LATUDA® (lurasidone HCl) 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 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.

LATUDA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*

1. INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in four 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration]*.

4. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [*see Adverse Reactions (6.6)*].

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) [*see Drug Interactions (7.1)*].

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. LATUDA is not approved for the treatment of dementia-related psychosis [*see Boxed Warning*].

5.2 Cerebrovascular Adverse Reactions, Including Stroke

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. LATUDA 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 LATUDA.

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 creatinine 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. If reintroduced, 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 that 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 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 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 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, LATUDA 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 LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

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. 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. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Pooled data from short-term, placebo-controlled studies are presented in Table 1.

Table 1: Change in Fasting Glucose

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
Mean Change from Baseline (mg/dL)					
	n=438	**n=71**	**n=352**	**n=270**	**n=283**
Serum Glucose	-0.7	-0.6	2.5	-0.9	2.5
Proportion of Patients with Shifts to ≥ 126 mg/dL					
Serum Glucose (≥ 126 mg/dL)	8.6% (34/397)	11.7% (7/60)	14.3% (47/328)	10.0% (24/241)	10.0% (26/260)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236) and +1.2 mg/dL at week 52 (n=244).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 2.

Table 2: Change in Fasting Lipids

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
Mean Change from Baseline (mg/dL)					
	n=418	**n=71**	**n=341**	**n=263**	**n=268**
Total cholesterol	-8.5	-12.3	-9.4	-9.8	-3.8
Triglycerides	-15.7	-29.1	-6.2	-14.2	-3.1
Proportion of Patients with Shifts					
Total Cholesterol (≥ 240 mg/dL)	6.6% (23/350)	13.8% (8/58)	7.3% (21/287)	6.9% (15/216)	3.8% (9/238)
Triglycerides (≥ 200 mg/dL)	12.5% (39/312)	14.3% (7/49)	14.0% (37/264)	8.7% (17/196)	10.5% (22/209)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n=238) and -3.5 (n=238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled studies are presented in Table 3. The mean weight gain was 0.75 kg for LATUDA-treated patients compared to 0.26 kg for placebo-treated patients. In study 3 [*see Clinical Studies (14.1)*] change in weight from baseline for olanzapine was 4.15 kg. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 5.6% for LATUDA-treated patients versus 4.0% for placebo-treated patients.

Table 3: Mean Change in Weight (kg) from Baseline

	Placebo (n=450)	LATUDA 20 mg/day (n=71)	LATUDA 40 mg/day (n=358)	LATUDA 80 mg/day (n=279)	LATUDA 120 mg/day (n=291)
All Patients	0.26	-0.15	0.67	1.14	0.68

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303) and -0.71 kg at week 52 (n=244).

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin 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 with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and was -0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose-dependent (Table 4).

Table 4: Median Change in Prolactin (ng/mL) from Baseline

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
All Patients	-0.6 (n=430)	-1.1 (n=70)	0.3 (n=351)	1.1 (n=259)	3.3 (n=284)
Females	-1.5 (n=102)	-0.7 (n=19)	-0.9 (n=99)	2.0 (n=78)	6.7 (n=70)
Males	-0.5 (n=328)	-1.2 (n=51)	0.5 (n=252)	0.9 (n=181)	3.1 (n=214)

The proportion of patients with prolactin elevations ≥ 5x ULN was 3.6% for LATUDA-treated patients versus 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 8.3% for LATUDA-treated patients versus 1% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.9% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189) and -3.3 ng/mL at week 52 (n=243).

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. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology]*. 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.

5.7 Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. 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 LATUDA 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 LATUDA and have their WBC followed until recovery.

5.8 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.4% (4/1004), 0.2% (1/455)] and syncope [< 0.1% (1/1004), 0%]. Assessment of orthostatic hypotension defined by vital sign changes (≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 1.4% with LATUDA 80 mg and 1.7% with LATUDA 120 mg compared to 0.9% with placebo.

LATUDA 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 (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.9 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that 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.

In short-term placebo-controlled trials, seizures/convulsions occurred in < 0.1% (1/1004) of patients treated with LATUDA compared to 0.2% (1/455) placebo-treated patients.

5.10 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence was reported in 26.5% (77/291) of patients receiving LATUDA 120 mg/day. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

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 LATUDA 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 *[see Patient Counseling Information (17.9)]*.

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

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% (6/1004) for LATUDA treated patients compared to 0.4% (2/455) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13 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. LATUDA is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.7, 8.8)]*. LATUDA 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 *[see Warnings and Precautions (5.1, 5.8)]*.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

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

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.14)]*

The information below is derived from a clinical study database for LATUDA consisting of over 2096 patients with schizophrenia exposed to one or more doses with a total experience of 624 patient-years. Of these patients, 1004 participated in short-term placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg or 120 mg once daily. A total of 533 LATUDA-treated patients had at least 24 weeks and 238 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. Treatment-emergent adverse events were defined as adverse experiences, which started or worsened on or after the date of the first dose through seven days after study medication discontinuation. There was no attempt to use investigator causality assessments; i.e., all events meeting the defined criteria, regardless of investigator causality are included. It is important to emphasize that, although the reactions occurred during treatment with LATUDA, they were not necessarily caused by it. The label should be read in its entirety to gain an understanding of the safety profile of LATUDA.

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 studies. 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

The following findings are based on the short-term placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n = 1004).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea, parkinsonism and agitation.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.4% (94/1004) LATUDA-treated patients and 5.9% (27/455) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 5.

Table 5: Adverse Reaction in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=455)**	**All LATUDA (N=1004)**
Gastrointestinal Disorders		
Nausea	6	12
Vomiting	6	8
Dyspepsia	6	8
Salivary hypersecretion	<1	2
General Disorders and Administration Site Conditions		
Fatigue	3	4
Musculoskeletal and Connective Tissue Disorders		
Back Pain	3	4
Nervous System Disorders		
Somnolence*	10	22
Akathisia	3	15
Parkinsonism**	5	11
Dystonia***	1	5
Dizziness	3	5
Psychiatric Disorders		
Insomnia	7	8
Agitation	3	6
Anxiety	3	6
Restlessness	2	3

Note: Figures rounded to the nearest integer
*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor
***Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

6.3 Dose-Related Adverse Reactions

Based on the pooled data from the placebo-controlled, short-term, fixed-dose studies, among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA, the apparent dose-related adverse reactions were akathisia and somnolence (Table 6).

