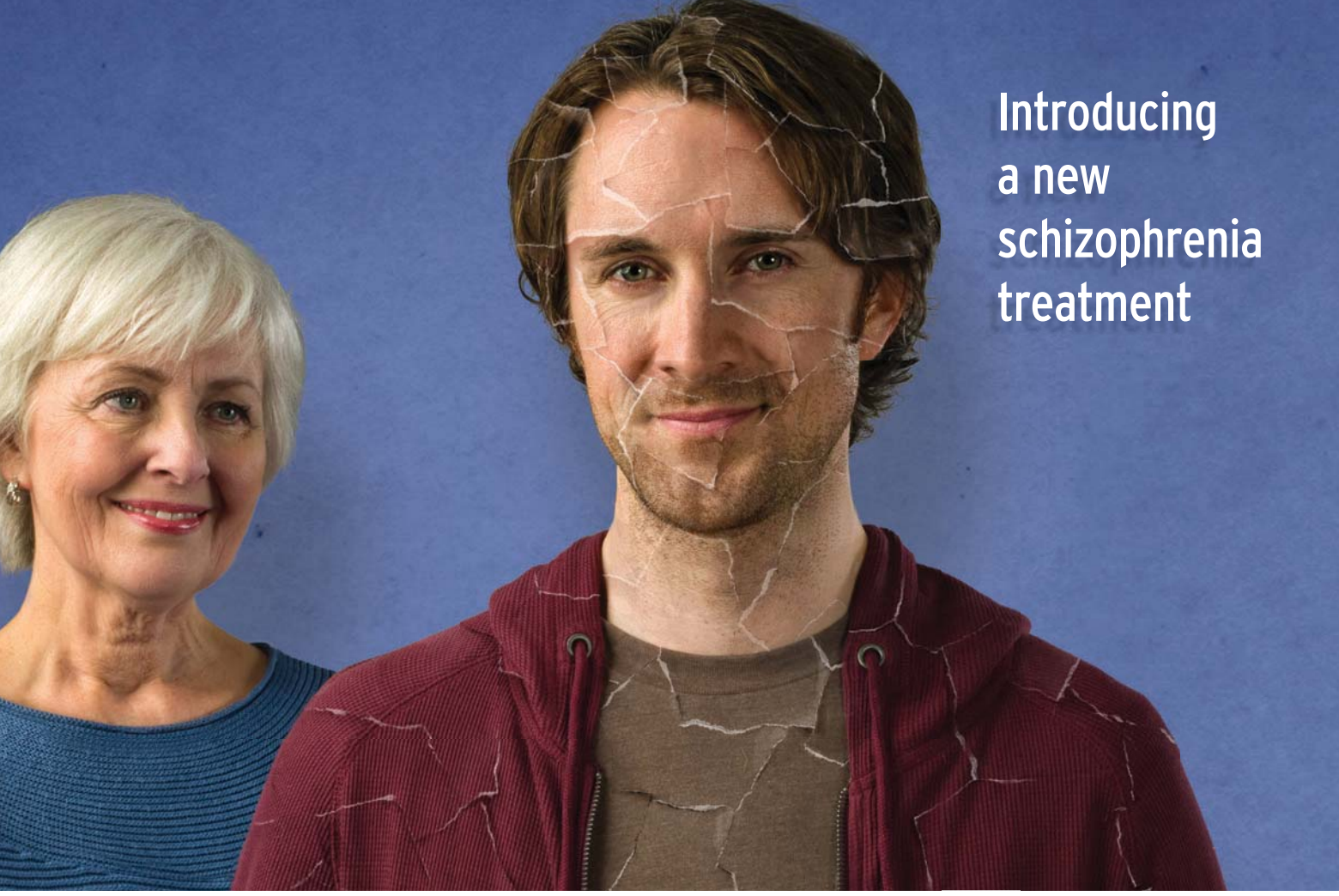

IMPORTANT SAFETY INFORMATION FOR LATUDA

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

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. LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke: LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The 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.

