somnolence/sedation, dizziness, constipation, blurred vision.

These are not all the possible adverse events of OLEPTRO™.

DRUG INTERACTIONS

- MAOIs: MAOIs should not be used within 14 days of OLEPTRO™.
- CNS Depressants: Trazodone may enhance effects of alcohol, barbiturates, or other CNS depressants.
- CYP3A4 Inhibitors: May necessitate a lower dose of OLEPTRO™.
- CYP3A4 Inducers: (e.g., carbamazepine): May necessitate a higher dose of OLEPTRO™.
- Digoxin or Phenytoin: Monitor for increased serum levels.
- Serotonergic Medications: Serotonin syndrome has been reported.
- NSAIDs, Aspirin, or Other Anticoagulants: Potential for increased risk of bleeding.
- Warfarin: Monitor for increased or decreased prothrombin time.

References: 1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000. **2.** Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. *Psychiatry.* 2009;6(5):20-33. **3.** Data on file, Labopharm Inc. **4.** OLEPTRO™ Prescribing Information.

Visit the OLEPTRO™ website at www.oleptro.com or call 1-877-345-6177.

ANGELINI | labopharm

OLEPTRO™ (trazodone hydrochloride) extended-release tablets
Rx Only
Brief summary: for complete details, please see full Prescribing Information for Oleptro.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Oleptro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Oleptro is not approved for use in pediatric patients [***see Warnings and Precautions and Patient Counseling Information***].

INDICATIONS AND USAGE: Oleptro™ is indicated for the treatment of major depressive disorder (MDD) in adults. The efficacy of Oleptro has been established in a trial of outpatients with MDD as well as in trials with the immediate release formulation of trazodone [***see Clinical Studies***].
CONTRAINDICATIONS: None.
WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk – Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders and these disorders themselves are the strongest predictors of suicide. There has been a long standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 – 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1: Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated

Age Range	Increases Compared to Placebo
< 18	14 additional cases
18 – 24	5 additional cases
	Decreases Compared to Placebo
25 – 64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Oleptro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions –** The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with antidepressants alone and may occur with trazodone treatment, but particularly with concomitant use of other serotoninergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Treatment with Oleptro and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. Oleptro should not be used within 14 days of an MAOI [***see Warnings and Precautions and Drug Interactions***]. If concomitant treatment with Oleptro and an SSRI, SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Oleptro with serotonin precursors (such as tryptophan) is not recommended. **Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania –** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Oleptro is not approved for use in treating bipolar depression. **QT Prolongation and Risk of Sudden Death –** Trazodone is known to prolong the QT/QTc interval. Some drugs that prolong the QT/QTc interval can cause Torsades de Pointes with sudden, unexplained death. The relationship of QT prolongation is clearest for larger increases (20 msec and greater), but it is possible that smaller QT/QTc prolongations may also increase risk, especially in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or a genetic predisposition to prolonged QT/QTc. Although Torsades de Pointes has not been observed with the use of Oleptro at recommended doses in premarketing trials, experience is too limited to rule out an increased risk. However, there have been postmarketing reports of Torsades de Pointes with the immediate-release form of trazodone (in the presence of multiple confounding factors), even at doses of 100 mg per day or less. **Use in Patients with Heart Disease –** Trazodone hydrochloride is not recommended for use during the initial recovery phase of myocardial infarction. Caution should be used when administering Oleptro to patients with cardiac disease and such patients should be closely monitored, since antidepressant drugs (including trazodone hydrochloride) may cause cardiac arrhythmias. QT prolongation has been reported with trazodone therapy [***see Warnings and Precautions***]. Clinical studies in patients with pre-existing cardiac disease indicate that trazodone hydrochloride may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, tachycardia with syncope, and Torsades de Pointes. Postmarketing events have been reported at doses of 100 mg or less with the immediate-release form of trazodone. Concomitant administration of drugs that prolong the QT interval or that are inhibitors of CYP3A4 may increase the risk of cardiac arrhythmia. **Orthostatic Hypotension and Syncope –** Hypotension, including orthostatic hypotension and syncope has been reported in patients receiving trazodone hydrochloride. Concomitant use with an antihypertensive may require a reduction in the dose of the antihypertensive drug. **Abnormal Bleeding –** Postmarketing data have shown an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal (GI) bleeding. While no association between trazodone and bleeding events, in particular GI bleeding, was shown, patients should be cautioned about potential risk of bleeding associated with the concomitant use of trazodone and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. Other bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. **Interaction with MAOIs –** In patients receiving serotonergic drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal reactions including hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuation in vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued antidepressant treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of serotonergic antidepressants and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Oleptro should not be used in combination with an MAOI or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Oleptro before starting an MAOI. **Priapism –** Rare cases of priapism (painful erections greater than 6 hours in duration) were reported in men receiving trazodone. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Men who have an erection lasting greater than 6 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention [***see Adverse Reactions and Overdosage***]. Trazodone should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease). **Hyponatremia –** Hyponatremia may occur as a result of treatment with antidepressants. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with antidepressants. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of Oleptro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Potential for Cognitive and Motor Impairment –** Oleptro may cause somnolence or sedation and may impair the mental and/or physical ability required for the performance of potentially hazardous tasks. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely. **Discontinuation Symptoms –** Withdrawal symptoms including anxiety, agitation and sleep disturbances, have been reported with trazodone. Clinical experience suggests that the dose should be gradually reduced before complete discontinuation of the treatment.
ADVERSE REACTIONS: The following serious adverse reactions are described elsewhere in the labeling: Clinical Worsening and Suicide Risk [***see Boxed Warning and Warnings and***

Precautions]; Serotonin Syndrome or NMS-like Reactions [***see Warnings and Precautions***]; QT Prolongation and Risk of Sudden Death [***see Warnings and Precautions***]; Orthostatic Hypotension [***see Warnings and Precautions***]; Abnormal bleeding events [***see Warnings and Precautions***]; Priapism [***see Warnings and Precautions***]; Hyponatremia [***see Warnings and Precautions***]; Cognitive and Motor Impairment [***see Warnings and Precautions***]; Discontinuation symptoms [***see Warnings and Precautions***]. The most common adverse reactions (reported in ≥5% and at twice the rate of placebo) are: somnolence/sedation, dizziness, constipation, vision blurred. Table 2 presents the summary of adverse events (AEs) leading to discontinuation of Oleptro treatment with an incidence of at least 1% and at least twice that for placebo.

Table 2: Adverse Events with Discontinuation as Action Taken (≥1% Incidence and Incidence 2x Placebo)

	Oleptro N = 202
Somnolence/Sedation	8 (4.0%)
Dizziness	7 (3.5%)
Confusional state	2 (1.0%)
Coordination abnormal	2 (1.0%)
Headache	2 (1.0%)
Nausea	2 (1.0%)
Balance disorder / Gait disturbance	2 (1.0%)

Clinical Studies Experience – The data described below reflects exposure in a clinical trial of 406 patients, including 204 exposed to placebo and 202 exposed to Oleptro. Patients were between 18-80 years of age and 69.3% and 67.5% of patients had at least one previous episode of depression in the last 24 months in the placebo and active-treated group, respectively. In individual patients, doses were flexible and ranged from 150 to 375 mg per day. The mean daily dose during the 6-week treatment period was 310 mg. The tablets were administered orally and were given once a day for a total duration of 8 weeks, including the titration period. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Table 3 presents the summary of all treatment emergent AEs that occurred at an incidence of ≥ 5% in the Oleptro group, whether considered by the clinical investigator to be related to the study drug or not.