Table 6: Dose-Related Adverse Events

	Percentage of Subjects Reporting Reaction				
Adverse Event Term	**Placebo (N=455) (%)**	**LATUDA 20 mg/day (N=71) (%)**	**LATUDA 40 mg/day (N=360) (%)**	**LATUDA 80 mg/day (N=282) (%)**	**LATUDA 120 mg/day (N=291) (%)**
Akathisia	3	6	11	15	22
Somnolence*	10	15	19	23	26

Note: Figures rounded to the nearest integer
*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

6.4 Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% versus 5.1% for placebo-treated patients; and the incidence of akathisia for LATUDA-treated patients was 15.0% versus 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of LATUDA, 120 mg/day (Table 7).

Table 7: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (N=455) (%)	LATUDA 20 mg/day (N=71) (%)	LATUDA 40 mg/day (N=360) (%)	LATUDA 80 mg/day (N=282) (%)	LATUDA 120 mg/day (N=291) (%)
All EPS events	9	10	24	26	39
All EPS events, excluding Akathisia/ Restlessness	5	6	13	11	22
Akathisia	3	6	11	15	22
Dystonia*	1	0	4	5	7
Parkinsonism**	5	6	10	7	17
Restlessness	2	1	4	1	3

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.2; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 16.0%; placebo, 7.6%) and the SAS (LATUDA, 5.3%; placebo, 2.5%).

Dystonia

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.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.7% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 4.2% LATUDA 40 mg, 4.6% LATUDA 80 mg and 6.5% LATUDA 120 mg) compared to 0.7% of subjects receiving placebo. Seven subjects (0.7%, 7/1004) discontinued clinical trials due to dystonic events – 4 were receiving LATUDA 80 mg/day and 3 were receiving LATUDA 120 mg/day.

6.5 Laboratory Test Abnormalities and ECG Changes in Clinical Studies

Laboratory Test Abnormalities

In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements; triglycerides or glucose from Baseline to Endpoint [*see Warnings and Precautions (5.5)*]. There were also no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. LATUDA was associated with a dose-related increase in prolactin concentration [*see Warnings and Precautions (5.6)*]

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% (30/977) of LATUDA-treated patients and 1.4% (6/439) on placebo. The threshold for high creatinine value varied from ≥ 1.1 to ≥ 1.3 mg/dL based on the centralized laboratory definition for each study [*see Dosage in Special Population; Use in Specific Populations*].

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).

ECG Changes

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

6.6 Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2096 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 listed in Table 5 are not included. Although the reactions reported occurred during treatment with LATUDA, 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 (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia;* ***Rare:*** *leukopenia, neutropenia*
Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*
Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*
Eye disorders: ***Frequent:*** *blurred vision*
Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis, dysphagia*
General Disorders and Administrative Site Conditions: ***Rare:*** *Sudden death*
Investigations: ***Frequent:*** *CPK increased*
Metabolic and Nutritional System Disorders: ***Frequent:*** *decreased appetite*
Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*
Nervous System Disorders: ***Infrequent:*** *tardive dyskinesia, cerebrovascular accident, dysarthria, syncope;* ***Rare:*** *neuroleptic malignant syndrome, seizure*
Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;* ***Rare:*** *suicidal behavior*
Renal and Urinary Disorders: I***nfrequent:*** *dysuria;* ***Rare:*** *renal failure*
Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*
Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*
Vascular Disorders: ***Infrequent:*** *hypertension, orthostatic hypotension*

7 DRUG INTERACTIONS

Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 8). LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]*.

Table 8: Summary of Effect of Coadministered Drugs on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia

Coadministered drug	Dose schedule		Effect on LATUDA pharmacokinetics		Recommendation
	Coadministered drug	LATUDA	C_{max}	AUC	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 5 days	10 mg single dose	6.9-times LATUDA alone	9-times LATUDA alone	Should not be coadministered with LATUDA
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/day for 5 days	20 mg single dose	2.1-times LATUDA alone	2.2-times LATUDA alone	LATUDA dose should not exceed 40 mg/day if coadministered
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	1/7th of LATUDA alone	1/5th of LATUDA alone	Should not be coadministered with LATUDA
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	0.9-times LATUDA alone	1.1- times LATUDA alone	No LATUDA dose adjustment required.

7.2 Potential for LATUDA to Affect Other Drugs

Digoxin (P-gp substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

Midazolam (CYP3A4 substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

Oral Contraceptive (estrogen/progesterone): Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of LATUDA in pregnant women.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 3 and 12 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area.

No adverse developmental effects were seen in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately equal to the MRHD based on body surface area.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Labor and Delivery

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

8.4 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Breast feeding in women receiving LATUDA should be considered only if the potential benefit justifies the potential risk to the child.

8.5 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.6 Geriatric Use

Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), lurasidone concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology]*. No dose adjustment is necessary in elderly patients.

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

8.7 Renal Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe renal impairment ($Cl_{cr} \geq 10$ mL/min to < 50 mL/min).

After administration of a single dose of 40 mg LATUDA to patients with mild, moderate and severe renal impairment, mean C_{max} increased by 40%, 92% and 54%, respectively and mean $AUC_{(0-\infty)}$ increased by 53%, 91% and 2- times, respectively compared to healthy matched subjects.

8.8 Hepatic Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of LATUDA 20 mg, lurasidone mean $AUC_{(0-last)}$ was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean C_{max} was 1.3, 1.2 and 1.3-times higher for mild, moderate and severe hepatically impaired patients respectively, compared to the values for healthy matched subjects.

