Key Benefits

- *Broad definition of Insured includes the business entity and any present or former partner, executive officer, director, stockholder or employee*
- *Payment under the policy of Defense Expenses is in addition to the Limit of Liability (except as respects information privacy coverage)*
- *Reimbursement of up to $1,000 per day for loss of earnings resulting from the insured professional being away from the practice at the insurer's request to assist in defense of claims*
- *Coverage for costs incurred to defend a hearing or disciplinary action before a state or other licensing board or government body*
- *Punitive and exemplary damages where insurable by law*
- *Medical Payments coverage for injuries sustained by persons on your premises, regardless of fault*
- *Notice provision allows for reporting of incidents that have not yet resulted in actual claims*
- *Insured's consent is required for any settlement recommended by the insurer; policy provides for arbitration by your peers to resolve any "consent to settle issues"*
- *Extended reporting period coverage is available whereby claims may be reported if first made after the insured's death, permanent disability or retirement*
- *Premium for the extended reporting period coverage may be waived under certain circumstances*

Limits

- *Up to $2 million per claim/$6 million policy aggregate for Professional Liability and Business Liability*

Premium Credits Available

- *Completion of approved risk management seminars*
- *Favorable claim history*
- *Child and Adolescent Psychiatry*
- *Newly established practice*
- *Part-time practice or temporary suspension of practice*
- *Insureds new to program*
- *Members in training*

Please contact The American Professional Agency, Inc. for information regarding this program. Applications, information and rates can be obtained by calling 800-421-6694 or visiting www.americanprofessional.com

Insuring Company

ALLIED WORLD ASSURANCE COMPANY

and subsidiaries including
Darwin National Assurance Company

Program Administrator

American Professional Agency, Inc.

Danny Wedding, Mary Ann Boyd & Ryan M. Niemiec

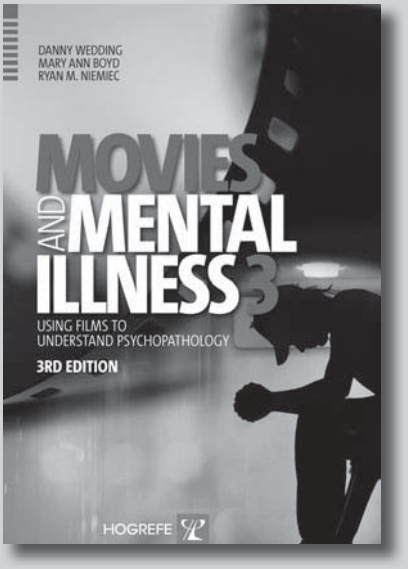
Movies and Mental Illness

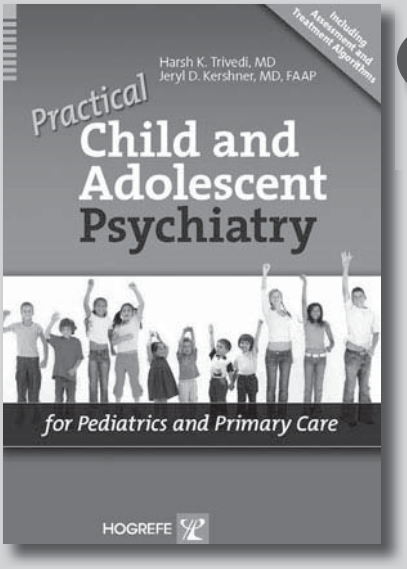
New edition!

Using Films to Understand Psychopathology

3rd, revised and expanded edition 2010, xii + 340 pages, US $49.00, ISBN: 978-0-88937-371-6

- The popular and critically acclaimed teaching tool – movies as an aid to learning about mental illness – has just got even better!
- Now with even more practical features and expanded contents: full film index, "Authors' Picks", sample syllabus, more international films.





Free slides for teachers and sample pages at **www.hogrefe.com**

Harsh K. Trivedi, MD & Jeryl D. Kershner, MD, FAAP

Practical Child and Adolescent Psychiatry for Pediatrics and Primary Care

2009, xvii + 230 pages, US $49.00, ISBN: 978-0-88937-349-5

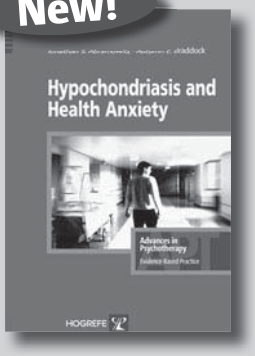
Starting with common chief complaints, this ground-breaking text provides systematic algorithms which guide you through each step of the evaluation and treatment process. By using innovative tables, figures, and programmed text, your clinical input leads you to the key information that you need.

From the series:
Advances in Psychotherapy – Evidence-Based Practice

Advances in Psychotherapy – Evidence-Based Practice is a series of authoritative, practice-oriented, easy-to-read, and compact guides for psychiatrists and other mental health professionals about psychotherapy treatments that work. Find out more at **www.hogrefe.com**.

- **Practice oriented:** The main emphasis is on information that therapists and practitioners can use in their daily practice
- **Easy to read:** The most important information is summarized in tables, illustrations, or displayed boxes, and highlighted by marginal notes
- **Authoritative:** Each volume is written and edited by leading authorities
- **Compact:** each volume consists of 80–100 pages
- **Low price:** each volume only US $29.80

New!



Available series titles:

Bipolar Disorder (Vol. 1) • **Heart Disease** (Vol. 2) • **Obsessive-Compulsive Disorder** (Vol. 3) • **Childhood Maltreatment** (Vol. 4) • **Schizophrenia** (Vol. 5) • **Treating Victims of Mass Disaster and Terrorism** (Vol. 6) • **Attention-Deficit/Hyperactivity Disorder in Children & Adults** (Vol. 7) • **Problem and Pathological Gambling** (Vol. 8) • **Chronic Illness in Children and Adolescents** (Vol. 8) • **Alcohol Use Disorders** (Vol. 10) • **Chronic Pain** (Vol. 11) • **Social Anxiety Disorder** (Vol. 12) • **Eating Disorders** (Vol. 13) • **Suicidal Behavior** (Vol. 14) • **Substance Use Problems** (Vol. 15) • **Elimination Disorders** (Vol. 16) • **Sexual Violence** (Vol. 17) • **Depression** (Vol. 18) • **Hypochondriasis and Health Anxiety** (Vol. 19) • **Public Health Tools for Practicing Psychologists** (Vol. 20)

Order online at **www.hogrefe.com** or (in the US) call toll-free **(800) 228-3749**

HOGREFE

Hogrefe Publishing
30 Amberwood Parkway · Ashland, OH 44805 · USA
Tel: (800) 228-3749 · Fax: (419) 281-6883
E-Mail: customerservice@hogrefe.com

Call for Nominations

The Institute of Living/Hartford Hospital is pleased to announce that nominations are now being accepted for the 2011 C. Charles Burlingame Award. This award, honoring an outstanding leader in psychiatric education, research or administration, is made in the memory of Dr. Burlingame, psychiatrist-in-chief from 1931 to 1950.

We invite you to nominate a person who has significantly advanced the field of psychiatry. The nomination must include a current curriculum vitae and two letters of support describing the candidate's achievements.

The winner of the Burlingame Award will be notified by February 15, 2011, and invited to present an original paper as the focal point of the award day events. The award, which will be presented at The Institute in the fall of 2011, includes a commemorative certificate and a $2500 honorarium plus expenses.

The Institute of Living is a comprehensive behavioral health system for the evaluation and treatment of psychiatric and addiction disorders. We offer a full continuum of services to patients and remain committed to the highest standards of clinical care, research and education.

Past Recipients

1988 Robert Kellner, M.D., Ph.D.
1989 William T. Carpenter, Jr., M.D.
1990 Dennis P. Cantwell, M.D.
1991 George E. Vaillant, M.D.
1992 A. John Rush, M.D.
1993 John C. Nemiah, M.D.
1994 Maurice J. Martin, M.D.
1995 Otto F. Kernberg, M.D.
1996 Charles P. O'Brien, M.D., Ph.D.
1997 Glen Owen Gabbard, M.D.
1998 Lissy F. Jarvik, M,D., Ph.D.
1999 Nancy C. Andreasen, M.D., Ph.D.
2000 Lewis L. Judd, M.D.
2001 Paul S. Appelbaum, M.D.
2002 Charles B. Nemeroff, M.D., Ph.D.
2003 Dilip V. Jeste, M.D.
2004 David H. Barlow, Ph.D.
2005 Herbert D. Kleber, M.D.
2006 Daniel N. Stern, M.D.
2007 Jerrold F. Rosenbaum, M.D.
2008 K. Ranga Rama Krishnan, M.D.
2009 David J. Kupfer, M.D.
2010 Professor Sir Michael Rutter

THE INSTITUTE OF LIVING
HARTFORD HOSPITAL

Nominations should be sent no later than January 15, 2011 to:
Harold I. Schwartz, M.D.
Psychiatrist-in-Chief and Vice-President, Behavioral Health
The Institute of Living/Hartford Hospital
200 Retreat Avenue
Hartford, CT 06106
or e-mailed to Ruth Black at rblack@harthosp.org

Volunteer for DSM-5 Field Trials

American Psychiatric Institute for Research and Education
Practice Research Network is recruiting

Practicing Psychiatrists

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.