Table 3: Most Common Treatment Emergent Adverse Events (≥ 5% of Patients on Active Treatment)

Preferred Term	Placebo N = 204	Oleptro N = 202
Somnolence/Sedation	39 (19%)	93 (46%)
Headache	55 (27%)	67 (33%)
Dry mouth	26 (13%)	51 (25%)
Dizziness	25 (12%)	50 (25%)
Nausea	26 (13%)	42 (21%)
Fatigue	17 (8%)	30 (15%)
Diarrhea	23 (11%)	19 (9%)
Constipation	4 (2%)	16 (8%)
Back pain	7 (3%)	11 (5%)
Vision blurred	0 (0%)	11 (5%)

Sexual Dysfunction – Adverse events related to sexual dysfunction (regardless of causality) were reported by 4.9% and 1.5% of patients treated with Oleptro and placebo, respectively. In the Oleptro group, ejaculation disorders occurred in 1.5% of patients, decreased libido occurred in 1.5% of patients, and erectile dysfunction and abnormal orgasm < 1% of patients. **Vital Signs and Weight –** There were no notable changes in vital signs (blood pressure, respiratory rate, pulse) or weight in either treatment group. Following is a list of treatment-emergent adverse reactions with an incidence of ≥ 1% to < 5% (i.e., less common) in patients treated with Oleptro. This listing is not intended to include reactions (i) already listed in previous tables or elsewhere in the labeling (ii) for which the association with treatment is remote, (iii) which were so general as to be uninformative, and (iv) which were not considered to have significant clinical implications. Reactions are classified by body-system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in less than 1/100 patients. **Ear and Labyrinth Disorders –** *Infrequent:* hypoacusis, tinnitus, vertigo; **Eye Disorders –** *Frequent:* visual disturbance; *Infrequent:* dry eye, eye pain, photophobia; **Gastrointestinal Disorders –** *Frequent:* abdominal pain, vomiting; *Infrequent:* reflux esophagitis; **General Disorders and Administration Site Conditions –** *Frequent:* edema; *Infrequent:* gait disturbance; **Immune System Disorders –** *Infrequent:* hypersensitivity; **Musculoskeletal and Connective Tissue Disorders –** *Frequent:* musculoskeletal complaints, myalgia; *Infrequent:* muscle twitching; **Nervous System Disorders –** *Frequent:* coordination abnormal, dysgeusia, memory impairment, migraine, paraesthesia, tremor; *Infrequent:* amnesia, aphasia, hypoesthesia, speech disorder; **Psychiatric Disorders –** *Frequent:* agitation, confusional state, disorientation; **Renal and Urinary Disorders –** *Frequent:* micturition urgency; *Infrequent:* bladder pain, urinary incontinence; **Respiratory, Thoracic and Mediastinal Disorders –** *Frequent:* dyspnea; **Skin and Subcutaneous Tissue Disorders –** *Frequent:* night sweats; *Infrequent:* acne, hyperhidrosis, photosensitivity reaction; **Vascular Disorders –** *Infrequent:* flushing. **Postmarketing Experience –** Spontaneous reports regarding trazodone hydrochloride received from postmarketing experience include the following: abnormal dreams, agitation, alopecia, anxiety, aphasia, apnea, ataxia, breast enlargement or engorgement, cardiospasm, cerebrovascular accident, chills, cholestasis, clitorism, congestive heart failure, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hirsutism, hyperbilirubinemia, increased amylase, increased salivation, insomnia, leukocytosis, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/ vomiting (most frequently), paresthesia, paranoid reaction, priapism [***see Warnings and Precautions and Patient Counseling Information***], pruritus, psoriasis, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo, and weakness. Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation. In postmarketing surveillance, prolonged QT interval, Torsades de Pointes, and ventricular tachycardia have been reported with the immediate-release form of trazodone at doses of 100 mg per day or less [***see Warnings and Precautions***].

DRUG INTERACTIONS: MAOIs – MAOIs should not be used within 14 days of Oleptro [***see Warnings and Precautions***]. **Central Nervous System (CNS) Depressants –** Trazodone may enhance the response to alcohol, barbiturates, and other CNS depressants. **Cytochrome P450 3A4 Inhibitors –** In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with cytochrome P450 3A4 (CYP3A4) inhibitors. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10 healthy subjects. The Cmax of trazodone increased by 34%, the AUC increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered. It is likely that ketoconazole, indinavir, and other CYP3A4 inhibitors such as itraconazole may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. If trazodone is used with a potent CYP3A4 inhibitor, the risk of cardiac arrhythmia may be increased [***see Warnings and Precautions***] and a lower dose of trazodone should be considered. **Cytochrome P450 Inducers (e.g., carbamazepine) –** Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg per day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone and m-chlorophenlypiperazine (an active metabolite) by 76% and 60% respectively, compared to pre-carbamazepine values. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs. **Digoxin and Phenytoin –** Increased serum digoxin or phenytoin levels have been reported in patients receiving trazodone concurrently with either of these drugs. Monitor serum levels and adjust dosages as needed. **Serotonergic Drugs –** Based on the mechanism of action of Oleptro and the potential for serotonin syndrome, caution is advised when Oleptro is co-administered with other drugs that may affect the neurotransmitter systems [***see Warnings and Precautions***]. **NSAIDs, Aspirin, or Other Drugs Affecting Coagulation or Bleeding –** Due to a possible association between serotonin modulating drugs and gastrointestinal bleeding, patients should be monitored for and cautioned about the potential risk of bleeding associated with the concomitant use of trazodone and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding [***see Warnings and Precautions***]. **Warfarin –** There have been reports of altered (either increased or decreased) prothrombin times in taking both warfarin and trazodone.

USE IN SPECIFIC POPULATIONS: Pregnancy; Pregnancy Category C – Trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30 – 50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15 – 50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Oleptro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers –** Trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when Oleptro is administered to a nursing woman. **Pediatric Use –** Safety and effectiveness in the pediatric population have not been established [***see Boxed Warning and Warnings and Precautions***]. Oleptro should not be used in children or adolescents. **Geriatric Use –** Of 202 patients treated with Oleptro in the clinical trial, there were 9 patients older than 65. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical literature and experience with trazodone have not identified differences in responses between elderly and younger patients. However, as experience in the elderly with Oleptro is limited, it should be used with caution in geriatric patients. Antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients who may be at greater risk for this adverse reaction [***see Warnings and Precautions***]. **Renal Impairment –** Oleptro has not been studied in patients with renal impairment. Trazodone should be used with caution in this population. **Hepatic Impairment –** Oleptro has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population.

DRUG ABUSE AND DEPENDENCE: Controlled Substance – Oleptro is not a controlled substance. **Abuse –** Although trazodone hydrochloride has not been systematically studied in preclinical or clinical studies for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical studies with Oleptro. However, it is difficult to predict the extent to which a CNS-active drug will be misused, diverted, and abused. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of trazodone hydrochloride (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience – It is expected that the health risks associated with overdose of Oleptro are most likely similar to those for trazodone immediate-release formulations. Death from overdose has occurred in patients ingesting trazodone and other CNS depressant drugs concurrently (alcohol; alcohol and chloral hydrate and diazepam; amobarbital; chlordiazepoxide; or meprobamate). The most severe reactions reported to have occurred with overdose of trazodone alone have been priapism, respiratory arrest, seizures, and ECG changes, including QT prolongation. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions. **Management of Overdose –** There is no specific antidote for Oleptro overdose. Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Forced diuresis may be useful in facilitating elimination of the drug. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

Labopharm Europe Limited
Unit 5, The Seapoint Building
44/45 Clontarf Road, Dublin 3, IRELAND

With the recommended starting dose—

SAPHRIS® delivers effective symptom control with documented safety and tolerability

SAPHRIS® is an atypical antipsychotic agent indicated for:

- Acute treatment of schizophrenia in adults
- Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults

We have a lot to look forward to

Selected Safety Information

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**
- **Analyses of 17 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 2.6% in the placebo group**
- **Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature**
- **SAPHRIS® is not approved for the treatment of patients with dementia-related psychosis**

Cerebrovascular Adverse Events

- 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. SAPHRIS® is not approved for the treatment of patients with dementia-related psychosis

Please see additional Selected Safety Information continued on next page.