8.9 Gender

Population pharmacokinetic evaluation indicated that the mean AUC of LATUDA was 18% higher in women than in men, and correspondingly, the apparent oral clearance of LATUDA was lower in women. Mean C_{max} of LATUDA was similar between women and men. No dosage adjustment of LATUDA is recommended based on gender.

8.10 Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of LATUDA, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of LATUDA. No dosage adjustment of LATUDA is recommended based on race.

8.11 Smoking Status

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

10. OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies involving more than 2096 patients and/or healthy subjects, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

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.

SUNOVION

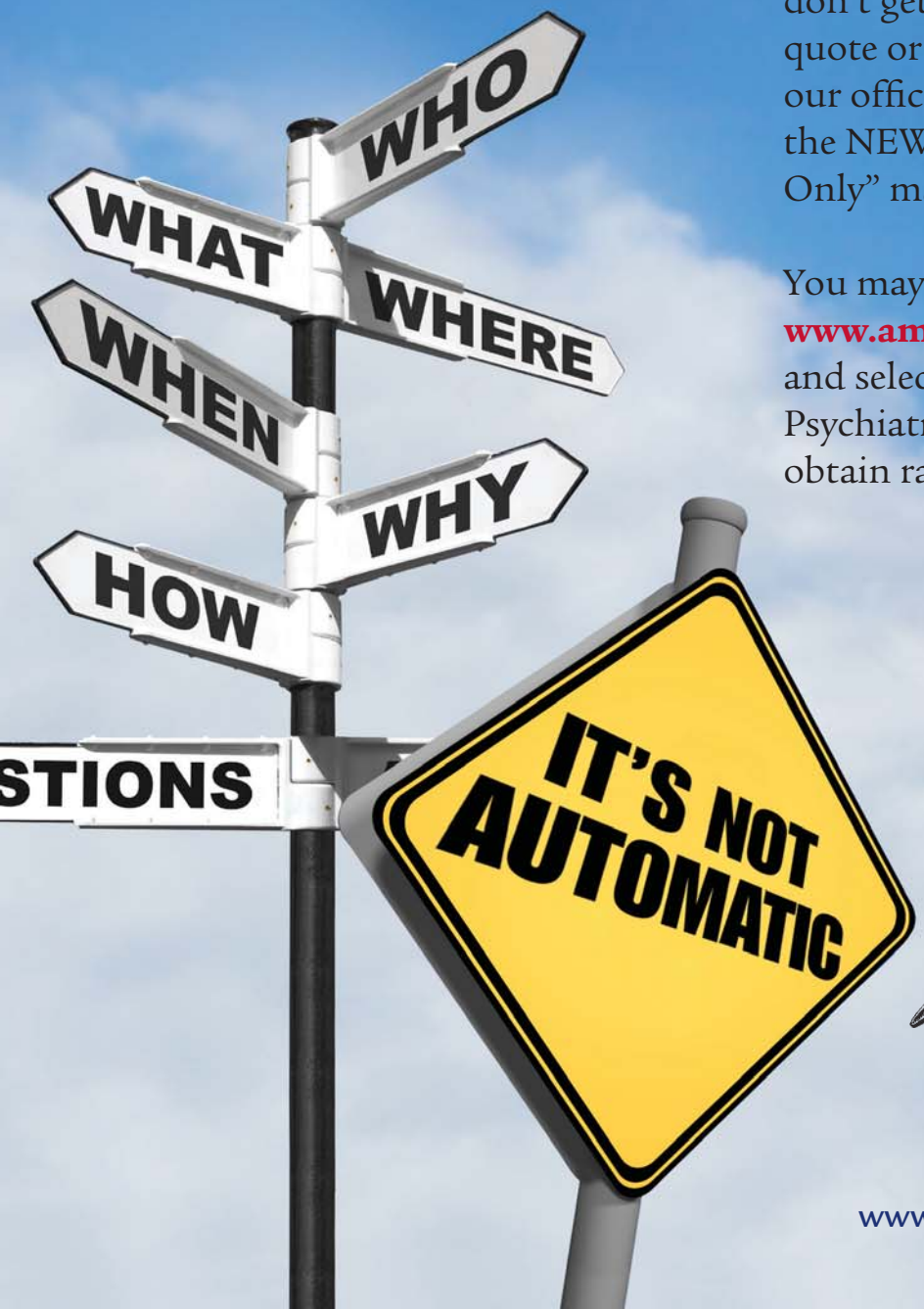
Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752,

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

Revised: October 2010
901456R01

We would like to clear up the confusion about renewing your APA-endorsed Malpractice Insurance Policy, starting with some words of caution...*it's not automatic!*

Important: The American Psychiatric Association has changed malpractice insurance carriers.



If you are not already insured with the American Professional Agency, Inc. don't get left behind! To receive a quote or application please contact our office at **877-740-1777** regarding the NEW APA-endorsed "Members Only" malpractice program.

You may also visit our website at **www.americanprofessional.com** and select the link for the American Psychiatric Association members to obtain rates and forms.

American Professional Agency, Inc.

www.americanprofessional.com

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.

Complex puzzles. Comprehensive solutions.

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

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. 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 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 50 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 communities. 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. To learn more, visit UPMCPhysicianResources.com.

UPMC
LIFECHANGINGMEDICINE

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

You care

for your patients with schizophrenia and want to offer treatment choices that are right for them.

So open up and have the important conversation about long-acting injections. You might be surprised by what comes of it.

Janssen
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

November 2010

01PM10146R1

Now Approved...
and Coming Soon

NUEDEXTA™
(dextromethorphan HBr and quinidine sulfate) Capsules

View full Prescribing Information at NUEDEXTA.com today.

AVANIR™ pharmaceuticals

PHARMAVITE

Clinical Evidence: SAM-e Supplements Can Aid Antidepressants

As a healthcare professional, you rely on evidence-based treatments to decide what will best benefit your patients with major depressive disorder (MDD). A recent study shows S-adenosyl-L-methionine (SAM-e) can enhance the efficacy of antidepressants.[1] This new clinical trial is the latest documenting the use of SAM-e to treat depression and enhance mood.