Practicing psychiatrists interested in volunteering for potential participation in DSM-5 field trials should send an email to aparesearch@psych.org with the following information:

- Full name
- Institution or organizational affiliation
- Mailing address
- Job title
- Preferred e-mail
- Area of expertise (e.g., child psychiatry, geriatric psychiatry, etc.)

This information will help determine your eligibility to participate in the DSM-5 field trials.

For information about revisions to the DSM please visit www.DSM5.org

The American Psychiatric Institute for Research and Education is a 501 (c) (3) subsidiary of the American Psychiatric Association.

For your adult patients with schizophrenia

BECOME A FAN

OF MOVING FORWARD WITH SYMPTOM CONTROL

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

BECOME A FAN

INDICATION

FANAPT is an atypical antipsychotic agent indicated for the acute treatment of schizophrenia in adults. In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

IMPORTANT SAFETY INFORMATION

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

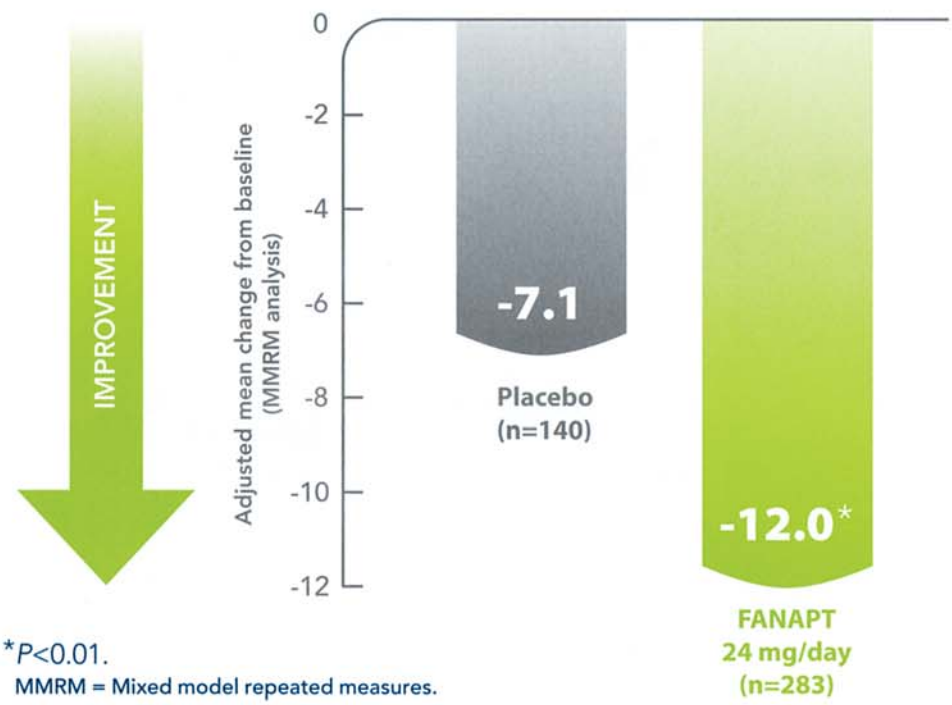
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death 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. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

*Please see brief summary of Prescribing Information, including **Boxed WARNING**, after page 8.*
Please see additional Important Safety Information on pages 6-7.

BECOME A FAN
OF IMPROVEMENT IN OVERALL SYMPTOMS WITH FANAPT

FANAPT improved total symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS)[1,2]



*$P<0.01$.
MMRM = Mixed model repeated measures.

Results are from a 4-week, double-blind, randomized, parallel-group, placebo- and active-controlled multicenter trial of patients with schizophrenia that evaluated the efficacy of FANAPT. The primary endpoint was change in baseline in PANSS total score at the end of treatment (day 28). The mean baseline score for FANAPT was 92.88 and 90.48 for placebo. FANAPT was titrated starting at 1 mg twice daily on day 1 of treatment, and increasing to 2, 4, 6, 8, 10, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7. FANAPT appeared to have similar efficacy to the active control in this trial, which also needed a slow titration to the target dose.[1,2]

Although there is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained, it is generally recommended that responding patients be continued beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.[1]

IMPORTANT SAFETY INFORMATION

FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. Therefore FANAPT must be titrated as directed. FANAPT should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

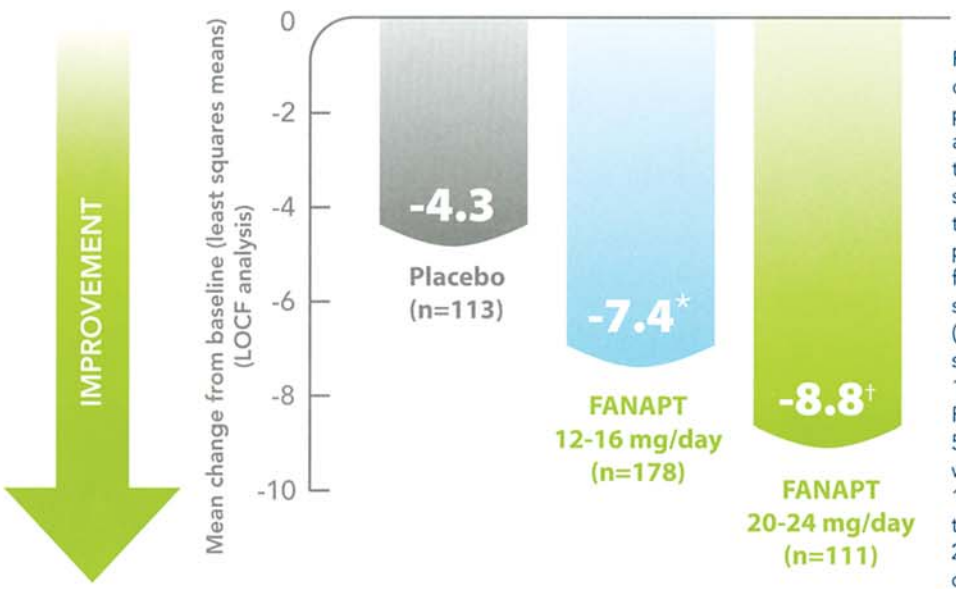
*Please see brief summary of Prescribing Information, including **Boxed WARNING**, after page 8.*

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

BECOME A FAN

BECOME A FAN OF FANAPT EFFICACY

FANAPT improved total symptoms, as measured by the Brief Psychiatric Rating Scale (BPRS)[1,3]



Unadjusted *P* values vs placebo:
*0.033 (12-16 mg/day).
†0.005 (20-24 mg/day).

LOCF = Last observation carried forward.

Results are from a 6-week, double-blind, randomized, parallel-group, placebo- and active-controlled multicenter trial of patients with schizophrenia that evaluated the efficacy of FANAPT. The primary endpoint was change from baseline in BPRS total score at the end of treatment (day 42). The mean baseline scores were 54.6 for FANAPT 12-16 mg/day, 55.1 for FANAPT 20-24 mg/day, and 55.5 for placebo. FANAPT was titrated starting at 1 mg twice daily on day 1 of treatment, and increasing to 2, 4, 6, 8, 10, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, as needed. The active control in this trial appeared to be superior to FANAPT within the first 2 weeks, which may in part be explained by the more rapid titration that was possible for that drug.[1,3]

IMPORTANT SAFETY INFORMATION

FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (e.g., paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec. No cases of torsades de pointes or other severe cardiac arrhythmias were observed during the premarketing clinical program. FANAPT should be avoided in combination with other drugs that are known to prolong QTc. FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias, and in circumstances that may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval. Use caution and consider dose modification. Patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

BECOME A FAN OF FANAPT

FANAPT is a distinct molecule[1]:

FANAPT:

- Is a mixed D_2/5-HT_2 antagonist with a high affinity for 5-HT_{2A} receptors, a low affinity for H_1 receptors, and no appreciable affinity for cholinergic muscarinic receptors*
- Is not a derivative or metabolite of another antipsychotic agent

*The clinical significance of the receptor-binding affinity of FANAPT is unknown.

Discontinuation rates due to adverse events (AEs) were similar to placebo[1]

Discontinuation rates due to AEs

FANAPT ≥10 mg/day (N=874)	Placebo (N=587)
5%	5%

Data above based on pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies. The types of adverse events that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

Most common adverse reactions ≥5% in patients treated with FANAPT that occurred at a rate of at least twice that of placebo for at least 1 dose[1]

- Dizziness
- Dry mouth
- Fatigue
- Nasal congestion
- Somnolence
- Tachycardia
- Orthostatic hypotension
- Weight increase

Data above based on pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies.