Please see accompanying brief summary of full Prescribing Information, including BOXED WARNING.

Saphris® (asenapine)
sublingual tablets 5 and 10 mg
Treat for today and tomorrow

Additional Selected Safety Information

Neuroleptic Malignant Syndrome (NMS)
- NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including SAPHRIS®
- NMS can cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure
- Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems

Tardive Dyskinesia (TD)
- The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase
- However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD
- If signs and symptoms appear, discontinuation should be considered

Hyperglycemia and Diabetes Mellitus
- Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics
- Patients with risk factors for diabetes mellitus who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and 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 also undergo fasting blood glucose testing
- In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the antipsychotic drug

Weight Gain
- There were differences in mean weight gain between SAPHRIS®-treated and placebo-treated patients in short-term schizophrenia trials (1.1 kg vs 0.1 kg) and in bipolar mania trials (1.3 kg vs 0.2 kg). In a 52-week study, the proportion of patients with a ≥7% increase in body weight was 14.7%

Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects
- SAPHRIS® may induce orthostatic hypotension and syncope
- SAPHRIS® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, conditions which would predispose them to hypotension, and in the elderly
- SAPHRIS® should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, respiratory or central nervous system depression
- Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs

Leukopenia, Neutropenia, and Agranulocytosis
- In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS®
- Patients with a preexisting low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and SAPHRIS® should be discontinued at the first sign of a decline in WBC in the absence of other causative factors

QT Prolongation
- SAPHRIS® was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo
- No patients treated with SAPHRIS® experienced QTc increases ≥60 msec from baseline measurements, nor did any experience a QTc of ≥500 msec
- SAPHRIS® should be avoided in combination with other drugs known to prolong QTc interval, in patients with congenital prolongation of QT interval or a history of cardiac arrhythmias, and in circumstances that may increase the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval

Hyperprolactinemia
- Like other drugs that antagonize dopamine D_2 receptors, SAPHRIS® can elevate prolactin levels, and the elevation can persist during chronic administration. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds

Seizures
- SAPHRIS® should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (eg, Alzheimer's dementia)

Dysphagia
- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia
- SAPHRIS® is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia

Potential for Cognitive and Motor Impairment
- Somnolence was reported in patients treated with SAPHRIS®
- 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 SAPHRIS® therapy does not affect them adversely

Body Temperature Regulation
- Appropriate care is advised when prescribing SAPHRIS® for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration

Suicide
- The possibility of suicide attempt is inherent in psychotic illnesses and bipolar disorder. Close supervision of high-risk patients should accompany drug therapy
- Prescriptions for SAPHRIS® should be written for the smallest quantity of tablets in order to reduce the risk of overdose

Hepatic Impairment
- SAPHRIS® is not recommended in patients with severe hepatic impairment

Drug Interactions
- The risks of using SAPHRIS® in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of SAPHRIS®, caution should be used when it is taken in combination with other centrally acting drugs or alcohol
- Coadministration of SAPHRIS® with strong CYP1A2 inhibitors (fluvoxamine) or compounds which are both CYP2D6 substrates and inhibitors (paroxetine) should be done with caution

Commonly Observed Adverse Reactions
(≥5% and at least twice that for placebo)
- In short-term bipolar mania trials with SAPHRIS® 5 or 10 mg BID vs placebo:
  —Somnolence (24% vs 6%), dizziness (11% vs 3%), extrapyramidal symptoms other than akathisia (7% vs 2%), and weight increased (5% vs <1%)
- In short-term schizophrenia trials with SAPHRIS® 5 or 10 mg BID vs placebo:
  —Akathisia (6% vs 3%), oral hypoesthesia (numbing of the tongue [5% vs 1%]), and somnolence (13% vs 7%)

Please see accompanying brief summary of full Prescribing Information, including BOXED WARNING.

MERCK

Saphris® (asenapine)
sublingual tablets 5 and 10 mg
Treat for today and tomorrow

SAPHRIS®
(asenapine) sublingual tablets

BRIEF SUMMARY (For full Prescribing Information, see package insert.)

WARNING: 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. Analyses of 17 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. SAPHRIS® (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

SAPHRIS is indicated for the acute treatment of schizophrenia in adults *[see Clinical Studies (14.1)]*. The physician who elects to use SAPHRIS 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

SAPHRIS is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults *[see Clinical Studies (14.2)]*. If SAPHRIS is used for extended periods in bipolar disorder, the physician should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient *[see Dosage and Administration (2.2)]*.

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. SAPHRIS 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. SAPHRIS 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

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SAPHRIS. 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. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection) 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

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 Tardive Dyskinesia (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, SAPHRIS 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 SAPHRIS, drug discontinuation should be considered. However, some patients may require treatment with SAPHRIS 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. In clinical trials of SAPHRIS, the occurrence of any adverse reaction related to glucose metabolism was less than 1% in both the SAPHRIS 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 reactions is not completely understood. However, epidemiological studies, which did not include SAPHRIS, suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions 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 antipsychotic drug.

5.6 Weight Gain

In short-term schizophrenia and bipolar mania trials, there were differences in mean weight gain between SAPHRIS-treated and placebo-treated patients. In short-term, placebo-controlled schizophrenia trials, the mean weight gain was 1.1 kg for SAPHRIS-treated patients compared to 0.1 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.9% for SAPHRIS-treated patients versus 2% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean weight gain for SAPHRIS-treated patients was 1.3 kg compared to 0.2 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 5.8% for SAPHRIS-treated patients versus 0.5% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia or schizoaffective disorder, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 14.7%. **Table 1** provides the mean weight change from baseline and the proportion of patients with a weight gain of ≥7% categorized by Body Mass Index (BMI) at baseline:

TABLE 1: Weight Change Results Categorized by BMI at Baseline: Comparator-Controlled 52-Week Study in Schizophrenia

	BMI < 23 SAPHRIS N=295	BMI 23 - ≤ 27 SAPHRIS N=290	BMI > 27 SAPHRIS N=302
Mean change from Baseline (kg)	1.7	1	0
% with ≥ 7% increase in body weight	22%	13%	9%

5.7 Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects

SAPHRIS may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its α1-adrenergic antagonist activity. In short-term schizophrenia trials, syncope was reported in 0.2% (1/572) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0.3% (1/378) of patients treated with placebo. In short-term bipolar mania trials, syncope was reported in 0.3% (1/379) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0% (0/203) of patients treated with placebo. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, syncope was reported in 0.6% (11/1953) of patients treated with SAPHRIS.

Four normal volunteers in clinical pharmacology studies treated with either intravenous, oral, or sublingual SAPHRIS 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.

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). SAPHRIS 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. SAPHRIS 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 (7)]*. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count

(WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and SAPHRIS should be discontinued at the first sign of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue SAPHRIS and have their WBC followed until recovery.