SAM-e Improves Depression Symptoms

Trials since the 1970s have documented the effective and safe use of SAM-e in helping improve depression symptoms. The U.S. Agency for Healthcare Research and Quality (AHRQ) concluded in its peer-reviewed evidence report: "SAM-e is more effective than placebo for relief of symptoms of depression. Treatment with SAM-e was equivalent to standard therapy for depression."[2]

Specifically, the AHRQ noted SAM-e, compared with a placebo, had an effect equivalent to clinically meaningful improvement on the Hamilton Depression Rating Scale of five to six points. Also, comparison of SAM-e with tricyclic antidepressants suggested equivalent efficacy.

The AHRQ also stated "side effects of SAM-e seem relatively minor." Mild side effects reported include: mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness, heart palpitations and anxiety/nervousness. Occurrence of these effects usually was similar to that of placebo and lower than antidepressants.

Of note, AHRQ reviewed 28 controlled trials. In comparison, the New Drug Application to the Food and Drug Administration (FDA) for the antidepressant paroxetine included data from 17 trials, of which only six showed efficacy compared to a placebo.[3]

SAM-e Effective, Well-Tolerated as SSRIs Adjunctive

When MDD patients experience an incomplete response, switching or augmenting their antidepressant medications may be appropriate. A new double-blind, randomized trial suggests that SAM-e can be an effective, relatively well-tolerated, adjunctive treatment for adults with MDD who do not respond to their treatment with selective serotonin reuptake inhibitor (SSRI) antidepressant medications.[1]

Patients receiving SAM-e had a significantly greater response rate compared to those receiving a placebo, 36.1 vs. 17.6 percent ($P<0.05$), as measured by a 50 or more percent reduction in HAM-D scores, the study's primary end point. Similarly, remission of depression symptoms–reaching a final HAM-D score of seven or less by the end of the six-week treatment period–was significantly greater with SAM-e than placebo, 25.8 vs. 11.7 percent ($P<0.05$). The trial used a SAM-e dose of 800 mg twice daily. The National Institute of Mental Health funded the study and Pharmavite LLC, a subsidiary of Otsuka Pharmaceutical Co., Ltd. and makers of Nature Made SAM-e Complete®, provided the SAM-e and placebo pills.

SAM-e is Essential

SAM-e is naturally found in every human cell and is involved in many essential body processes. SAM-e is part of the formation and metabolism of hormones, DNA, RNA, proteins and phospholipids. SAM-e also helps enable conversion of the neurotransmitters- norepinephrine into epinephrine and serotonin into melatonin. Depression studies document that norepinephrine and serotonin are involved in regulating mood, but the exact ways in which they work is unknown.

The liver is the primary site of making SAM-e. Formation of SAM-e uses the essential amino acid methionine (MET) and ATP. While the body can make ATP, MET must come from high quality proteins in the diet. Nutritional status as well as aging, because it hinders MET absorption, and certain conditions, such as fatty liver disease and hepatitis, can decrease SAM-e production.[4,5]

Safe Use of SAM-e

Studies indicate that the mood benefits of SAM-e use are likely evident after 7 to 14 days. SAM-e is best taken in the morning on an empty stomach with a starting dose of 400 mg/day for 7 to 10 days, with an increase if desired results are not experienced to 800 mg/day for the next 7 to 10 days, and then to 1,200 mg/day if still not experiencing the desired results.

It is always advisable for a patient to consult a health care professional regarding dietary supplements to understand dosages for individual needs and potential interactions with other medication. Although generally considered as safe, SAM-e has not been evaluated in children or pregnant or lactating women. Use with bipolar (manic) depression should **not** be considered without first consulting with the patient's physician because of an 11-patient study reporting patients experiencing elevated mood, including mania or euphoria with SAM-e.

The FDA, the Federal Trade Commission and each state regulates the dietary supplement industry.

SAM-e tablets frequently come in 200 or 400 mg enteric-coated tablets. SAM-e is primarily absorbed in the intestines, so enteric coating of tablets helps prevent stomach digestion. **For more information** about SAM-e, visit www.NatureMade.com or call toll-free at 1-800-276-2878.

[1]Papakostas GI, et. al. S-Adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. Am J Psychiatry 2010; 167:942–948. [2]Hardy M, et al. *S-Adenosyl-L-Methionine for Treatment of Depression, Osteoarthritis, and Liver Disease* Evidence Report/Technology Assessment: Number 64. AHRQ Publication No. 02-E033, August 2002. Agency for Healthcare Research and Quality. [3]FDA NDA for Paxil. Freedom of Information Services Inc. Document 108232. [4]Lieber CS. CYP2E1: from ASH to NASH. *Hepatol Res* 2004;28:1-11. [5]Poirier LA, Brown AT, et al. Blood S-adenosylmethionine concentrations and lymphocyte methylenetetrahydrofolate reductase activity in diabetes mellitus and diabetic nephropathy. *Metabolism* 2001;50:1014-18.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

Treat Her Depression With Once-daily OLEPTRO™

- Significant improvement in mean HAMD-17 total score as early as week 1 and throughout an 8-week clinical study vs placebo ($P<0.05$)[1,2]
  - — Full antidepressant effect may take 4 to 6 weeks
- In the clinical study, no notable impact on weight and low incidence of sexual dysfunction[1-3]
- Controlled release over 24 hours[1-3]
- Once-daily dosing in the evening[3]
  - — Recommended starting dose of 150 mg

Once-daily

Oleptro™

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

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

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

inhibitors of CYP3A4 may increase the risk of cardiac arrhythmia in these patients. Trazodone is not recommended for use during the initial recovery phase of myocardial infarction.

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

References: 1. Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. *Psychiatry.* 2009;6(5): 20-33. **2.** Data on file, Angelini Labopharm. **3.** OLEPTRO™ Prescribing Information.