IMPORTANT SAFETY INFORMATION

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

*Please see brief summary of Prescribing Information, including **Boxed WARNING**, after page 8.*

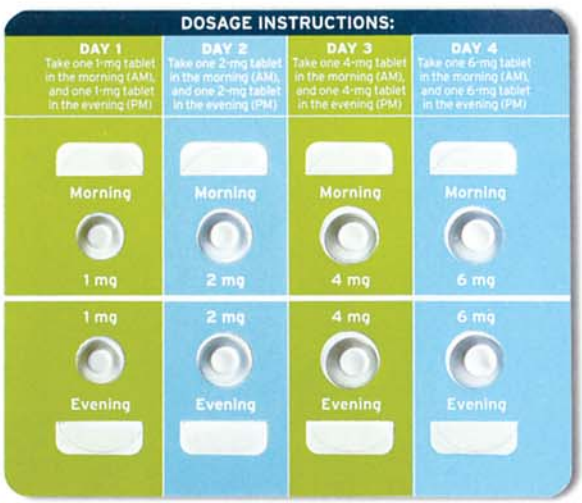
 Please see additional Important Safety Information on pages 6-7.

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
BECOME A FAN

BECOME A FAN
OF REACHING THE LOWEST EFFECTIVE DOSE IN 4 DAYS

A titration pack makes it simple to reach an efficacious dose range[1]

Treatment Initiation
Titrate to the lowest efficacious dose (6 mg twice daily by day 4).



- FANAPT must be titrated from a low starting dose to avoid orthostatic hypotension. The recommended starting dose is 1 mg twice daily. Increases to reach the target dose range of 6-12 mg twice daily (12-24 mg/day) may be made with daily dosage adjustments not to exceed 2 mg twice daily (4 mg/day). The maximum recommended dose is 12 mg twice daily (24 mg/day)[1]
  - — Control of symptoms may be delayed during the first 1 to 2 weeks of treatment[1]
- The titration pack is available as both sample and prescription

FANAPT can be administered without regard to meals[1]

The efficacy of FANAPT has been demonstrated at 6 mg twice daily, with dosing flexibility up to 12 mg twice daily[1]

(tablets actual size)

IMPORTANT SAFETY INFORMATION

FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product.

References: 1. FANAPT [prescribing information]. Rockville, MD: Vanda Pharmaceuticals Inc; July 2009. **2.** Data on file. Study number: VP-VYV-683-3101. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2007. **3.** Data on file. BPRS Analysis: IL0522A3005. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2008.

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

INDICATION

FANAPT is an atypical antipsychotic agent indicated for the acute treatment of schizophrenia in adults. In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

IMPORTANT SAFETY INFORMATION

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. Analysis of seventeen placebo-controlled trials (modal duration 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 the risk of death 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. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

Contraindications: FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product.

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

QT Prolongation: FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (e.g., paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec. No cases of torsades de pointes or other severe cardiac arrhythmias were observed during the premarketing clinical program. FANAPT should be avoided in combination with other drugs that are known to prolong QTc. FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias, and in circumstances that may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval. Use caution and consider dose modification. Patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

Neuroleptic Malignant Syndrome (NMS): Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. NMS can cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysarrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management of this syndrome should include immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If patient requires antipsychotic drug treatment after recovery from NMS, reintroduction should be carefully considered and patient should be carefully monitored.

Tardive Dyskinesia (TD): The risk of developing tardive dyskinesia, and the likelihood that it will become irreversible, may increase as the duration of treatment and the total cumulative dose increases. 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, drug discontinuation should be considered.

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

Hyperglycemia and Diabetes: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. 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 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 antidiabetic treatment despite discontinuation of the antipsychotic.

Weight Gain: The mean weight change from baseline to endpoint in the short-term studies was -0.1 kg for placebo versus 2.0 kg for FANAPT-treated patients. Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

Seizures: As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia.

Orthostatic Hypotension and Syncope: FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. Therefore FANAPT must be titrated as directed. FANAPT should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: In clinical trial and post-marketing experience with antipsychotic agents, events of leukopenia/neutropenia have been reported temporally. Agranulocytosis (including death) has also been reported. Patients with a pre-existing low white blood cell count 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 should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds.

Body Temperature Regulation: Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which 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.

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. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets in order to reduce the risk of overdose.

Priapism: Three cases of priapism have been reported in the pre-marketing FANAPT program. Severe priapism may require surgical intervention.

Cognitive and Motor Impairment: FANAPT, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

Commonly observed adverse events: Commonly observed adverse reactions (incidence ≥5% and twofold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increase.

Specific Populations

Pregnancy: FANAPT is Pregnancy Category C.

Hepatic Impairment: FANAPT is not recommended for patients with hepatic impairment.

Drug Interactions: Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. FANAPT has the potential to enhance the effect of certain antihypertensive agents. Coadministration of FANAPT with potential CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) and potential CYP3A4 inhibitors (e.g., ketoconazole) should be done with caution. FANAPT dose should be reduced as directed.

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

For your adult patients with schizophrenia

BECOME A FAN OF FANAPT

BECOME A FAN OF IMPROVEMENT IN OVERALL SYMPTOMS WITH FANAPT

FANAPT was proven effective in improving symptoms in 2 clinical trials, as measured by[1]:

- Positive and Negative Syndrome Scale (PANSS) total score (4-week trial)
- Brief Psychiatric Rating Scale (BPRS) total score (6-week trial)

See pages 2-3 for details of the pivotal FANAPT clinical trials.

BECOME A FAN OF FANAPT, A DISTINCT MOLECULE

- FANAPT is a mixed D_2/5-HT_2 antagonist with a high affinity for 5-HT_{2A} receptors, a low affinity for H_1 receptors, and no appreciable affinity for cholinergic muscarinic receptors[1,*]

*The clinical significance of the receptor-binding affinity of FANAPT is unknown.

BECOME A FAN OF FANAPT DISCONTINUATION RATES DUE TO ADVERSE EVENTS THAT WERE SIMILAR TO PLACEBO (5%)[1]

BECOME A FAN OF FANAPT DOSING AND ADMINISTRATION

- Titrate to the lowest efficacious dose by day 4[1]
  - — From a low starting dose to avoid orthostatic hypotension
- A titration pack makes it simple to reach an efficacious dose range and is available as a sample and by prescription
- Dosed twice daily with or without food

IMPORTANT SAFETY INFORMATION

Commonly observed adverse reactions (incidence ≥5% and twofold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increase.

*Please see brief summary of Prescribing Information, including **Boxed WARNING**, after page 8.*

Please see Important Safety Information on pages 6-7.

See package insert for full Prescribing Information at www.Fanapt.com.

Fanapt® (iloperidone) tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

BECOME A FAN

NOVARTIS

Patient Assistance NOW
Novartis. The care you want. The help you need.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

8/10

FNP-1005220

FANAPT™ *(iloperidone)* **tablets**
Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for full prescribing information.

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. Analysis of seventeen placebo-controlled trials (modal duration 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 the risk of death 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. FANAPT is not approved for the treatment of patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

FANAPT™ tablets are indicated for the acute treatment of adults with schizophrenia *[see Clinical Studies (14) in the full prescribing information]*.

When deciding among the alternative treatments available for this condition, the prescriber should consider the finding that FANAPT is associated with prolongation of the QTc interval *[see Warnings and Precautions (5.2)]*. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether FANAPT will cause torsade de pointes or increase the rate of sudden death is not yet known.

Patients must be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the acute treatment of schizophrenia *[see Dosage and Administration (2.1) and Clinical Studies (14) in the full prescribing information]*.

The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2.3) in the full prescribing information]*.

4 CONTRAINDICATIONS

FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis Increased Mortality

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

Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 QT Prolongation

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

The use of FANAPT should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thiordazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism *[see Drug Interactions (7.1)]*, and in patients with reduced activity of CYP2D6 *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. FANAPT should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 ms.

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.3 Neuroleptic Malignant Syndrome (NMS)

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

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

The management of this syndrome should include: (1) immediate discontinuation of the 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

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, which may 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 on 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 is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered increases. 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 tardive dyskinesia, 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, FANAPT should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. 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 tardive dyskinesia appear in a patient on FANAPT, drug discontinuation should be considered. However, some patients may require treatment with FANAPT despite the presence of the syndrome.

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because FANAPT was not marketed at the time these studies were performed, it is not known if FANAPT is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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 antidiabetic treatment despite discontinuation of the suspect drug.

5.6 Weight Gain

Based on the pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the proportions of patients having a weight gain of ≥7% body weight was 12% for FANAPT 10-16 mg/day, 18% for FANAPT 20-24 mg/day, and 13% for FANAPT (combined doses) versus 4% for placebo. The mean weight change from baseline to endpoint in the short-term studies was -0.1 kg for placebo versus 2.0 kg for FANAPT-treated patients. Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

5.7 Seizures

In short-term placebo-controlled trials (4- to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with FANAPT compared to 0.3% (2/587) on placebo. As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.8 Orthostatic Hypotension and Syncope

FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its alpha1-adrenergic antagonist properties. In double-blind placebo-controlled short-term studies, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1344) of patients treated with FANAPT, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20-24 mg/day, 3% of patients given 10-16 mg/day, and 1% of patients given placebo. More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

FANAPT should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.9 Leukopenia, Neutropenia and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include preexisting 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 should discontinue FANAPT at the first sign of a 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 FANAPT and have their WBC followed until recovery.