5.9 QT Prolongation

The effects of SAPHRIS on the QT/QTc interval were evaluated in a dedicated QT study. This trial involved SAPHRIS 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. At these doses, SAPHRIS was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo. No patients treated with SAPHRIS experienced QTc increases ≥60 msec from baseline measurements, nor did any patient experience a QTc of ≥500 msec.

Electrocardiogram (ECG) measurements were taken at various time points during the SAPHRIS clinical trial program (5 mg or 10 mg twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for SAPHRIS and placebo in these short-term trials. There were no reports of Torsade de Pointes or any other adverse reactions associated with delayed ventricular repolarization.

The use of SAPHRIS 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). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in 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 bradycardia; hypokalemia or hypomagnesemia; and presence of congenital prolongation of the QT interval.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, SAPHRIS can elevate 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. In SAPHRIS clinical trials, the incidences of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo *[see Adverse Reactions (6.2)]*.

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. 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.

5.11 Seizures

Seizures were reported in 0% and 0.3% (0/572, 1/379) of patients treated with doses of 5 mg and 10 mg twice daily of SAPHRIS, 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 SAPHRIS, including long-term trials without comparison to placebo, seizures were reported in 0.3% (5/1953) of patients treated with SAPHRIS. As with other antipsychotic drugs, SAPHRIS 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 patients 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was reported in patients treated with SAPHRIS. It was usually transient with the highest incidence reported during the first week of treatment. In short-term, fixed-dose, placebo-controlled schizophrenia trials, somnolence was reported in 15% (41/274) of patients on SAPHRIS 5 mg twice daily and in 13% (26/208) of patients on SAPHRIS 10 mg twice daily compared to 7% (26/378) of placebo patients. In short-term, placebo-controlled bipolar mania trials of therapeutic doses (5-10 mg twice daily), somnolence was reported in 24% (90/379) of patients on SAPHRIS compared to 6% (13/203) of placebo patients. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, somnolence was reported in 18% (358/1953) of patients treated with SAPHRIS. Somnolence (including sedation) led to discontinuation in 0.6% (12/1953) of patients in short-term, placebo-controlled trials.

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 SAPHRIS therapy does not affect them adversely.

5.13 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 trials with SAPHRIS, including long-term trials without comparison to placebo, the incidence of adverse reactions suggestive of body temperature increases (pyrexia and feeling hot) was ≤1%. Appropriate care is advised when prescribing SAPHRIS 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.

5.14 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 SAPHRIS should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.15 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 SAPHRIS as compared to 0% (0/378, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, dysphagia was reported in 0.1% (2/1953) of patients treated with SAPHRIS.

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SAPHRIS is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia *[see also Warnings and Precautions (5.1)]*.

5.16 Use in Patients with Concomitant Illness

Clinical experience with SAPHRIS in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

SAPHRIS has not been evaluated 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 SAPHRIS, caution should be observed in cardiac patients *[see Warnings and Precautions (5.6)]*.

6 ADVERSE REACTIONS

The most common adverse reactions (≥5% and at least twice the rate on placebo) in schizophrenia were akathisia, oral hypoesthesia, and somnolence.

The most common adverse reactions (≥5% and at least twice the rate on placebo) in bipolar disorder were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight increased.

The information below is derived from a clinical trial database for SAPHRIS consisting of over 3350 patients and/or normal subjects exposed to one or more sublingual doses of SAPHRIS. 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 or 10 mg twice daily, with a total experience of approximately 611 patient-years). A total of 486 SAPHRIS-treated patients were treated for at least 24 weeks and 293 SAPHRIS-treated patients had at least 52 weeks of exposure.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced a treatment-emergent adverse event of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while 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 SAPHRIS was administered in doses ranging from 5 to 10 mg twice daily.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9% of SAPHRIS-treated subjects and 10% of placebo subjects discontinued due to adverse reactions. There were no drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS at the rate of at least 1% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in SAPHRIS-Treated Schizophrenic Patients: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in **Table 2**.

TABLE 2: Adverse Reactions Reported in 2% or More of Subjects in one of the SAPHRIS Dose Groups and Which Occurred at Greater Incidence Than in the Placebo group in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo N=378	SAPHRIS 5 mg twice daily N=274	SAPHRIS 10 mg twice daily N=208	All SAPHRIS[§] 5 or 10 mg twice daily N=572
Gastrointestinal disorders				
Constipation	6%	7%	4%	5%
Dry mouth	1%	3%	1%	2%
Oral hypoesthesia	1%	6%	7%	5%
Salivary hypersecretion	0%	<1%	4%	2%
Stomach discomfort	1%	<1%	3%	2%
Vomiting	5%	4%	7%	5%
General disorders				
Fatigue	3%	4%	3%	3%
Irritability	<1%	2%	1%	2%
Investigations				
Weight increased	<1%	2%	2%	3%
Metabolism disorders				
Increased appetite	<1%	3%	0%	2%
Nervous system disorders				
Akathisia*	3%	4%	11%	6%
Dizziness	4%	7%	3%	5%
Extrapyramidal symptoms (excluding akathisia)†	7%	9%	12%	10%
Somnolence‡	7%	15%	13%	13%
Psychiatric disorders				
Insomnia	13%	16%	15%	15%
Vascular disorders				
Hypertension	2%	2%	3%	2%

* Akathisia includes: akathisia and hyperkinesia.

† Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia).

‡ Somnolence includes the following events: somnolence, sedation, and hypersomnia.

§ Also includes the Flexible-dose trial (N=90).

Dose-Related Adverse Reactions: Of all the adverse reactions listed in **Table 2**, the only apparent dose-related adverse reaction was akathisia.

Adult Patients with Bipolar Mania: The following findings are based on the short-term placebo-controlled trials for bipolar mania (a pool of two 3-week flexible-dose trials) in which sublingual SAPHRIS was administered in doses of 5 mg or 10 mg twice daily.

Adverse Reactions Associated with Discontinuation of Treatment: Approximately 10% (38/379) of SAPHRIS-treated patients in short-term, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with about 6% (12/203) on placebo. The most common adverse reactions associated with discontinuation in subjects treated with SAPHRIS (rates at least 1% and at least twice the placebo rate) were anxiety (1.1%) and oral hypoesthesia (1.1%) compared to placebo (0%).

Adverse Reactions Occurring at an Incidence of 2% or More Among SAPHRIS-Treated Bipolar Patients: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute therapy (up to 3-weeks in patients with bipolar mania) are shown in **Table 3**.

TABLE 3: Adverse Reactions Reported in 2% or More of Subjects in one of the SAPHRIS Dose Groups and Which Occurred at Greater Incidence Than in the Placebo Group in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo N=203	SAPHRIS 5 or 10 mg twice daily* N=379
Gastrointestinal disorders		
Dry mouth	1%	3%
Dyspepsia	2%	4%
Oral hypoesthesia	<1%	4%
Toothache	2%	3%
General disorders		
Fatigue	2%	4%
Investigations		
Weight increased	<1%	5%
Metabolism disorders		
Increased appetite	1%	4%
Musculoskeletal and connective tissue disorders		
Arthralgia	1%	3%
Pain in extremity	<1%	2%
Nervous system disorders		
Akathisia	2%	4%
Dizziness	3%	11%
Dysgeusia	<1%	3%
Headache	11%	12%
Other extrapyramidal symptoms (excluding akathisia)†	2%	7%
Somnolence‡	6%	24%
Psychiatric disorders		
Anxiety	2%	4%
Depression	1%	2%
Insomnia	5%	6%

* SAPHRIS 5 to 10 mg twice daily with flexible dosing.