For more information, please visit www.oleptro.com.
For product questions, please call 1-877-345-6177.

ANGELINI | labopharm

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

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

INDICATIONS AND USAGE: Oleptro™ is indicated for the treatment of major depressive disorder (MDD) in adults. The efficacy of Oleptro has been established in a trial of outpatients with MDD as well as in trials with the immediate release formulation of trazodone [***see Clinical Studies***].

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk – Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders and these disorders themselves are the strongest predictors of suicide. There has been a long standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 – 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

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

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

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

ADVERSE REACTIONS: The following serious adverse reactions are described elsewhere in the labeling: Clinical Worsening and Suicide Risk [***see Boxed Warning and Warnings and***

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

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

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

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

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

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

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

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

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

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

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

ANGELINI | labopharm

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

Adult Psychiatry – Provo, Utah

Intermountain Healthcare is recruiting 1 BC/BE adult psychiatrist. Call is currently one in seven. Employment with the Intermountain Medical Group. Full Intermountain benefits. Relocation provided. EOE.

Intermountain Healthcare is frequently referenced nationally as one of the leaders in delivering high quality/low cost health care.

Utah County is one of the best places to live in the US with abundant seasonal recreation, great schools and a reasonable cost of living. Provo is a beautiful university community built along the slopes of the majestic Wasatch Mountains. It is a bustling community that provides the advantages of a small-town lifestyle along with the amenities offered in more cosmopolitan areas. Exciting outdoor adventures include hiking, backpacking, sightseeing and skiing.

Send/e-mail/fax CV to Intermountain Healthcare
Attn: Deanna Grange, Physician Recruiting Dept.
36 S. State Street, 21st Floor, Salt Lake City, UT
84111. 800-888-3134 Fax: 801-442-3388
PhysicianRecruit@imail.org
http://physicianjobsintermountain.org

Staff Clinician in Experimental Therapeutics & Pathophysiology Branch
Division of Intramural Research Program
National Institute of Mental Health
Bethesda, MD, USA

The National Institute of Mental Health (NIMH) Intramural Research Program, a major research component of the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS), housed at one of the premier research sites in the U.S., the 300 acre Bethesda campus of the NIH, near Washington D.C. with state-of-the-art clinical research unit and neuroimaging facilities (MRI, MRS, MEG, and polysomnography) dedicated to research, is recruiting a staff clinician to join the Experimental Therapeutics & Pathophysiology Branch of the Intramural Research Program of NIMH. Minimum qualifications are a doctoral degree, post-doctoral training, strong publication record, and demonstrated the ability to manage patients in research protocols and to effectively administrate resources when conducting clinical research (including recruitment, protocol development and implementation, and conducting single-site studies). The successful candidate will be primarily involved in patient research care and be part of a multidisciplinary team examining novel therapeutics and using neuroimaging and electrophysiological technologies to map brain activity associated with clinical response in patients with mood disorders. In addition to collaborative work within the team, there is opportunity for outstanding candidates to develop their own projects within the Branch.

Salaries are competitive and depend on level of experience. This is a full time position located in Bethesda, Maryland. 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**), Experimental Therapeutics & Pathophysiology Branch, 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

Adult Outpatient Psychiatry
Amery, Wisconsin

HealthPartners Medical Group is a top multi-specialty group practice based in Minneapolis/St. Paul, Minnesota and neighboring western Wisconsin communities. We seek BC/BE psychiatrists to join our talented team in providing comprehensive outpatient services, shared call and hospital rounding.

This full-time outpatient practice is based at the Amery Regional Medical Center, and teams with another of our psychiatrists in providing comprehensive behavioral health services to this charming western Wisconsin community and busy service area.

Forward your CV and cover letter to **lori.m.fake@healthpartners.com** or apply online at **www.healthpartners.jobs**.
For more details, call (800) 472-4695 x1. EOE

HealthPartners®
Medical Group

healthpartners.com regionshospital.com

CENTRAL NEW YORK PSYCHIATRIC CENTER

PSYCHIATRIST OPENINGS

Central New York Psychiatric Center, a State-operated, forensic, JCAHO Accredited Facility, is seeking

PSYCHIATRISTS / FULL TIME

for our Inpatient Facility in Marcy, NY, and for our Correction-based programs including: Arthurkill, Auburn, Clinton, Coillins, Elmira, Five Points, Great Meadow, Groveland, Hudson River VTC, Marcy RMHU, and Sullivan.

Board Certified: $174,798* · Licensed: $168,421
Limited Permit: $107,318-119,449*

*A 4% general salary increase is pending. NY State provides a generous and comprehensive benefits package including an outstanding Pension Plan; opportunities may exist for additional compensation and for NHSC Loan Forgiveness.

Contact: Dr. Jonathan Kaplan,
Clinical Director (Code 311)
Call at: 845-483-3443
Fax: 845-483-3455.
E-mail: CN00025@OMH.STATE.NY.US EOE/AA

For more information about Central New York Psychiatric Center, please visit the facility website:
www.omh.state.ny.us/omhweb/facilities/cnpc/facility.htm

James J. Peters
Department of Veterans Affairs
Medical Center
Bronx, New York

Combined Clinical & Research Fellowship Program in Psychiatry

The James J Peters VA Medical Center, an affiliate of the Mount Sinai School of Medicine in New York City, is soliciting applications for its Schizophrenia Research Fellowship Program. In addition to training in psychiatric services, fellows will participate in research aimed at improving outcomes in schizophrenia spectrum disorders and/or understanding their pathophysiology. The program offers a wide range of clinical, translational and basic research opportunities. Start dates are flexible. More information is available at http://www.mssm.edu/departments-and-institutes/psychiatry/programs-and-services/education/schizophrenia-fellowship.

Applicants must have completed ACGME-accredited training in psychiatry, be board eligible or board certified, and have an active license to practice medicine in the U.S. International medical graduates must also have a current visa and a valid ECFMG certificate. Applicants on a J-1 visa must have current ECFMG sponsorship. We are an Equal Opportunity Employer.