5.10 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadalsteroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

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 contemplated in a patient with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with FANAPT *[see Nonclinical Toxicology (13.1) in the full prescribing information]*. 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; the available evidence is considered too limited to be conclusive at this time.

In a short-term placebo-controlled trial (4-weeks), the mean change from baseline to endpoint in plasma prolactin levels for the FANAPT 24 mg/day-treated group was an increase of 2.6 ng/mL compared to a decrease of 6.3 ng/mL in the placebo-group. In this trial, elevated plasma prolactin levels were observed in 26% of adults treated with FANAPT compared to 12% in the placebo group. In the short-term trials, FANAPT was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.12 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. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.13 Suicide

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

5.14 Priapism

Three cases of priapism were reported in the pre-marketing FANAPT program. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. FANAPT shares this pharmacologic activity. Severe priapism may require surgical intervention.

5.15 Potential for Cognitive and Motor Impairment

FANAPT, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11.9% (104/874) of adult patients treated with FANAPT at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The information below is derived from a clinical trial database for FANAPT consisting of 2070 patients exposed to FANAPT at doses of 10 mg/day or greater, for the treatment of schizophrenia. All of these patients who received FANAPT were participating in multiple-dose clinical trials. The conditions and duration of treatment with FANAPT varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions, reactions were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportions of individuals who experienced a treatment-emergent adverse reaction 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 information presented in these sections was derived from pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received FANAPT at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among FANAPT-Treated Patients and More Frequent than Placebo

Table 1 enumerates the pooled incidences of treatment-emergent adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with FANAPT in any of the dose groups, and for which the incidence in FANAPT-treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 1: Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

	Percentage of Patients Reporting Reaction		
Body System or Organ Class Dictionary-derived Term	Placebo (N=587)	FANAPT 10-16 mg/day (N=483)	FANAPT 20-24 mg/day (N=391)
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5
Hypotension	<1	<1	3

*Table includes adverse reactions that were reported in 2% or more of patients in any of the FANAPT dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Dose-Related Adverse Reactions in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated with FANAPT, and for which the incidence in patients treated with FANAPT 20-24 mg/day were twice than the incidence in patients treated with FANAPT 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate for at least one dose: dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increased were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials

Pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies provided information regarding treatment-emergent EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 2.

Table 2: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (%) (N=587)	FANAPT 10-16 mg/day (%) (N=483)	FANAPT 20-24 mg/day (%) (N=391)
All EPS events	**11.6**	**13.5**	**15.1**
Akathisia	2.7	1.7	2.3
Bradykinesia	0	0.6	0.5
Dyskinesia	1.5	1.7	1.0
Dystonia	0.7	1.0	0.8
Parkinsonism	0	0.2	0.3
Tremor	1.9	2.5	3.1

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials

An examination of population subgroups in the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race *[see Warnings and Precautions (5.1)]*.

Laboratory Test Abnormalities in Clinical Trials

A between-group comparison of the pooled data from four placebo-controlled, 4- or 6-week studies, revealed no medically important differences between FANAPT and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry, including glucose. Similarly, there were no medically important changes in triglyceride and total cholesterol measurements (Table 3). There were no differences between FANAPT and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.

Table 3: Change in Lipids Compared to Placebo

Mean change from baseline (mg/dL)	Placebo (N=587)	FANAPT 10-16 mg/day (N=483)	FANAPT 20-24 mg/day (N=391)
Triglycerides	-26.5	-26.5	-8.8
Total Cholesterol	-7.7	-3.9	3.9

In short-term placebo-controlled trials (4- to 6-weeks), there were 1.0% (13/1342) iloperidone-treated patients with hematocrit at least one time below the extended normal range during post-randomization treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

Other Reactions During the Pre-marketing Evaluation of FANAPT

The following is a list of MedDRA terms that reflect treatment-emergent adverse reactions in patients treated with FANAPT at multiple doses ≥4 mg/day during any phase of a trial with the database of 3210 FANAPT-treated patients. All reported reactions are included except those already listed in Table 1, or other parts of the *Adverse Reactions (6)* section, those considered in the *Warnings and Precautions (5)*, those reaction terms which were so general as to be uninformative, reactions reported in fewer than 3 patients and which were neither serious nor life-threatening, reactions that are otherwise common as background reactions, and reactions considered unlikely to be drug related. It is important to emphasize that, although the reactions reported occurred during treatment with FANAPT, 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: frequent adverse events are those occurring in at least 1/100 patients (only those not listed in Table 1 appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders: Infrequent – anaemia, iron deficiency anemia; *Rare* – leukopenia

Cardiac Disorders: Frequent – palpitations; *Rare* – arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders: Infrequent – vertigo, tinnitus

Endocrine Disorders: Infrequent – hypothyroidism

Eye Disorders: Frequent – conjunctivitis (including allergic); *Infrequent* – dry eye, blepharitis, eyelid edema, eye swelling, lenticular opacities, cataract, hyperemia (including conjunctival)

Gastrointestinal Disorders: Infrequent – gastritis, salivary hypersecretion, fecal incontinence, mouth ulceration; *Rare* – aphthous stomatitis, duodenal ulcer, hiatus hernia, hyperchlorhydria, lip ulceration, reflux esophagitis, stomatitis

General Disorders and Administrative Site Conditions: Infrequent – edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; *Rare* – hyperthermia

Hepatobiliary Disorders: Infrequent – cholelithiasis

Investigations: Frequent: weight decreased; *Infrequent* – hemoglobin decreased, neutrophil count increased, hematocrit decreased

Metabolism and Nutrition Disorders: Infrequent – increased appetite, dehydration, hypokalemia, fluid retention

Musculoskeletal and Connective Tissue Disorders: Frequent – myalgia, muscle spasms; *Rare* – torticollis

Nervous System Disorders: Infrequent – paraesthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus; *Rare* – restless legs syndrome

Psychiatric Disorders: Frequent – restlessness, aggression, delusion; *Infrequent* – hostility, libido decreased, paranoia, anorgasmia, confusional state, mania, catatonia, mood swings, panic attack, obsessive-compulsive disorder, bulimia nervosa, delirium, polydipsia psychogenic, impulse-control disorder, major depression

Renal and Urinary Disorders: Frequent – urinary incontinence; *Infrequent* – dysuria, pollakiuria, enuresis, nephrolithiasis; *Rare* – urinary retention, renal failure acute

Reproductive System and Breast Disorders: Frequent – erectile dysfunction; *Infrequent* – testicular pain, amenorrhea, breast pain; *Rare* – menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis

Respiratory, Thoracic and Mediastinal Disorders: Infrequent – epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; *Rare* – dry throat, sleep apnea syndrome, dyspnea exertional

7 DRUG INTERACTIONS

Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. Due to its α1-adrenergic receptor antagonism, FANAPT has the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect FANAPT

Iloperidone is not a substrate for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of iloperidone with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for iloperidone metabolism. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., fluoxetine, paroxetine) can inhibit iloperidone elimination and cause increased blood levels.

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 4 days), a potent inhibitor of CYP3A4, with a 3 mg single dose of iloperidone to 19 healthy volunteers, ages 18-45, increased the AUC of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Iloperidone doses should be reduced by about one-half when administered with ketoconazole or other strong inhibitors of CYP3A4 (e.g., itraconazole). Weaker inhibitors (e.g., erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level.

Fluoxetine: Co-administration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2-3 fold, and decreased the AUC of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with fluoxetine. When fluoxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to the previous level.

Paroxetine: Co-administration of paroxetine (20 mg/day for 5-8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with paroxetine. When paroxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to previous levels.

Paroxetine and Ketoconazole: Co-administration of paroxetine (20 mg once daily for 10 days), a CYP2D6 inhibitor, and ketoconazole (200 mg twice daily) with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in a 1.4 fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4 fold decrease in the P95 in the presence of paroxetine. So giving iloperidone with inhibitors of both of its metabolic pathways did not add to the effect of either inhibitor given alone. Iloperidone doses should therefore be reduced by about one-half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor.

7.2 Potential for FANAPT to Affect Other Drugs

In vitro studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, or CYP2E1. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

Dextromethorphan: A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in C_{max} of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Fluoxetine: A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

7.3 Drugs that Prolong the QT Interval

FANAPT should not be used with any other drugs that prolong the QT interval *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

FANAPT caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m^2 basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m^2 basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m^2 basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

FANAPT was excreted in milk of rats during lactation. It is not known whether FANAPT or its metabolites are excreted in human milk. It is recommended that women receiving FANAPT should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

8.5 Geriatric Use

Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with FANAPT in pre-marketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia *[see Boxed Warning and Warnings and Precautions (5.1)]*. The safety and efficacy of FANAPT in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with FANAPT, vigilance should be exercised.