† Extrapyramidal symptoms included: dystonia, blepharospasm, torticollis, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, gait disturbance, masked facies, and tremor (excluding akathisia).

‡ Somnolence includes the following events: somnolence, sedation, and hypersomnia.

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.

Extrapyramidal Symptoms: In the short-term, placebo-controlled schizophrenia and bipolar mania trials, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). The mean change from baseline for the all-SAPHRIS 5 mg or 10 mg twice daily treated group was comparable to placebo in each of the rating scale scores.

In the short-term, placebo-controlled schizophrenia trials, the incidence of reported EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 10% versus 7% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 6% versus 3% for placebo. In short-term placebo-controlled bipolar mania trials, the incidence of EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 7% versus 2% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 4% versus 2% for placebo.

Laboratory Test Abnormalities: *Glucose:* The effects on fasting serum glucose levels in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes *[see also Warnings and Precautions (5.5)]*. In the short-term placebo-controlled schizophrenia trials, the mean increase in fasting glucose levels for SAPHRIS-treated patients was 3.2 mg/dL compared to a decrease of 1.6 mg/dL for placebo-treated patients. The proportion of patients with fasting glucose elevations ≥126 mg/dL (at Endpoint), was 7.4% for SAPHRIS-treated patients versus 6% for placebo-treated patients. In the short-term, placebo-controlled bipolar mania trials, the mean decreases in fasting glucose levels for both SAPHRIS-treated and placebo-treated patients were 0.6 mg/dL. The proportion of patients with fasting glucose elevations ≥126 mg/dL (at Endpoint), was 4.9% for SAPHRIS-treated patients versus 2.2% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of fasting glucose was 2.4 mg/dL.

Lipids: The effects on total cholesterol and fasting triglycerides in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes. In short-term, placebo-controlled schizophrenia trials, the mean increase in total cholesterol levels for SAPHRIS-treated patients was 0.4 mg/dL compared to a decrease of 3.6 mg/dL for placebo-treated patients. The proportion of patients with total cholesterol elevations ≥240 mg/dL (at Endpoint) was 8.3% for SAPHRIS-treated patients versus 7% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in total cholesterol levels for SAPHRIS-treated patients was 1.1 mg/dL compared to a decrease of 1.5 mg/dL in placebo-treated patients. The proportion of patients with total cholesterol elevations ≥240 mg/dL (at Endpoint) was 8.7% for SAPHRIS-treated patients versus 8.6% for placebo-treated patients. In short-term, placebo-controlled schizophrenia trials, the mean increase in triglyceride levels for SAPHRIS-treated patients was 3.8 mg/dL compared to a decrease of 13.5 mg/dL for placebo-treated patients. The proportion of patients with elevations in triglycerides ≥200 mg/dL (at Endpoint) was 13.2% for SAPHRIS-treated patients versus 10.5% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean decrease in triglyceride levels for SAPHRIS-treated patients was 3.5 mg/dL versus 17.9 mg/dL for placebo-treated subjects. The proportion of patients with elevations in triglycerides ≥200 mg/dL (at Endpoint) was 15.2% for SAPHRIS-treated patients versus 11.4% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean decrease from baseline of total cholesterol was 6 mg/dL and the mean decrease from baseline of fasting triglycerides was 9.8 mg/dL.

Transaminases: Transient elevations in serum transaminases (primarily ALT) in the short-term schizophrenia and bipolar mania trials were more common in treated patients but mean changes were not clinically relevant. In short-term, placebo-controlled schizophrenia trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 1.6 units/L compared to a decrease of 0.4 units/L for placebo-treated patients. The proportion of patients with transaminase elevations ≥3 times ULN (at Endpoint) was 0.9% for SAPHRIS-treated patients versus 1.3% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 8.9 units/L compared to a decrease of 4.9 units/L in placebo-treated patients. The proportion of patients with transaminase elevations ≥3 times upper limit of normal (ULN) (at Endpoint) was 2.5% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. No cases of more severe liver injury were seen.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of ALT was 1.7 units/L.

Prolactin: The effects on prolactin levels in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant changes in mean change in baseline. In short-term, placebo-controlled schizophrenia trials, the mean decreases in prolactin levels were 6.5 ng/mL for SAPHRIS-treated patients compared to 10.7 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥4 times ULN (at Endpoint) were 2.6% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in prolactin levels was 4.9 ng/mL for SAPHRIS-treated patients compared to a decrease of 0.2 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥4 times ULN (at Endpoint) were 2.3% for SAPHRIS-treated patients versus 0.7% for placebo-treated patients.

In a long-term (52-week), double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean decrease in prolactin from baseline for SAPHRIS-treated patients was 26.9 ng/mL.

Other Adverse Reactions Observed During the Premarketing Evaluation of SAPHRIS: Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with sublingual SAPHRIS at multiple doses of ≥5 mg twice daily during any phase of a trial within the database of adult patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions already listed in other parts of *Adverse Reactions (6)*, or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* are not included. Although the reactions reported occurred during treatment with SAPHRIS, they were not necessarily caused by it. Reactions 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.

Blood and lymphatic disorders: <1/1000 patients: thrombocytopenia; *≥1/1000 patients and <1/100 patients:* anemia

Cardiac disorders: ≥1/1000 patients and <1/100 patients: tachycardia, temporary bundle branch block

Eye disorders: ≥1/1000 patients and <1/100 patients: accommodation disorder

Gastrointestinal disorders: ≥1/1000 patients and <1/100 patients: oral paraesthesia, glossodynia, swollen tongue

General disorders: <1/1000 patients: idiosyncratic drug reaction

Investigations: ≥1/1000 patients and <1/100 patients: hyponatremia

Nervous system disorders: ≥1/1000 patients and <1/100 patients: dysarthria

7 DRUG INTERACTIONS

The risks of using SAPHRIS in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of SAPHRIS, caution should be used when it is taken in combination with other centrally-acting drugs or alcohol.

Because of its α1-adrenergic antagonism with potential for inducing hypotension, SAPHRIS may enhance the effects of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect SAPHRIS

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450isoenzymes (predominantly CYP1A2). The potential effects of inhibitors of several of these enzyme pathways on asenapine clearance were studied.

TABLE 4: Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Recommendation
	Coadministered drug	Asenapine	C_{max}	$AUC_{0-\infty}$	
Fluvoxamine (CYP1A2 inhibitor)	25 mg twice daily for 8 days	5 mg Single Dose	+13%	+29%	Coadminister with caution*

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations. AUC: Area under the curve.

TABLE 4: Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers *(cont)*

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Recommendation
	Coadministered drug	Asenapine	C_{max}	$AUC_{0-\infty}$	
Paroxetine (CYP2D6 inhibitor)	20 mg once daily for 9 days	5 mg Single Dose	–13%	–9%	No SAPHRIS dose adjustment required *[see Drug Interactions (7.2)]*
Imipramine (CYP1A2/2C19/3A4 inhibitor)	75 mg Single Dose	5 mg Single Dose	+17%	+10%	No SAPHRIS dose adjustment required
Cimetidine (CYP3A4/2D6/1A2 inhibitor)	800 mg twice daily for 8 days	5 mg Single Dose	–13%	+1%	No SAPHRIS dose adjustment required
Carbamazepine (CYP3A4 inducer)	400 mg twice daily for 15 days	5 mg Single Dose	–16%	–16%	No SAPHRIS dose adjustment required
Valproate (UGT1A4 inhibitor)	500 mg twice daily for 9 days	5 mg Single Dose	2%	–1%	No SAPHRIS dose adjustment required

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations. AUC: Area under the curve.