For further information, contact:
William Byne, M.D., Ph.D.
william.byne@mssm.edu
(718) 584-9000, ext 6041

MSSM
MOUNT SINAI SCHOOL OF MEDICINE

Adult Psychiatry – Ogden, Utah

Intermountain Healthcare is recruiting1 BC/BE adult psychiatrist to join an employed group of 8. Position is one of a mixed practice (inpatient and outpatient). Currently the group prefers to share the amount of inpatient work, so it is about 12 days per month. On weekends an APRN takes 1st call and the physician is the backup. Weekend call is only Saturday or Sunday. Practice is primarily 30 hours per week in the outpatient setting. Guaranteed salary with transition to production. Full benefits including defined pension and 401k match. Relocation provided. EOE.

The Ogden area has a population of over 400,000. It is gaining recognition as a great place to live with easy access to outdoor activities. *Forbes* ranked Ogden #2 on their list of America's Most Livable Cities in 2010. *Outside Magazine* and *Men's Journal* ranked it in the top 8 Best Towns in which to live.

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: 801-442-3388
PhysicianRecruit@imail.org
http://physicianjobsintermountain.org

STAFF PSYCHIATRIST

Pathways, Inc., the longest operating multi-service mental health agency in St. Mary's County, located on Maryland's western shore of the Chesapeake Bay, has an excellent opportunity to serve Southern Maryland residents. We seek a licensed, board certified/board eligible Psychiatrist to assume the position of Staff Psychiatrist in our outpatient mental health clinic. The preferred candidate will be credentialed with most major insurance companies. The selected candidate will provide psychiatric evaluations, prescribe and manage medications, assume responsibility for the medical aspects of quality management for his/her patients, and consult with clinical staff on shared patients.

St. Mary's County is scenically bordered on either side by two major rivers: the Patuxent and Potomac. The Southern Maryland region, the fastest growing in the state, uniquely offers a blend of colonial history and advanced technology-based industry in a location adjacent to the Baltimore-D.C corridor.

We offer strongly competitive compensation with no on-call requirement. Wage and other terms are negotiable. If interested please submit your C.V. and letter of interest to:

Jack Dent, Administrative Officer
Pathways, Inc.
P.O. Box 129
Hollywood, MD 20636
301-373-3065 ext. 208
Fax 301-373-3265
E-mail jdent@pathwaysinc.org

Department of Psychiatry at the
University of South Carolina School of Medicine
is seeking a

Chairman of Psychiatry

The Department of Psychiatry works in collaboration with the public and private sectors, hospital based medicine as well as research, academics and education which include Child, Adolescent and Adult Psychiatry. We offer comprehensive mental health services through Palmetto Health Alliance and the Department of Mental Health and the affiliated William Bryan Dorn VA Medical Center. The Department of Psychiatry provides assessment, therapy and consultation in all areas related to psychiatric disorders, behavioral disorders and mental health.

- Compensation: to commensurate with experience
- Malpractice
- Medical insurance
- Retirement program
- Approximately 24 full-time faculty members
- Comprehensive Residency & Fellowship Program
- Fellowship in Geriatrics Psychiatry
- Research Opportunities

Interested candidates should forward CV's ONLY to:
jwt.dna@mindspring.com
and/or contact J. W. Taylor @ 1-800-933-1884

IN PATIENT AND OUTPATIENT ADULT PSYCHIATRISTS NEEDED IN WAUSAU, WISCONSIN

Aspirus Behavioral Medicine Clinic

Seeking BC/BE outpatient Psychiatrists to join their team of psychiatrists and psychologists. Sorry, this is not a J1/H1B opportunity. 1:8 weekend call required.

Bridge Community Health Care

Seeking BC/BE outpatient Psychiatrist to help build a new program due to community need. National Health Service Corp Scholar & Loan Repayers welcome. This is a J1/H1B opportunity. 1:8 weekend call required.

North Central Health Care

Seeking 1 BC/BE inpatient and 1 BC/BE outpatient Psychiatrist to join their team of physicians. Sorry, this is not a J1/H1B opportunity. 1:8 weekend call required.

You'll enjoy a large referral area with a sizeable population outside of the city limits including 20 counties. Compensation and benefit packages are highly competitive.

Located in North Central Wisconsin, the area is surrounded by lakes, forests and hills which provide year-round outdoor recreation. The Wausau area enjoys the perfect combination of big-city amenities with small-town hospitality.

We invite you to join a first-rate medical community and a family-friendly quality of life.

Please forward your CV to Jamie Sitko.

Phone: 800-792-8728
Email: Jamie.Sitko@aspirus.org
www.aspirus.org

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.

At **Kaiser Permanente Colorado** we believe our achievements are best measured by the health and wellness of the community we serve. That's why we provide a fully integrated system of care guided by values such as integrity, quality, service and results. That's also why we give our physicians the tools, flexibility and freedom they need to get the best outcomes possible for their patients. We currently have four opportunities for BC/BE Physicians in the **Denver** area.

- **REGIONAL DEPARTMENT CHIEF, ADDICTION MEDICINE**
- **CHILD or ADULT PSYCHIATRIST**
- **INPATIENT PSYCHIATRIST**
- **GEROPSYCHIATRIST**

The advantages of working with us include our state-of-the-art electronic medical records system, collegial team environment and excellent compensation and benefit package. You'll also enjoy living in Colorado, an area known for its beautiful natural attractions and four season recreational amenities. Our mild temperatures and diverse culture make us an ideal place for those who love a community rich in arts and entertainment.

If you believe in getting more out of life, contact the Colorado Permanente Medical Group today.