Tardive Dyskinesia (TD): The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

- **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. 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 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.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

LATUDA, a once-daily, oral atypical antipsychotic[1]

- The efficacy of LATUDA was established in 2 studies for each dose
- The safety and tolerability of LATUDA were evaluated in multiple studies
- The recommended starting dose is 40 mg/day taken with food (at least 350 calories) with no initial dose titration required. The maximum recommended dose is 80 mg/day
  - For patients with moderate and severe renal or hepatic impairment, the dose of LATUDA should not exceed 40 mg/day
  - When coadministered with a moderate CYP3A4 inhibitor such as diltiazem, the dose of LATUDA should not exceed 40 mg/day
  - LATUDA should not be administered with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin

NEW

Latuda®

(lurasidone HCl) tablets
40mg and 80mg

INDICATION AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in four 6-week controlled studies of adult patients with schizophrenia. 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.

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

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

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. Patients with a preexisting low white blood cell count (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 a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. 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 all patients who are vulnerable to hypotension.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer's dementia).

Potential for Cognitive and Motor Impairment: 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. 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.

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.

Suicide: The possibility of 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.

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.

DRUG INTERACTIONS

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.

ADVERSE REACTIONS

Commonly Observed Adverse Reactions (≥5% and at least twice that for placebo): The most commonly observed adverse reactions in patients treated with LATUDA in short-term clinical studies were somnolence, akathisia, nausea, parkinsonism, and agitation.

Reference: 1. LATUDA prescribing information. Sunovion Pharmaceuticals Inc. October 2010.

FOR MORE INFORMATION, PLEASE CALL 1-888-394-7377
OR VISIT **www.LatudaHCP.com**.

SUNOVION

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: ***Infrequent:*** *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.

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For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
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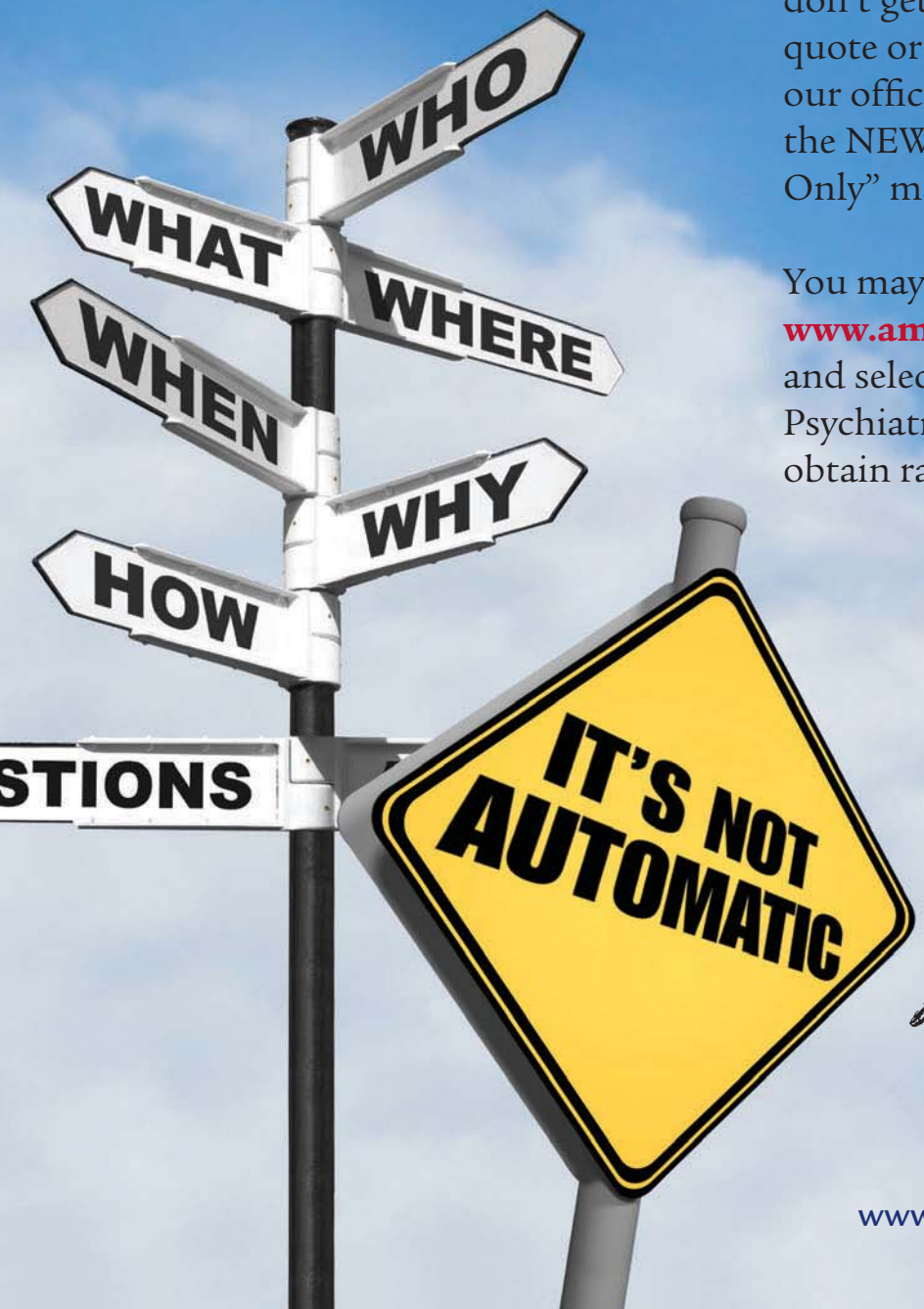