7.2 Potential for SAPHRIS to Affect Other Drugs

Coadministration with CYP2D6 Substrates: *In vitro* studies indicate that asenapine weakly inhibits CYP2D6.

Following coadministration of dextromethorphan and SAPHRIS in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with SAPHRIS 5 mg twice daily decreased the DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032. In a separate study, coadministration of a single 75-mg dose of imipramine with a single 5-mg dose of SAPHRIS did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate). Thus, *in vivo*, SAPHRIS appears to be at most a weak inhibitor of CYP2D6. Coadministration of a single 20-mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg SAPHRIS twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure. Asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

SAPHRIS should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

In a study in which rats were treated from day 6 of gestation through day 21 postpartum with intravenous doses of asenapine of 0.3, 0.9, and 1.5 mg/kg/day (0.15, 0.4, and 0.7 times the MRHD of 10 mg twice daily given sublingually on a mg/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.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Asenapine is excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SAPHRIS is administered to a nursing woman. It is recommended that women receiving SAPHRIS should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of SAPHRIS in the treatment of schizophrenia and bipolar mania did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Of the approximately 2250 patients in premarketing clinical studies of SAPHRIS, 1.1% (25) were 65 years of age or over. Multiple factors that might increase the pharmacodynamic response to SAPHRIS, 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 SAPHRIS are at an increased risk of death compared to placebo. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6 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)]*.

8.7 Hepatic Impairment

In subjects with severe hepatic impairment who were treated with a single dose of SAPHRIS 5 mg, asenapine exposures (on average), were 7-fold higher than the exposures observed in subjects with normal hepatic function. Thus, SAPHRIS is not recommended in patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

Management of Overdosage: There is no specific antidote to SAPHRIS. 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 SAPHRIS-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.

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As the 2013 date for publication of the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) draws near, the research and clinical experts working on DSM-5 will be finalizing the diagnostic criteria and testing potential revisions and assessment tools in field trials across a number of clinical settings.

The DSM-5 Field Trials involving practicing psychiatrists will focus primarily on 1) the feasibility and clinical utility of the proposed modifications to the diagnostic criteria for a broad range of disorders in the full range of clinical settings, and 2) the feasibility and clinical utility of cross-cutting and diagnostic-specific dimensional measures that are incorporated into the diagnostic scheme for DSM-5.

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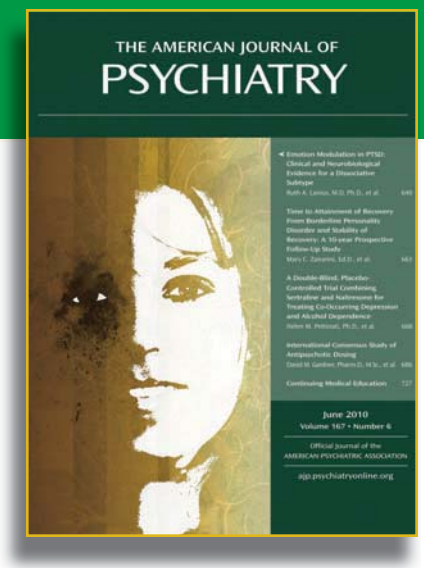

Official Journal of the American Psychiatric Association

Edited by Robert Freedman, M.D.

- AJP saw its 2009 Impact Factor rise almost two full points point to reach 12.52, placing it 2nd among the 117 psychiatry journals indexed, while still remaining the far-and-away leader in total citations.

- According to the May 2010 Thomson Scientific Essential Science Indicators, five of the Top 44 most highly cited articles in psychiatry/psychology appeared in *The American Journal of Psychiatry*. No other journal had more!

- *The American Journal of Psychiatry* (AJP) is again the #1 journal in psychiatry in terms of immediacy according to Thomson Scientific's Immediacy Index. This important performance metric is calculated by dividing the number of citations to articles published in a given year by the number of articles published in that year.

- The Immediacy Index is a good measure of how quickly a given journal's articles are cited—AJP's #1 placement is a result of publishing articles that are relevant, covering current "hot" topics and cutting-edge research, and getting these findings to the field faster with AJP in Advance, the Journal's online-ahead-of-print publication protocol.

- A recent poll conducted by the BioMedical & Life Sciences Division of The Special Libraries Associaton identified the 100 most influential journals in all of Biology & Medicine over the last 100 years. *The American Journal of Psychiatry* was among those honored, the only psychiatry/psychology journal represented.

No other psychiatric journal reaches more psychiatrists with greater impact or immediacy than the journal that the overwhelming majority of psychiatrist considers essential: AJP.

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Chair, Department of Psychiatry

The UMDNJ-School of Osteopathic Medicine is currently seeking a Chair for the Department of Psychiatry, which is one of the largest providers of adult and child psychiatric services in five South Jersey counties, six hospitals and 14 different community organizations, With a mission dedicated to education, practice and research, the faculty consists of 30 Psychiatrists, 10 Advanced Practice Psychiatric Nurses and two Psychologists.

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The inspired candidate we seek must be a Board certified Psychiatrist (D.O. or M.D.) with ten years of professional experience, including prior experiences in a management role. MBA is a plus. Must have the academic and professional experience to qualify as a Professor (preferred) or Associate Professor and must provide examples of leadership, academic strength, clinical strength (peer recognition, reputation, patient satisfaction) and management strength (coaching, type and quality of management experience, advanced degree with experience).

Applicants should submit a letter of interest and curriculum vitae to: **Vincent DeRisio, DO, Associate Dean for Clinical Affairs, c/o Ms. Tammy Merchant, UMDNJ-School of Osteopathic Medicine, One Medical Center Drive, Academic Center, Suite 305, Stratford, NJ 08084, E-mail: merchata@umdnj.edu**. Electronic submissions are encouraged, although paper applications will also be accepted. UMDNJ is an AA/EOE, M/F/D/V.

UMDNJ School of Osteopathic Medicine
University of Medicine & Dentistry of New Jersey

NIAAA National Institute on Alcohol Abuse and Alcoholism

Department of Health and Human Services
National Institutes of Health
National Institute on
Alcohol Abuse and Alcoholism

Director, Division of Treatment and Recovery Research (DTRR)

The National Institute on Alcohol Abuse and Alcoholism (NIAAA), a major research component of the National Institutes of Health (NIH) and the Department of Health and Human Services (HHS), is recruiting for a senior executive to serve as the Director of the Division of Treatment and Recovery Research (DTRR).

The Director, DTRR, provides national leadership for research on the treatment of alcohol use disorders, including setting scientific priorities through the development of long-term strategic plans and execution of funding decisions. In this capacity, the Director, DTRR leads the Division's efforts on planning, stimulating, developing, and supporting clinical research on cutting-edge therapies for alcoholism. Clinical research at the NIAAA encompasses medications development, behavioral therapies, combined medications and behavioral therapies, recovery research, health services research, and the translation of research into clinical practice. Medications development is one of the NIAAA's top research priorities. The Director, DTRR, oversees the NIAAA's work on the full continuum of research included under medications development—from human laboratory studies to clinical trials, which requires close collaboration with internal and external scientists and researchers with other Federal State and Local government agencies, and national and international research organizations. The Director, DTRR serves as the principal advisor to the Director, NIAAA on alcohol treatment and recovery issues and advises the National Advisory Council on pending grant applications and the status of programs in the federal and private sector.