Call Chantal Papez at **1-866-239-1677**
Chantal.papez@kp.org
http://physiciancareers.kp.org/co

KAISER PERMANENTE®

Colorado Permanente Medical Group P.C. EOE/M/F/V

Adult Psychiatry – St. George, Utah

Intermountain Healthcare is recruiting 1 BC/BE adult psychiatrist to join our Medical Group. Outpatient medicine with only 1 weekend per month of inpatient coverage. 4-day clinic week. Call: 1 in 4. Physician will assist in the management of patients with spine and pain disorders with concomitant psychiatric illnesses. Interest/ability in providing outpatient chemical dependency consultation/direction care for chemical dependency in a setting of chronic pain. Interest/ability in leading/directing the cognitive behavioral therapy component of a functional restoration program for spine and pain disorders is highly desirable. This is a key position, and in some cases the psychiatrist will function as the point person. The spine program is based on a one-stop-shopping concept. Psych will be involved to perform psych eval if that is what is determined as a key need or if patients are chemically dependent. The spine clinic piece will start out as one day per week and as the program grows, will never exceed two days per week. The outpatient clinic is fully staffed and well managed. Employment with salary guarantee transitioning to productivity and bonuses. Full Intermountain benefits. Relocation provided.

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: 801-442-3388
PhysicianRecruit@imail.org
http://physicianjobsintermountain.org

Dunedin, New Zealand

Senior Lecturer/ Associate Professor in Psychological Medicine/ Specialist Psychiatrist

(Confirmation Path)

Department of Psychological Medicine
Dunedin School of Medicine
and
Mental Health Services
Southern District Health Board

We are seeking applications from Medical Physicians registered or registrable in New Zealand as a Specialist Psychiatrist, for a joint academic/clinical position in the Department of Psychological Medicine, Dunedin School of Medicine. The appointment may be at Senior Lecturer level, or at Associate Professor level for appropriate applicants.

This is a full-time conjoint University/Hospital position and appointees will concurrently hold a position as Consultant to Southern District Health Board. The academic post will be 50% of full-time. This position is offered by the University and when combined with the Specialist position will amount to one full-time position.

Preference will be given to those with research experience. Excellent opportunities for research collaboration exist within the Department and on the University campus. Teaching responsibilities include undergraduate medical and postgraduate medical and non-medical courses. They will focus on Psychiatry and in addition may include participation in Behavioural Medicine, Health Psychology and Communication Skills, teaching these largely in a multi-disciplinary, integrated manner.

Specific enquiries may be directed to Professor Paul Glue, Head of Department, Department of Psychological Medicine, Tel 64 3 470 3867, Email paul.glue@otago.ac.nz

Information on the Southern District Health Board position is available from Dr James Knight, Tel 64 27 223 6386, Email James.Knight@southerndhb.govt.nz

Applications quoting reference number A10/142 close on Friday 11 February 2011.

APPLICATION INFORMATION

Send applications to the **Human Resources Division, Email job.applications@otago.ac.nz, Fax 64 3 479 8279.** With each application, please include an application form, an EEO information form, a covering letter and your curriculum vitae. T**he forms and a full job description are available at www.otago.ac.nz/jobs** Alternatively, contact the **Human Resources Division, Tel 64 3 479 8269, Email job.applications@otago.ac.nz**

EEO Employers Group

Equal opportunity in employment is University policy.

www.otago.ac.nz/jobs

We're recruiting Psychiatrists.

Where all your skills **come together** to treat the most complex needs.

We offer challenging and rewarding careers that allow you to enrich the futures of people who need you.

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

For career information, contact:
Michael Taylor
1-800-533-8847
michael.taylor@dhhs.nc.gov
www.dhhs.state.nc.us/dsohf/

dhhs Touching Lives Enriching Futures℠
Division of State Operated Healthcare Facilities
Department of Health and Human Services

PSYCHIATRISTS

NEEDED IN SOUTHERN OKLAHOMA

- EXCELLENT COMPENSATION - $250k/yr
- BOARD ELIGIBLE/BOARD CERTIFIED
- FULL TIME – MONDAY - FRIDAY
- NO ON-CALL, NIGHTS, OR WEEKENDS
- ANY STATE LICENSE
- NO BILLING OR COLLECTIONS
- MALPRACTICE PROVIDED

FOR MORE INFORMATION

Call Ryan at Sterling Medical Corp.

(800) 852-5678 ext. 157

fax (513) 984-4909, or

e-mail rtibbs@sterlingmedcorp.com

Academic Child Psychiatrist

Saint Louis University, a Catholic, Jesuit institution dedicated to student learning, research, health care, and service is seeking applicants for a tenure-track or non-tenure track appointment to establish a Division of Child Psychiatry in the Department of Neurology & Psychiatry.

The Department of Neurology & Psychiatry at Saint Louis University is seeking applicants for a position in child psychiatry. The individual will dedicate half their time at Saint Louis University in performance of child psychiatry services at Cardinal Glennon Children's Medical Center, one of the nation's leading pediatric hospitals, and development of a fellowship program. The remainder of the individual's duties will be to serve as director of the child and adolescent psychiatry services at CenterPointe Hospital. CenterPointe Hospital is a 104-bed private psychiatric facility, which includes 35 child/adolescent beds as well as adolescent intensive outpatient programs in four locations and an outpatient clinic. The individual will provide oversight and direction to both inpatient and outpatient child/adolescent services including leading weekly treatment team meetings, participation in medical staff committees, and providing services as an attending physician. It is the expectation that the candidate will develop a nationally recognized child psychiatry fellowship program and child psychiatry division within the Department of Neurology & Psychiatry in close collaboration with CenterPointe Hospital. Appointment at the associate professor or professor status is expected, depending on the candidate's qualifications.

Applicant must be BC/BE. Generous benefits, including excellent retirement package and tuition remission at SLU. Must be legally authorized to work in the USA. Position requires a background check for the successful candidate. Interested candidates must submit a cover letter, application, and current curriculum vitae to http://jobs.slu.edu.

Please send curriculum vitae, representative publications, description of research plans, statement of teaching and philosophy, and letters of reference to:

Henry Kaminski, M.D.
Chairman, Department of Neurology & Psychiatry
1438 South Grand Blvd.
St. Louis, MO 63104
hkaminsk@slu.edu

SAINT LOUIS UNIVERSITY

Saint Louis University is an affirmative action, equal opportunity employer and encourages nominations and applications of women and minorities.