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WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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.

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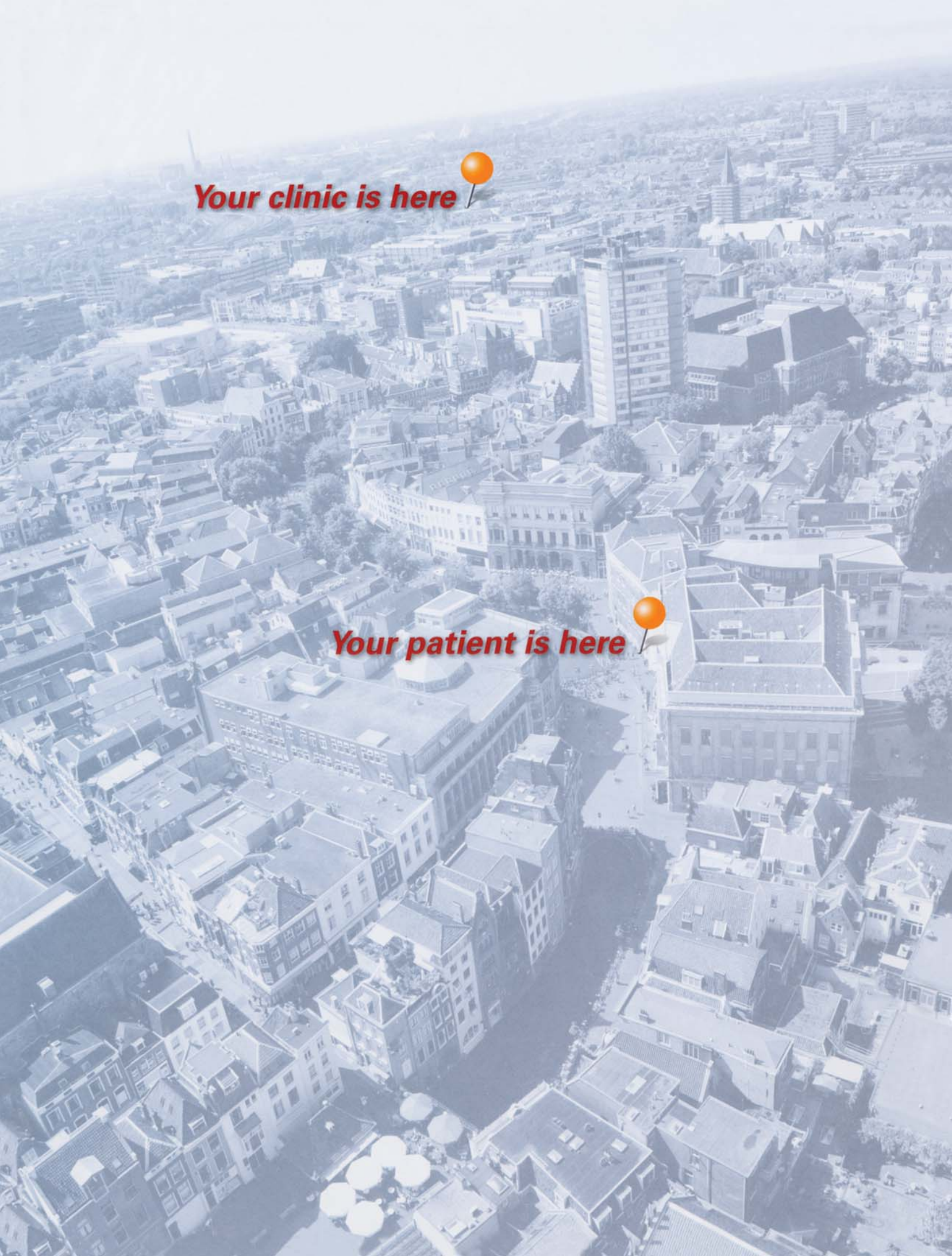
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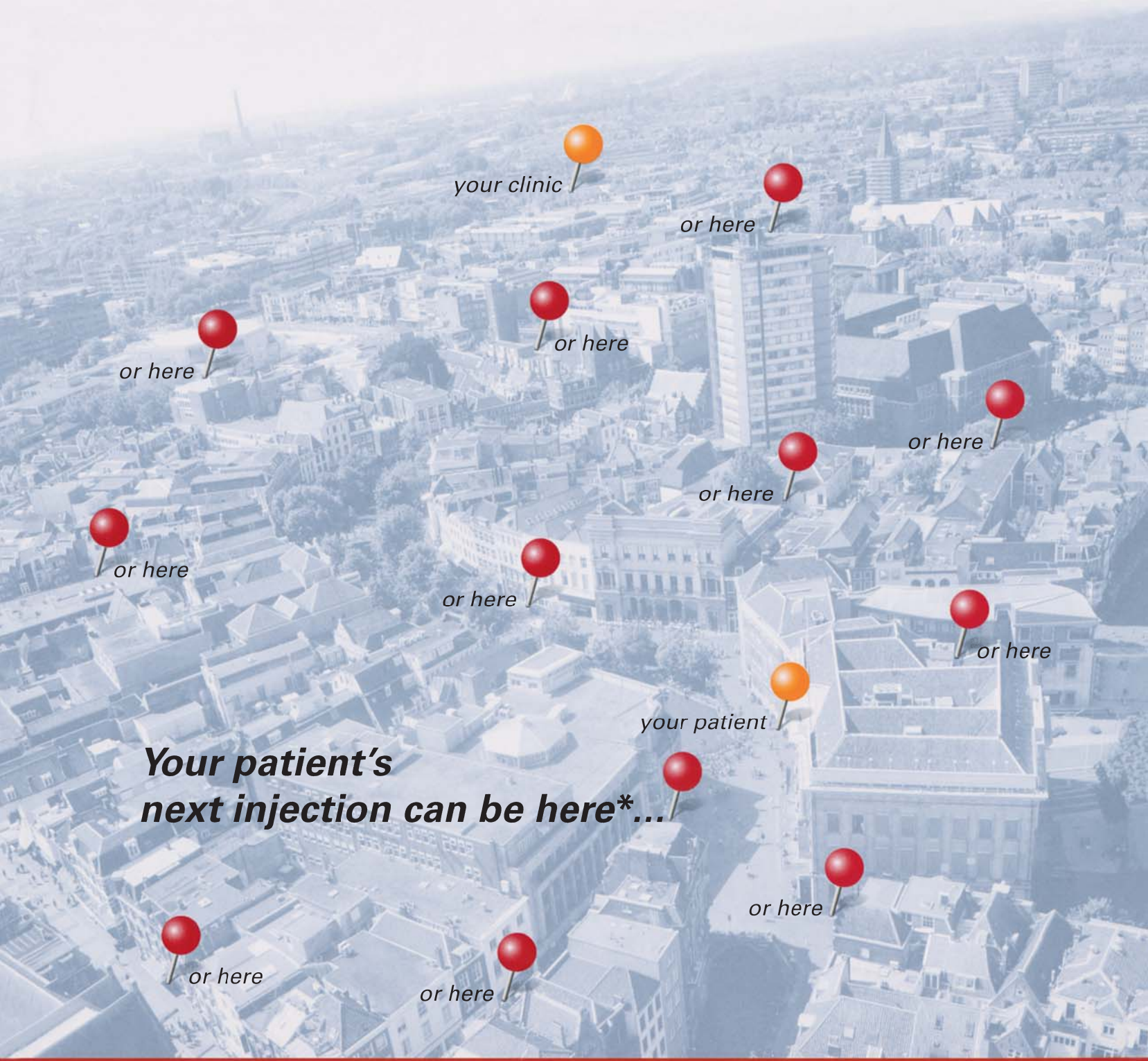