8.6 Renal Impairment

Because FANAPT is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of FANAPT. Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations (C_{max}) of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 any of the three analytes measured. $AUC_{0-\infty}$ was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

8.7 Hepatic Impairment

A study in mild and moderate liver impairment has not been conducted. FANAPT is not recommended for patients with hepatic impairment.

8.8 Smoking Status

Based on *in vitro* studies utilizing human liver enzymes, FANAPT is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FANAPT is not a controlled substance.

9.2 Abuse

FANAPT has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, FANAPT, will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of FANAPT misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of FANAPT was documented in eight patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a three-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a four-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms where those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension) of FANAPT.

10.2 Management of Overdose

There is no specific antidote for FANAPT. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

16 STORAGE

Store FANAPT tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect FANAPT tablets from exposure to light and moisture.

Distributed by Vanda Pharmaceuticals Inc., Rockville, MD 20850

Revised: 07/2009

Complex puzzles. Comprehensive solutions.

At Western Psychiatric Institute and Clinic of UPMC, we take on complex disorders that some other centers won't even attempt to treat.

But whether a patient has a difficult-to-treat disorder or one more easily treated, teams of specialists in psychiatry, psychopharmacology, clinical psychology, and medicine craft complete, individualized treatment plans that draw upon the latest clinical research, much of it conducted by our own investigators. Whether we're interpreting our clinical trial data or a patient's lab results, our work to advance the understanding and treatment of bipolar disorder, eating disorders, autism, and geriatric behavioral health issues is world-class. In fact, we have one of the world's most comprehensive programs for mood disorders, with research-based treatments for patients at every level of need, at every stage of life.

With nearly 400 inpatient psychiatric beds and 75 ambulatory programs, we care for people when they're feeling their worst *and* support them when they're at their best, back with their families in their home towns. Each year, Western Psychiatric helps people of all ages — at all stages of recovery, from all over the world — live healthier and more productive lives.

UPMC

UPMC.com | 1-800-533-UPMC

Affiliated with the **University of Pittsburgh School of Medicine**,
UPMC is ranked among the nation's best hospitals by *U.S.News & World Report*.

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.

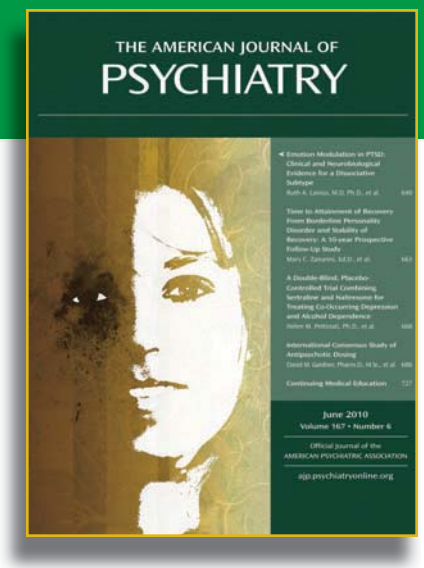
Schering-Plough

Manufactured by Catalent UK Swindon Zydis Ltd., Blagrove, Swindon, Wiltshire, SN5 8RU, UK.
Distributed by Schering Corporation, a subsidiary of Schering-Plough Corporation,
Kenilworth, NJ 07033 USA.
U.S. Patent No. 5,763,476.

33684002T-JBS
8/09

The American Journal of PSYCHIATRY

Latest IMPACT FACTOR 12.52!



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.

ISSN 0002-953X
ajp.psychiatryonline.org
To order a subscription, visit
www.appi.org.

American Psychiatric Publishing, Inc.
The *First* and *Last* Word in Psychiatry
American Psychiatric Publishing, Inc.
www.appi.org • 1-800-368-5777 • 703-907-7322
Find us on facebook and twitter Priority Code AH1036

When expressing emotions is a matter of chance, consider PBA

- Pseudobulbar affect (PBA) is a poorly understood neurologic condition characterized by episodes of crying or laughing that are sudden, frequent, and involuntary[1]
- PBA occurs in approximately 10% to 20% of patients with ALS, MS, stroke, traumatic brain injury, and other neurologic conditions[1]
- PBA can disrupt lives, causing significant functional impairment[1]
- Understanding PBA can be a relief to patients and their families

Learn more at PBAinfo.org

Reference: 1. Dark FL, McGrath JJ, Ron MA. Pathological laughing and crying. *Aust N Z J Psychiatry*. 1996;30(4):472-479.

AVANIR pharmaceuticals

pba
pseudobulbar affect

Clinical Research Fellowship in Psychopharmacology
The Experimental Therapeutics and Pathophysiology Branch in Mood Disorders
National Institute of Mental Health
Bethesda, MD, USA

The Division of Intramural Research Programs (DIRP) of The National Institute of Mental Health (NIMH), a major research arm of the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS) is recruiting Clinical Fellows to participate in research studies to investigate the pathophysiology of major depressive disorder and bipolar disorder, with the concomitant goal of developing innovative treatments for these disorders. This training program focuses on teaching the knowledge and skills necessary to conduct clinical trials and neurobiology research in mood disorders using a variety of psychophysiological, genetic, and neuroimaging methods. The successful candidate will have completed at least three years of psychiatry residency training, be eligible to obtain medical licensure in Maryland, and have experience diagnosing and treating major depressive disorder and bipolar disorder. This is a full time position located on the NIH campus in Bethesda, Maryland. Salary is commensurate with experience. Interested applicants should send a curriculum vitae, bibliography, statement of research interests, and three letters of recommendation to: Carlos Zarate, MD (**zaratec@mail.nih.gov**), The Experimental Therapeutics & Pathophysiology Branch, DIRP, NIMH, CRC, Bld. 10, Unit 7 Southeast, Room 7-3465, Bethesda, MD 20892-1282.

NIMH
National Institute of Mental Health

DHHS and NIH are Equal Opportunity Employers

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
Egomez.cdb@tachc.org

MAYO CLINIC

Heal the sick, advance the science, share the knowledge.

Child and Adolescent Psychiatrist

Mayo Clinic in Rochester, MN seeks an outstanding child and adolescent psychiatrist with expertise in the assessment and treatment of children with ADHD, mood and anxiety disorders. Experience with evidence-based (EB) assessment instruments (e.g., CAPA, K-SADS) and rating scales is needed. Experience and commitment to multidisciplinary clinical assessment and treatment, as well as team-based care and evidence-based treatment models are essential. Experience in implementing research-informed multidisciplinary clinical services is required, as is experience in leading multidisciplinary care teams in caring for children with ADHD, mood and anxiety disorders. Experience in group psychotherapy EB treatment models is also highly desired, as well as a background in research and quality improvement studies in real-world treatment settings. The position includes opportunities in leadership, program development and clinical research.

The child and adolescent psychiatrist will join 12 other child and adolescent psychiatrists in the Department of Psychiatry and Psychology, as well as eight child/pediatric psychologists and neuropsychologists, and a team of master's-level clinical social workers, clinical nurse specialists and psychologists. Abundant education/supervision opportunities are available within the accredited General and Child and Adolescent Psychiatry and Psychology post-doctoral programs, as well as residents from other departments.

Candidates must be eligible for licensure in the state of Minnesota and be board-certified through the American Board of Psychiatry and Neurology. The position carries an academic appointment in the Mayo Clinic College of Medicine, rank commensurate with experience. The compensation package at Mayo Clinic is competitive and includes exceptional professional benefits for retirement, travel and meeting participation, and minimal call. To learn more about Mayo Clinic and Rochester, MN, please visit **www.mayoclinic.org/physician-jobs**

Applications will be reviewed immediately and accepted until the position is filled. Please send a letter of intent and curriculum vitae, along with any representative publications to the Search Committee Chair. In addition, three letters of reference should be forwarded to the same, but under separate cover.

Peter S. Jensen, MD, Professor of Psychiatry
Search Committee Chair, Division of Child Psychiatry and Psychology
Department of Psychiatry and Psychology
Mayo Clinic c/o Sandra J. Stevens
200 First Street SW • Rochester, MN 55905
Email: stevens.sandra@mayo.edu

Mayo Foundation is an affirmative action and equal opportunity employer and educator. Post-offer/pre-employment drug screening is required.

Interventional Neuropsychiatrist

The Department of Psychiatry, (in collaboration with the Departments of Neurology and Radiology, and the Section of Neurosurgery) at Dartmouth Medical School (DMS) and Dartmouth-Hitchcock Medical Center (DHMC) is seeking a senior level faculty member to build and lead a new program in Interventional Neurotherapeutics.