The selected candidate will be expected to hold a M.D., Ph.D., or equivalent degree. Criteria for selection includes: experience in developing, implementing and/or evaluating behavioral and clinical therapies, specifically in the area of medications development, relevant to alcoholism; experience in managing/leading a complex clinical research organization, experience and expertise in communicating clinical, basic research and programmatic information to scientific and non-scientific audiences; a strong publication record in the field of clinical, behavioral, and medications development research and experience in developing, implementing and managing multidisciplinary and trans-disciplinary research programs on treatments for alcohol use disorders and determinants of post-treatment recovery.

The Director, DTRR, is an Excepted Service position (Title 42), and the successful candidate will be appointed at a salary commensurate with qualifications and experience. Full Federal benefits including leave, health and life insurance, long-term care insurance, retirement, and savings plan (401K equivalent) will be provided.

Interested candidates should submit a curriculum vitae, bibliography, and the names, addresses, contact numbers (phone and fax) and e-mail address of four references by the closing date to the following e-mail account:

E-mail: dtrrdirrecruit@mail.nih.gov

Applications will be accepted through September 15, 2010, or until the position is filled.

The NIH encourages the application and nomination of qualified women, minorities and individuals with disabilities. This position is subject to background investigation. The DHHS and NIH are Equal Opportunity Employers

ADULT PSYCHIATRY
Logan, Utah

One BC/BE adult psychiatrist is needed to join a partner who is employed by Intermountain Healthcare at Logan Regional Hospital. Position will be 30+ hours per week in an outpatient setting. Physician will also assist in coverage of inpatient services. Salary guarantee with transition to production. Signing bonus available. Full Intermountain benefits including defined pension and match in 401k. Moving allowance provided. EOE. Intermountain is frequently referenced nationally as one of the leaders in delivering high quality/low cost health care.

Logan is a beautiful university community of over 100,000. It is one of the top ten safest communities in which to live. Excellent primary care is available as well as a wide variety of specialty care. Logan fosters a wide variety of cultural, educational, recreational, sporting, commercial and health care opportune-ties. A moderate four seasons and majestic mountains allow for outstanding outdoor recreation opportunities. Along with the academic stimulation of Utah State University, Logan offers superb family living with quality school systems and reasonable living costs generally 10 to 25% less than other areas of the country.

Send/e-mail/fax CV to Intermountain Healthcare, Attn: Wilf Rudert, Physician Recruiting Dept., 36 S. State Street, 21st Floor, Salt Lake City, UT 84111.
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Central New York Psychiatric Center, a State-operated, JCAHO Accredited Facility, is seeking full time Psychiatrists at its main Inpatient Facility in Marcy, NY, and at its Forensic Outpatient Units throughout New York State, including: Albion, Clinton (Dannemora), Collins Downstate (Fishkill), Great Meadow (Comstock), 5 Points (Romulus), Groveland, Mid-State (Marcy), Sullivan (Fallsburg) and Wende (Alden). Comprehensive NY State Benefits package available. Outstanding NY State Pension Plan. Opportunity for Loan Forgiveness Program. Opportunities exist for additional compensation.

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$174,798 (general salary increase 4% in 2010 is scheduled).
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Direct Contact Information:
Dr. Jonathan Kaplan,
Clinical Director. Central New York Psychiatric Center
Box 300 Marcy, NY 13403.
Phone: (845) 483-3443, Fax: (845) 483-3455.
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For more information about Central New York Psychiatric Center, please visit the facility website:
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JOB SUMMARY/GENERAL OVERVIEW:

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The Cleveland Clinic has recently established the Lou Ruvo Center for Brain Health as a multi-site network of programs providing diagnostic and treatment services for persons with neurocognitive disorders.

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A faculty appointment commensurate with experience is available at the Cleveland Clinic Lerner College of Medicine.

MINIMUM REQUIREMENTS:

Board certification/eligibility in Neurology or Psychiatry. Valid and unrestricted license to practice medicine in the state of Ohio/Nevada. Previous experience in clinical practice, research and educational activities directly related to the major cognitive loss disorders.

Interested candidates should apply online at clevelandclinic.jobs, or contact Steve Niarhos at niarhos@ccf.org.

Cleveland Clinic is an equal opportunity employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and members of minority groups, as well as others who would bring additional dimensions to its research, teaching, and clinical missions. Cleveland Clinic is a smoke/drug-free work environment

St. Elizabeth's Medical Center

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PSYCHIATRIST

BOSTON

St. Elizabeth's Medical Center (SEMC) is seeking a BC/BE Psychiatrist for a position in Boston. In addition to the 32 adult beds, there is a new 16-bed inpatient geriatric psychiatry unit, an outpatient clinic, partial hospital program and a fully accredited Psychiatric Residency Program. Our specially trained team of health care professionals includes: Board-certified psychiatrists, internal medicine hospitalists, clinical social workers, geriatric and psychiatric nursing staff, nutritionists, occupational therapists, and physical therapists. Responsibilities will include clinical care, and teaching residents, medical students and physician assistants.

SEMC is a community-based 317-bed tertiary care hospital and part of Caritas Christi Health Care, the second largest health network in Eastern Massachusetts. Academic appointment available to qualified applicants. Competitive salary and excellent fringe benefits are offered.

Interested applicants should send a current CV, and contact information for three references to: Christine Kady, Physician Recruiter, at Christine.Kady@caritaschristi.org or call 617-562-7717.

Assistant or Associate Professor
Eastern Virginia Medical School

Eastern Virginia Medical School (EVMS) has initiated a search for a talented faculty member at the rank of Assistant or Associate Professor in the Department of Psychiatry and Behavioral Sciences. EVMS is located in a beautiful, coastal area of Virginia in the second largest metropolitan area in the state. This is a full-time position in a department that has a major commitment to clinical, educational and teaching activities. Clinical responsibilities include inpatient treatment, consultations, and emergency room evaluations at Sentara Norfolk General Hospital, as well as outpatient services at Eastern Virginia Medical School's Department of Psychiatry and Behavioral Sciences. Teaching responsibilities include education and supervision of psychiatric residents and medical students, as well as students from related disciplines, including Psychology and Art Therapy. The position will also emphasize participation in research activities within an academic culture, which places EVMS at the forefront of mental health advances. Currently the EVMS Department of Psychiatry includes 21 full-time faculty members, and the Residency Training Program has 16 residents and is fully accredited by ACGME. The successful candidate should have the ability to significantly contribute to the tripartite mission of education, research and patient-centered quality care. Eastern Virginia Medical School encourages all inquiries and all applications will be held in strictest confidence. Qualified applicants will be reviewed in the order by which their applications are received, and the process will continue until the current position is filled.

Please send letters of interest, accompanied by three letters of reference, to **Paul Sayegh MD, Vice-Chair, Department of Psychiatry and Behavioral Sciences, Hofheimer Hall, Suite 710, 825 Fairfax Avenue, Norfolk, VA 23507, Fax: 757-446-5918; E-mail: sayeghpa@evms.edu.** EVMS is an AA/EOE/Drug Free Workplace

PSYCHIATRIST | CentroMed

CentroMed is a community healthcare center located in San Antonio, TX. We provide medical, obstetric, dental, and mental health services with a team of 400+ employees. We are currently seeking a full-time adult psychiatrist to treat patients primarily with mood and anxiety disorders in an integrated health care setting.

This position does not have an on-call requirement. We offer psychiatric services, group, and individual counseling on an out-patient basis.