The Best Care -The Best Career

Veterans Affairs Medical Center San Francisco

JOIN US IN BEAUTIFUL NORTHERN CALIFORNIA!

PSYCHIATRIST

The Department of Veterans Affairs is seeking two full-time board certified or eligible psychiatrists to join the staff at the San Francisco VA Medical Center. There are two positions open in our Community Based Outpatient Clinics in Clearlake, CA and Santa Rosa, CA. Become a member of this health care team in providing state-of-the-art mental health services to our veterans. Mental health clinicians in each of these sites work closely with Primary Care in an integrated Primary Care/Mental Health model of care. The clinical responsibilities of these positions will emphasize psychopharmacologic therapies, but also includes psychiatric evaluations and consultations. Competitive salary negotiable, depending on qualifications. There is a generous incentive bonus along with comprehensive benefit programs. Interested candidates should forward their CV by email to Dr. Erick Hung at Erick.hung@va.gov or by fax at (415) 861-0323. Selected applicant is subject to random drug testing.

US CITIZENSHIP REQUIRED

THE DEPARTMENT OF VETERANS AFFAIRS IS AN EQUAL OPPORTUNITY EMPLOYER

San Francisco VA Medical Center

Program General Psychiatrist Medical Services

General Psychiatrist to work with adults and older adults within a multidisciplinary treatment team setting, performing psychiatric evaluations and providing medication management and consultation in a large CMHC (www.smh.org). Duties largely clinic-based, with limited nursing home consultation. Work is out-patient with no after-hours call. Malpractice insurance provided. Active WA medical license and DEA certificate and ability to provide services reimbursed by Medicare/Medicaid required. This is a full time position with excellent benefits available January 4, 2011.

Send letter of interest and C.V. to:

Sound Mental Health
Attn: Michael L. Snyder, M.D., CMO
1600 E. Olive Street
Seattle, WA 98122
Fax: (206) 302-2210
Email: MichaelS@smh.org

SMH is an EEO/AA Employer.

Candidates and Employers Connect through the APA Job Bank

psych.org/jobbank

Candidates

- Search the most comprehensive online listing of psychiatric positions at psych.org/jobbank.
- Register to post your resume, receive instant job alerts, use the career tools and more.
- Visit the redesigned and enhanced APA Job Bank website to find the ideal position!

Employers

- Use the many resources of the APA Job Bank to meet qualified candidates and make a smart recruitment decision.
- Advertise in the *Psychiatric News* or *Psychiatric Services* classifieds and the APA Job Bank and receive a 10% discount on each.

For more information, contact Lindsey Fox at 703-907-7331 classads@psych.org

APA JOB BANK
The best source for psychiatric job placement

Index to Advertisers
January 2011

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 $244.00, international $368.00. 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) 907-7889; 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.

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

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

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

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

261838-01

December 2009

FOR MAJOR DEPRESSIVE DISORDER

Help your patients

on a path forward with proven SNRI therapy

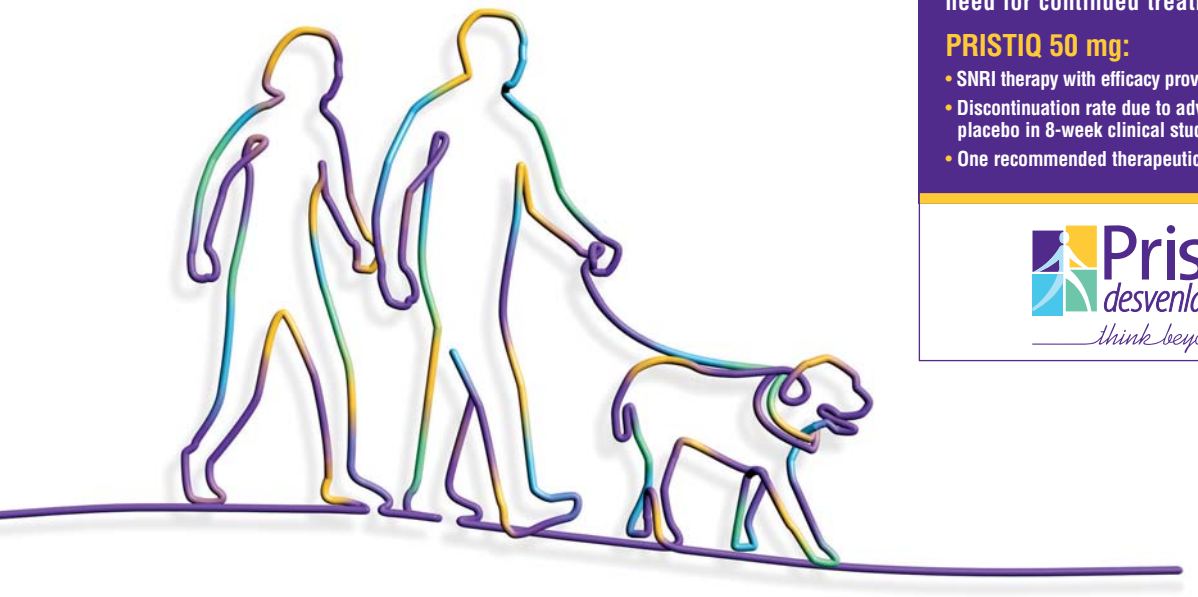
It's not just about starting your adult patients with MDD on therapy; it's about helping them toward their treatment goals. Patients should be periodically reassessed to determine the need for continued treatment.[1]

PRISTIQ 50 mg:

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

Pristiq® desvenlafaxine 50 mg

think beyond start™



Important Treatment Considerations for PRISTIQ

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

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

Contraindications

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

Warnings and Precautions

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

Adverse Reactions

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

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

Please see brief summary of Prescribing Information on adjacent pages.

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

Pristiq®
EXTENDED-RELEASE TABLETS

Pfizer