The successful candidate will be an established clinical scientist who will strengthen existing basic, translational, and clinical research programs at DMS and DHMC that address the treatment of neuropsychiatric disorders such as refractory mood disorders, substance use disorders, cognitive impairment associated with brain disease and obsessive-compulsive disorder. He/she will have a track record of federal funding in his/her area of interest and experience in the application of neuromodulatory procedures such as deep brain stimulation, rTMS, ECT, VNS or related techniques to neuropsychiatric disorders. The successful candidate will strengthen collaborative links (and provide vision and leadership to) between existing programs at DMS and DHMC in the clinical and experimental use of deep brain stimulation and vagus nerve stimulation, animal models of alcoholism, human and animal neuroimaging, neuro-psychopharmacology, epilepsy and neuropathic pain, as well as animal and human studies of neural circuitry related to reward behavior and attentional mechanisms.

Curriculum vitae, a letter of interest, and representative publications should be addressed to Thomas McAllister, MD, Search Co-Chair, and sent to Kami Carter at Kami.L.Carter@Dartmouth.edu.

Dartmouth Medical School is an Equal Opportunity/ Affirmative Action Employer and encourages applications from women and members of minority groups.

Psychiatrist Opening

Boston, MA: December 2010 Opening for 2, Half-time Psychiatrists at Brigham & Women's Hospital (BWH), member, Partners HealthCare. Each position is for a 0.5 FTE psychiatrist to care for predominately monolingual Spanish-speaking adults. One position is at Brookside Community Health Center (3297 Washington St. Jamaica Plain), a comprehensive multi-disciplinary site and the other at Spanish Clinic (75 Frances St, Boston), a primary care practice. Responsibilities include: collaborating with program director in providing clinical leadership of interdisciplinary team that includes psychologists, social workers, and substance abuse specialists (Brookside); performing comprehensive psychiatric evaluations, pharmacotherapy and psychotherapy when indicated; referring to social services as needed, working closely with co-located primary care and Ob/Gyn specialists and performing crisis evaluations (at Spanish Clinic). Positions include professional appointment at BWH and Harvard Medical School. Can be combined as a Full-Time Position if candidate is interested.

Requirements: M.D. or D.O., plus completion of accredited Psychiatric Residency. Must be: BC or BE in Psychiatry (American Board of Psychiatry & Neurology); Full MA. Medical License; Fluency in Spanish & English.

We are an equal opportunity employer committed to workforce diversity.

Competitive Salary and Excellent Benefits package offered through Brigham and Women's Hospital

All interested parties should send or fax their resume to:

Paula McNichols, Executive Director
Brookside Community Health Center
3297 Washington St., Jamaica Plain, MA 02130.
Phone: 617-983-6039
Fax: 617-524-1716
E-mail: pmcnichols@partners.org

Cleveland Clinic

LEADERSHIP IN THE FUTURE OF HEALTHCARE

We are seeking Neurologists and Neuropsychiatrists for Cleveland and Las Vegas, Nevada.

Neurologists & Neuropsychiatrists

LOU RUVO CENTER FOR BRAIN HEALTH

Cleveland, Ohio | Las Vegas, Nevada

JOB SUMMARY/GENERAL OVERVIEW:

The physician will provide direct patient assessment services and participate in advancing clinical trials and translational research for neurocognitive disorders, including Alzheimer's disease, frontotemporal dementia and related conditions.

The physician will work directly with Dr. Jeffrey Cummings to advance the neurocognitive diagnostic and therapeutic programs in Cleveland, Las Vegas and other Cleveland Clinic campuses.

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.

Clinical trials and translational research are integrated into clinical care to accelerate drug development for these devastating disorders. Development of care paths, guidelines and treatment standards are important objectives of the innovative program.

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

PSYCHIATRIST
Affective Disorders Specialist

The Department of Psychiatry is seeking a **Psychiatrist—Affective Disorders Specialist** to join the faculty of Dartmouth Medical School at Dartmouth-Hitchcock Medical Center in Lebanon, NH.

This newly created position, Director of the Affective Disorders Service, will develop and lead an affective disorders program that involves research, clinical care and teaching. The successful applicant will provide clinical consultations and supervise affective disorder specialty care. He/she will lead affective disorders training for medical students, residents and fellows. In addition, he/she will be expected to build an externally supported affective disorders research program.

The ideal candidate will be a skilled clinician and enthusiastic teacher, with strong interest and experience in research related to affective disorders. Candidates should be board certified or eligible in Psychiatry. Academic rank and salary will be consistent with experience. A letter of interest, CV and three letters of reference should be addressed to William C. Torrey MD, Vice Chair for Clinical Services for the Department of Psychiatry and chair of this search, and sent to Kami Carter at Kami.L.Carter@Dartmouth.edu.

Dartmouth College is an Equal Opportunity/Affirmative Action Employer and encourages applications from women and members of minority groups.

UNC
LINEBERGER COMPREHENSIVE CANCER CENTER
N.C. CANCER HOSPITAL

PSYCHIATRIST

The Department of Psychiatry and the Lineberger Comprehensive Cancer Center of the University of North Carolina (UNC) School of Medicine at Chapel Hill are seeking an early career psychiatrist to join the UNC Psycho-oncology Service.

DESCRIPTION

This is a full time fixed-term position at the (Clinical track) Clinical Assistant or Clinical Associate Professor level. This clinical service is a component of the UNC Comprehensive Cancer Support Program.

Responsibilities will include: providing inpatient and outpatient clinical consultation and psychiatric management for cancer patients; medical leadership for a multidisciplinary psycho-oncology team; teaching medical students, residents, and other health care trainees and clinicians; and participation in the clinical research activities of the Comprehensive Cancer Support Program.

The successful candidate should have strong clinical skills, a record of scholarly achievement; evidence of effective leadership and demonstrated ability to promote a collegial environment that fosters ongoing collaboration. Candidates should have clinical experience working with cancer patients as evidenced by completion of a fellowship in psycho-oncology or psychosomatic medicine, or similar training at the interface of psychiatry and medicine. Special consideration will be given to candidates with an established record of extramural funding.

Applicants must have an M.D. and be eligible for North Carolina licensure. Rank and salary will be commensurate with experience.

CONTACT

Applicants should forward curriculum vitae and three letters of reference to Donald L. Rosenstein, M.D., Director, Comprehensive Cancer Support Program, 3134 Physicians Office Building, 170 Manning Drive, CB# 7305, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7305

The University of North Carolina at Chapel Hill is an Equal Opportunity employer.

Henry Ford MEDICAL GROUP

MEDICAL DIRECTOR
MAPLEGROVE CENTER & CHIEF OF SUBSTANCE ABUSE SERVICES
HENRY FORD BEHAVIORAL HEALTH SERVICES

The Henry Ford Health System (HFHS) invites applications and nominations for Medical Director, Maplegrove Center, and Chief of Substance Abuse Services, Henry Ford Behavioral Health Services. Maplegrove Center is a 64-bed facility located on the beautiful Henry Ford West Bloomfield Hospital campus in southeast Michigan, providing inpatient, day hospital, and outpatient services to patients of all ages suffering from addiction. Maplegrove Center is a member of the HFHS's Division of Behavioral Health Services, a large award-winning service line of hospitals and clinics responsible for the provision of mental health care to patients across the HFHS.

Behavioral Health Services is one of several members of the Henry Ford Health System, a large vertically integrated and rapidly growing regional academic health system known for innovation and excellence in health care and health care research, with internal and external funding of more than $60 million. HFHS ranks in the top 6% of all institutions granted funding by the NIH and U.S. Public Health Service. HFHS also provides education and training to thousands of medical students, residents, fellows, and other trainees each year.

The position of Medical Director represents an opportunity for an accomplished leader with excellent administrative and organizational skills to provide strategic leadership and direction for all HFHS substance abuse services. The successful candidate will provide day-to-day leadership and management of Maplegrove Center and the HFHS's substance abuse services; all programmatic, educational, and research components of these services; and all advocacy efforts of these services with local, state, and national agencies and organizations. Faculty appointments at our affiliated university partners, will be based on qualifications and experience.

The Medical Director, Maplegrove Center, and Chief of Substance Abuse Services, reports to C. Edward Coffey MD, HFHS Vice President and CEO, Behavioral Health Services. Candidates must be board certified in Psychiatry or Internal/Family Medicine, with expertise/certification in Substance Abuse care, and eligible for a Michigan licensure. Excellent business, clinical, and teaching skills in addition to a high level of personal and professional integrity required. Experience as a vice Chair or Division/Training Program Director in a major academic institution is highly desirable.