The ideal candidate will have at least two years of adult psychiatry and counseling experience. Bi-lingual skills in Spanish are a definite plus. Must have an unrestricted license in Texas prior to practicing.

We offer a competitive compensation package. This position is eligible for the student loan repayment program through the National Health Service Corps.

Please address questions or forward CV to the following:

Ernesto Gomez, Ph.D.
President & CEO
CentroMed
3750 Commercial Ave
San Antonio, TX 78221

Phone: (210) 334-3703
Fax: (210) 271-7208
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dose-dependent increase in the proportion of patients who developed sustained hypertension. **Abnormal Bleeding-** SSRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma-**Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania-**During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease-**Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1)*]. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation-** Dose-related elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [*see Adverse Reactions (6.1)*]. **Discontinuation of Treatment with Pristiq-** Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in major depressive disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [*see Dosage and Administration (2.4) and Adverse Reactions (6.1) in full prescribing information*]. **Renal Impairment-**In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [*see Clinical Pharmacology (12.6) in full prescribing information*]. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [*see Dosage and Administration (2.2) in full prescribing information*]. **Seizure-**Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hyponatremia-** Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6) in full prescribing information*]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine-** Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia-** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

ADVERSE REACTIONS: Clinical Studies Experience: The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥5% and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Adverse reactions reported as reasons for discontinuation of treatment- The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). Common adverse reactions in placebo-controlled MDD studies- Table 3 in full PI shows the incidence of common adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. Cardiac disorders: Palpitations, Tachycardia, Blood pressure increased; Gastrointestinal disorders: Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; General disorders and administration site conditions: Fatigue, Chills, Feeling jittery, Asthenia; Metabolism and nutrition disorders: Decreased appetite, weight decreased; Nervous system disorders: Dizziness, Somnolence, Headache, Tremor, Paraesthesia, Disturbance in attention; Psychiatric Disorders: Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; Renal and urinary disorders: Urinary hesitation; Respiratory, thoracic, and mediastinal disorders: Yawning; Skin and subcutaneous tissue disorders: Hyperhidrosis, Rash; Special Senses: Vision blurred; Mydriasis, Tinnitus, Dysgeusia; Vascular Disorders: Hot flush. Sexual function adverse reactions-Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). Men Only: Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; Women Only: Anorgasmia; Other adverse reactions observed in premarketing clinical studies: Other infrequent adverse reactions occurring at an incidence of <2% in MDD patients treated with Pristiq were: *Immune system disorders* – Hypersensitivity. *Investigations* – Weight increased, liver function test abnormal, blood prolactin increased. *Nervous system disorders* – Convulsion, syncope, extrapyramidal disorder. *Musculoskeletal and connective tissue disorders* – Musculoskeletal stiffness. *Psychiatric disorders* – Depersonalization, hypomania. *Respiratory, thoracic and mediastinal disorders* – Epistaxis. *Vascular disorders* – Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [*see Warnings and Precautions (5.7)*]. Discontinuation events-Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥5% include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information*]. Laboratory, ECG and vital sign changes observed in MDD clinical studies-The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. *Lipids*-Elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [*see Warnings and Precautions (5.8)*]. *Proteinuria*-Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. *ECG changes*-Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. *Vital sign changes*-Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. *Orthostatic hypotension*- In the short-term, placebo-controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease ≥30 mm Hg from supine to standing position) occurred more frequently in patients ≥65 years of age receiving Pristiq (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients <65 years of age receiving Pristiq (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218). **Adverse Reactions Identified During Post-Approval Use-** The following adverse reaction has been identified during post-approval use of Pristiq. Because post-approval reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: *Skin and subcutaneous tissue disorders* – Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*]. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*]. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)-** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-** There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects– Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects-Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (0-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-** Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [*see Adverse Reactions (6)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.12)*]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-** The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [*see Clinical Pharmacology (12.6)*].

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

This brief summary is based on Pristiq Prescribing Information W10529C009, revised September 2009.

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December 2009

FOR MAJOR DEPRESSIVE DISORDER

Help your patients on a path forward with proven SNRI therapy

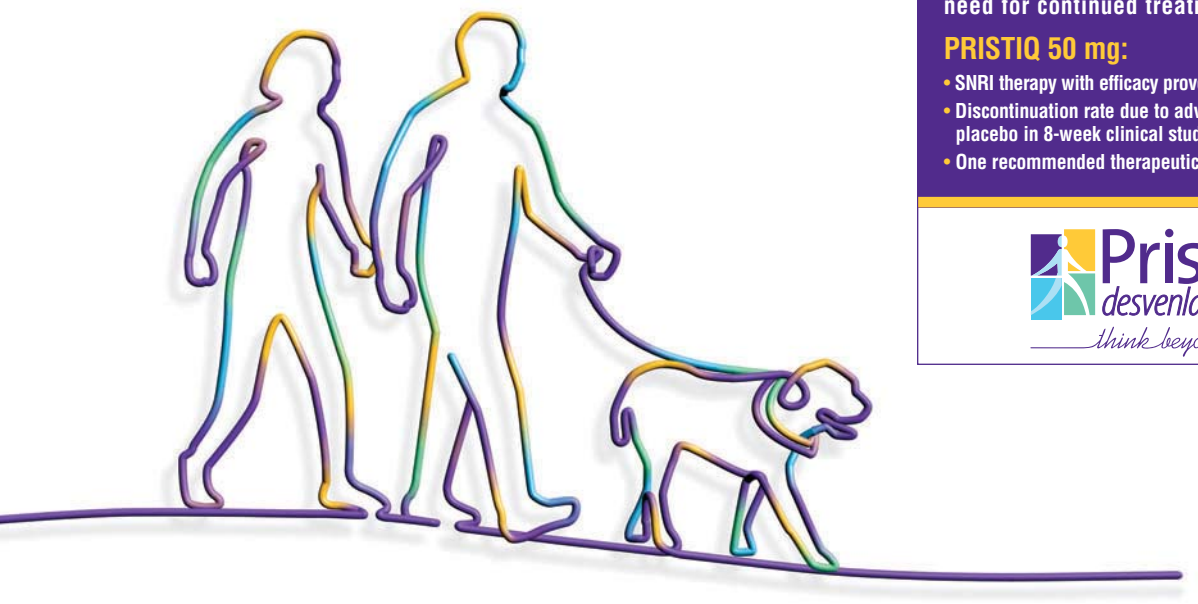
It's not just about starting your adult patients with MDD on therapy; it's about helping them toward their treatment goals. Patients should be periodically reassessed to determine the need for continued treatment.[1]

PRISTIQ 50 mg:

- **SNRI therapy with efficacy proven in 8-week clinical studies**
- **Discontinuation rate due to adverse events comparable to placebo in 8-week clinical studies**
- **One recommended therapeutic dose from the start[1]**

Pristiq® desvenlafaxine 50 mg

think beyond start™



Important Treatment Considerations for PRISTIQ

PRISTIQ is indicated for the treatment of major depressive disorder in adults.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PRISTIQ or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PRISTIQ is not approved for use in pediatric patients.

Contraindications

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

Warnings and Precautions

- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.**
- Development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions have been reported with SNRIs and SSRIs alone, including PRISTIQ treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs that impair the metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. If concomitant use with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.
- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose rather than abrupt cessation is recommended whenever possible.
- The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.
- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence ≥5% and ≥2x the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

Reference: 1. Pristiq® (desvenlafaxine) Prescribing Information, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent pages.

For more information on PRISTIQ, please visit **www.PristiqHCP.com**.

Pristiq®
EXTENDED-RELEASE TABLETS

Pfizer