A generous compensation package offers a very competitive salary and benefits. Send CV with cover letter to: C. Edward Coffey, M.D., CEO, Behavioral Health Services, 1 Ford Place,1F, Detroit, MI 48202. Email: akorine1@hfhs.org. AA/EEO

Psychiatrist
Mid-South Health Systems, Arkansas

Mid-South Health Systems, a premier community mental health center located in Northeast Arkansas is currently recruiting for a Psychiatrist to serve primarily adult clients in our 12 county catchement area in the Delta region. Most clinics served are an hour or less from Memphis, Tennessee or less than 2 hours from Little Rock, Arkansas. A current, unrestricted license to practice medicine in the state of Arkansas as well as a Controlled Substances Registration Certificate is required. The successful candidate will be part of strong multi-disciplinary treatment teams that includes 6 psychiatrists, 1 pediatrician, 3 child psychiatrists and 1 physician in addition to numerous psychologists, strong nursing staffs and licensed mental health professionals in each clinic. Arkansas State University is a short drive and boasts a student body in excess of 10,000 students. We offer competitive wages and an outstanding benefits package that includes company paid employee dental, vision, life, accidental death and dismemberment and long term disability; paid vacation, sick and personal time and a 10% employer contribution to a 401k retirement plan. In addition, our sites have been approved for the National Health Service Corp Loan Repayment Program. For immediate consideration please contact Bonnie White, CEO at 870.972.4015. You may fax or email a current vitae to: fax 870.972.4973 or email bwhite@mshs.org.

DARTMOUTH MEDICAL SCHOOL
DARTMOUTH-HITCHCOCK MEDICAL CENTER

Child and Adolescent Psychiatrist
Keene, New Hampshire

The Department of Psychiatry is seeking a Child and Adolescent Psychiatrist and an Adult Psychiatrist to join our faculty at Monadnock Family Services in Keene, NH.

These positions will involve supervising community oriented treatment teams, providing behavioral and psychopharmacological consultation, performing evaluations and providing ongoing medication management. Monadnock Family Services is an innovative behavioral health agency with a 100-year history of providing high-quality services in a creative and supportive climate. The agency is a leader in area of health and social services, alliances, and partnerships. The beautiful Monadnock region of N.H. (90 miles from Boston) offers many excellent recreational and cultural activities.

Academic duties may include teaching and supervision of medical students and residents. Candidates should be board certified or eligible in Child and Adolescent Psychiatry for the child position and in general psychiatry for the adult position. These positions will include appointments at Dartmouth Medical School and salaries commensurate with experience. Weeknight and weekend call schedules are reasonable.

A letter of interest, curriculum vitae and three letters of recommendation addressed to William Torrey, MD, Vice Chair for Clinical Services should be sent to Kami Carter at Kami.L.Carter@Dartmouth.edu.

Dartmouth Medical School is an equal opportunity/ affirmative action employer and encourages applications from women and members of minority groups.

We're recruiting Psychiatrists.

Make a difference in someone's life working in North Carolina's Psychiatric Hospitals, Substance Abuse, Neuro-Medical Treatment, or Developmental Disability Centers.

- Loan repayment program
- Excellent health insurance
- State retirement package
- Paid malpractice insurance

Where all your skills Come Together to treat the most complex needs

Learn more at
www.dhhs.state.nc.us/dsohf/
or
michael.taylor@dhhs.nc.gov

dhhs

Touching Lives Enriching Futures℠

Division of State Operated Healthcare Facilities
NC Department of Health and Human Services

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.
800-888-3134. Fax: 801-442-2999.
PhysicianRecruit@imail.org
http://intermountain.net/docjobs

Scenic California Central Coast

Atascadero State Hospital
BE/BC Psychiatrist

Atascadero State Hospital now pays board certified psychiatrists starting at $223,464 and advancing stepwise to $255,732. Atascadero is the nation's premier center for the treatment of forensically committed mentally ill patients. Our hospital is a teaching site affiliated with the University of California, accredited by JCAHO, and recipient of the prestigious Codman Award. All of our psychiatrists are board eligible and most are board certified. Many of our psychiatrists have forensic subspecialty boards.

We are located midway between San Francisco and Los Angeles on the scenic central California Coast, south of Big Sur. We offer a spectacularly beautiful environment in San Luis Obispo County with temperate climate, beaches, world class wineries, cultural activities, golfing, sailing, riding, clean air, and excellent schools through the University level.

Our benefit package is valued at an additional 39%, which includes retirement plans (including safety retirement), health plans, professional liability coverage, paid holidays, educational leave, and generous annual leave. On-call duty is compensated hour for hour over and above the base salary. Applicants must hold a current California license, or have pending application with the Medical Board of California.
For a prompt and confidential review, send CV to:

Jeanne Garcia, M.D.
P. O. Box 7001
Atascadero, CA 93423-7001
(805) 468-2005 or fax (805) 468-2138
or e-mail us: jeanne.garcia@ash.dmh.ca.gov

We are an equal opportunity employer.

Volunteer for DSM-5 Field Trials

American Psychiatric Institute for Research and Education
Practice Research Network is recruiting

Practicing Psychiatrists

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.

Practicing psychiatrists interested in volunteering for potential participation in DSM-5 field trials should send an email to aparesearch@psych.org with the following information:

- Full name
- Institution or organizational affiliation
- Mailing address
- Job title
- Preferred e-mail
- Area of expertise (e.g., child psychiatry, geriatric psychiatry, etc.)

This information will help determine your eligibility to participate in the DSM-5 field trials.

For information about revisions to the DSM please visit www.DSM5.org

The American Psychiatric Institute for Research and Education is a 501 (c) (3) subsidiary of the American Psychiatric Association.

INPATIENT PSYCHIATRIST

DARTMOUTH MEDICAL SCHOOL. The Department of Psychiatry, in a unique collaboration with the State of New Hampshire, is seeking a **PSYCHIATRIST** to join our faculty at the New Hampshire Hospital.

New Hampshire Hospital is a 132-bed acute psychiatric facility located in Concord, NH. New Hampshire Hospital is the clinical and research core facility for an innovative, statewide, comprehensive mental health system. Psychiatrists with expertise in general inpatient psychiatry, geriatric, or forensic psychiatry are encouraged to apply.

Academic duties include teaching and supervision of medical students and residents. Research opportunities available and encouraged.

Candidates should be board certified or eligible in Psychiatry. Academic rank and salary will be consistent with experience. A letter of interest, curriculum vitae and three letters of reference should be addressed to William C. Torrey MD, Vice Chair for Clinical Services for the Department of Psychiatry, and sent to Kami Carter at Kami.L.Carter@Dartmouth.edu.

Dartmouth College is an Equal Opportunity/Affirmative Action Employer and encourages applications from women and members of minority groups.

American Psychiatric Association Institute on Psychiatric Services

APA JOB BANK

Boston, MA ◆ October 14-16, 2010

APA Job Bank
psych.org/jobbank

Candidates and Employers Connect through the APA Job Bank at the Institute on Psychiatric Services in Boston, October 14-16

- Visit the APA Job Bank booth during the Institute on Psychiatric Services to search the most comprehensive online listing of psychiatric positions and other career resources.
- Use the APA Job Bank Conference Connection Tool to connect with prospective employers at the meeting.
- Visit psych.org/jobbank today and get your job posted in time for the meeting.
- Ask APA Job Bank representatives for a demonstration of the redesigned and enhanced web site features.
- Visit the APA Job Bank today to find the ideal position!

Location:
Boston Marriott
Copley Place Hotel
Second Floor

Thursday, October 14
1:30 - 5:45 pm

Friday, October 15
9:30 - 12:00 pm
1:30 - 5:45 pm

Saturday, October 16
9:30 - 12:00 pm

For more information, contact:
Lindsey Fox at 703.907.7331
or lfox@psych.org

Index to Advertisers

October 2010

The publication of an advertisement in this journal does not imply endorsement of the product or service by the American Psychiatric Association.

Subscription and Business Information

The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1000 Wilson Blvd., Suite 1825, Arlington, VA 22209-3901. Subscriptions (per year): individual $230.00, international $347.00. For additional subscription options, including single issues and student rates, please contact Customer Service at 1-800-368-5777 or email appi@psych.org. Institutional subscriptions are tier priced. For institutional site license or pricing information, contact 703-907-8538 or email institutions@psych.org.

Business communications, address changes, and subscription questions from APA members should be directed to the Division of Member Services: (888) 35-PSYCH (toll-free). Nonmember subscribers should call the Circulation Department (800) 368-5777. Author inquiries should be directed to the Journal editorial office: (703) 907-7885 or (703) 907-7884; fax (703) 907-1096; e-mail ajp@psych.org.

Business Management: Nancy Frey, Director, Publishing Services; Laura G. Abedi, Associate Director, Production; Alison Jones, Advertising Prepress Manager; Robert Pursell, Associate Publisher Advertising, Sales and Marketing.

Pharmaceutical Print Advertising: Frank Cox, Kathleen Harrison, Valentin Torres, Pharmaceutical Media, Inc. 30 East 33rd Street, New York, NY 10016. (212) 685-5010; fax (212) 685-6126; e-mail vtorres@pminy.com.

Nonpharmaceutical and Online Sales: Brian Skepton, (703) 907-7332; e-mail bskepton@psych.org.

Pages are produced using Adobe InDesign CS4. Printed by RR Donnelley, Mendota, IL., on acid-free paper effective with Volume 164, Number 11, November 2007.

Periodicals postage paid at Arlington, VA, and additional mailing offices. POSTMASTER: Send address changes to The American Journal of Psychiatry, Circulation Department, American Psychiatric Association, 1000 Wilson Blvd., Suite 1825, Arlington, VA 22209-3901.

Indexed in Abstracts for Social Workers, Academic Abstracts, Biological Abstracts, Chemical Abstracts, Chicago Psychoanalytic Literature Index, Cumulative Index to Nursing Literature, Excerpta Medica, Hospital Literature Index, Index Medicus, International Nursing Index, Nutrition Abstracts, Psychological Abstracts, Science Citation Index, Social Science Source, and Social Sciences Index.

GEODON® (ziprasidone HCl) Capsules

GEODON® (ziprasidone mesylate) injection for intramuscular use

BRIEF SUMMARY: See package insert for full prescribing 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 seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

INDICATIONS

GEODON is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients.

DOSAGE AND ADMINISTRATION

Schizophrenia GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment. Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials. *Maintenance Treatment*—While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically stable and then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving GEODON. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment. **Bipolar I Disorder** *Acute Treatment of Manic or Mixed Episodes*—Dose Selection: Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range 40 mg to 80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg. *Maintenance Treatment* (as an adjunct to lithium or valproate)—Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg to 80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment. **Acute Treatment of Agitation in Schizophrenia** *Intramuscular Dosing*—The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied. If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended. Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously. Intramuscular Preparation for Administration GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration. Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **Dosing in Special Populations** *Oral:* Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. GEODON is not approved for use in children or adolescents. *Intramuscular:* Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

CONTRAINDICATIONS

QT Prolongation Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning [see **WARNINGS**]. Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

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. GEODON is not approved for the treatment of dementia-related psychosis (see BOXED WARNING).

QT Prolongation and Risk of Sudden Death Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see **CONTRAINDICATIONS**).

QT Prolongation in Clinical Trials A study directly comparing the QT/QT_c prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of ziprasidone on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole

200 mg twice daily). In placebo-controlled trials, oral ziprasidone increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. **QT Prolongation and Torsade De Pointes** Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals. Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) (see **ADVERSE REACTIONS**). A study evaluating the QT/QT_c prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances 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 QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. **Electrolyte Disturbances May Increase The Risk of QT Prolongation** It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. **Neuroleptic Malignant Syndrome (NMS)** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. 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. 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. **Tardive Dyskinesia** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment 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. If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical anti-psychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia.

PRECAUTIONS

Leukopenia, Neutropenia, and Agranulocytosis In clinical trial and postmarketing experience, events of leukopenia/neutropenia and agranulocytosis (including fatal cases) have been reported temporally related to antipsychotic agents. 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 should discontinue GEODON 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/mm3) should discontinue GEODON and have their WBC followed until recovery. **Rash** In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued. **Orthostatic Hypotension** Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone. Ziprasidone should be used with particular caution in 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). **Seizures** In clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **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, and ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **BOXED WARNING** and **Increased Mortality in Elderly Patients with Dementia-Related Psychosis in WARNINGS**). **Hyperprolactinemia** As with other drugs that antagonize dopamine D2 receptors, ziprasidone elevates prolactin levels in humans. 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 contemplated 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; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment** Somnolence was a commonly reported adverse reaction in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely. **Priapism** One case of priapism was reported in the premarketing database. **Body Temperature Regulation** Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. **Suicide** The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce overdose risk. **Patients With Concomitant Illnesses** Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited. Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see **QT Prolongation and Risk of Sudden Death** in **WARNINGS** and **Orthostatic Hypotension in PRECAUTIONS**). **Information for Patients** To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients. **Laboratory Tests** Patients being considered for ziprasidone treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Discontinue ziprasidone in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**).

DRUG INTERACTIONS

(1) Ziprasidone should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents. (4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists. **Effect of Other Drugs on Ziprasidone** *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of ziprasidone. Ketoconazole, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect ziprasidone pharmacokinetics. Co-administration of 30 mL of Maalox® did not affect ziprasidone pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. **Effect of Ziprasidone on Other Drugs** *In vitro* studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement. Ziprasidone 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** in **PRECAUTIONS**). *Mutagenesis:* There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes. *Impairment of Fertility:* Ziprasidone increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m2 basis). The fertility of female rats was reduced.

USE IN SPECIFIC POPULATIONS

Pregnancy *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of ziprasidone on labor and delivery in humans is unknown. **Nursing Mothers** It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed. **Pediatric Use** The safety and effectiveness of ziprasidone in pediatric patients have not been established. **Geriatric Use** Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

ADVERSE REACTIONS

Adverse Findings Observed in Short-term, Placebo-Controlled Trials The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. **Adverse Events Associated With Discontinuation** *Schizophrenia:* Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**). *Bipolar Mania:* Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. **Adverse Events at an Incidence of ≥5% and at Least Twice the Rate of Placebo** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that

occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: *Body as a Whole*—asthenia, accidental injury, chest pain. *Cardiovascular*—tachycardia. *Digestive*—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. *Nervous*—extrapyramidal symptoms, somnolence, akathisia, dizziness. *Respiratory*—respiratory tract infection, rhinitis, cough increased. *Skin and Appendages*—rash, fungal dermatitis. *Special Senses*—abnormal vision. Bipolar Mania: *Body as a Whole*—headache, asthenia, accidental injury. *Cardiovascular*—hypertension. *Digestive*—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. *Musculoskeletal*—myalgia. *Nervous*—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. *Respiratory*—pharyngitis, dyspnea. *Skin and Appendages*—fungal dermatitis. *Special Senses*—abnormal vision. **Dose Dependency** An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. **Extrapyramidal Symptoms (EPS)** The incidence of reported EPS for ziprasidone patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo. **Dystonia** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. 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. Elevated risk of acute dystonia is observed in males and younger age groups. **Vital Sign Changes** Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. Weight gain was reported as an adverse event in 0.4% of both ziprasidone and placebo patients. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI. **ECG Changes** Ziprasidone is associated with an increase in the QT_c interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. **Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone in Schizophrenia** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare adverse events are those occurring in fewer than 1/1000 patients. *Body as a Whole*—Frequent: abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. *Cardiovascular System*—Frequent: tachycardia, hypertension, postural hypotension. Infrequent: bradycardia, angina pectoris, atrial fibrillation. Rare: first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. *Digestive System*—Frequent: anorexia, vomiting. Infrequent rectal hemorrhage, dysphagia, tongue edema. Rare: gum hemorrhage, jaundice, fecal impaction, gamma glutamyl trans-peptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. *Endocrine*—Rare: hypothyroidism, hyperthyroidism, thyroiditis. *Hemic and Lymphatic System*—Infrequent: anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy. Rare: thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. *Metabolic and Nutritional Disorders*—Infrequent: thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia. Rare: BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. *Musculoskeletal System*—Frequent: myalgia. Infrequent: tenosynovitis. Rare: myopathy. *Nervous System*—Frequent: agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy. Infrequent: paralysis. Rare: myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. *Respiratory System*—Frequent: dyspnea Infrequent pneumonia, epistaxis. Rare: hemoptysis, laryngismus. *Skin and Appendages*—Infrequent: maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. *Special Senses*—Frequent: fungal dermatitis. Infrequent: conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia. Rare: eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. *Urogenital System*—Infrequent: impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria. Rare: gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Findings Observed in Trials of Intramuscular Ziprasidone** In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone (≥5%) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence of ≥1% in Short-Term Fixed-Dose Intramuscular Trials** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of patients during acute therapy with intramuscular ziprasidone: *Body as a Whole*—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. *Cardiovascular*—postural hypotension, hypertension, bradycardia, vasodilation. *Digestive*—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. *Nervous*—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. *Respiratory*—rhinitis. *Skin and Appendages*—furunculosis, sweating. *Urogenital*—dysmenorrhea, priapism. **Other Events Observed During Post-marketing Use** Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following—*Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors), (see **WARNINGS**); *Digestive System Disorders:* Swollen Tongue; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Nervous System Disorders:* Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders:* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Ziprasidone is not a controlled substance.

OVERDOSAGE

In premarketing trials in over 5400 patients, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Revised January 2010

BIPOLAR I MAINTENANCE TREATMENT

GEODON + LITHIUM OR VALPROATE PROVEN SUPERIOR TO LITHIUM OR VALPROATE ALONE IN PREVENTING RELAPSE

GEODON®
(ziprasidone HCl) ***Capsules***

GEODON is indicated for acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder and for maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. For full symptoms and diagnostic criteria, see the *DSM-IV-TR®* (2000).

IMPORTANT SAFETY INFORMATION

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with certain other QT-prolonging drugs. GEODON has a greater capacity to prolong the QTc interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first. Hypokalemia may increase the risk of QT prolongation and arrhythmia.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

The most common adverse events (≥5%) associated with GEODON in the bipolar maintenance study were tremor and insomnia.

Please see brief summary of prescribing information on adjacent page.

For more information, please visit www.pfizerpro.com/GEODON