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December 2010 01JAN10053

Introducing the first and only FDA-approved treatment for pseudobulbar affect (PBA)[1]

About NUEDEXTA

NUEDEXTA™ is the first and only FDA-approved treatment for pseudobulbar affect (PBA). NUEDEXTA is an innovative combination of two well-characterized components; dextromethorphan hydrobromide (20 mg), the ingredient active in the central nervous system, and quinidine sulfate (10 mg), a metabolic inhibitor enabling therapeutic dextromethorphan concentrations. NUEDEXTA acts on sigma-1 and NMDA receptors in the brain, although the mechanism by which NUEDEXTA exerts therapeutic effects in patients with PBA is unknown.

NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA). PBA occurs secondary to a variety of otherwise unrelated neurological conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the patient's underlying emotional state. Studies to support the effectiveness of NUEDEXTA were performed in patients with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). NUEDEXTA has not been shown to be safe and effective in other types of emotional lability that can commonly occur, for example, in Alzheimer's disease and other dementias. The primary outcome measure, laughing and crying episodes, was significantly lower in the NUEDEXTA arm compared to placebo. The secondary outcome measure, the Center for Neurologic Studies Lability Scale (CNS-LS), demonstrated a significantly greater mean decrease in CNS-LS score from baseline for the NUEDEXTA arm compared to placebo.

NUEDEXTA Important Safety Information

NUEDEXTA can interact with other medications causing significant changes in blood levels of those medications and/or NUEDEXTA. NUEDEXTA is contraindicated in patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide) and should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine. NUEDEXTA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days.

Reconnect affect to emotion—with NUEDEXTA™

Significant relief from involuntary outbursts of crying and/or laughing[1-3]

- Reductions from baseline may be seen within the first week of treatment
- Efficacy was sustained over the course of 12 weeks
- The need for continued treatment should be reassessed periodically, as spontaneous improvement of PBA symptoms occurs in some patients

Helps patients achieve episode remission[2]

- Half of all patients taking NUEDEXTA were episode-free over their final 14 days in the study

Visit NUEDEXTA.com for more information

NUEDEXTA™
(dextromethorphan HBr and quinidine sulfate) Capsules

NUEDEXTA is contraindicated in patients with a known hypersensitivity to its components.

NUEDEXTA may cause serious side effects, including possible changes in heart rhythm. NUEDEXTA is contraindicated in patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes, in patients with heart failure as well as patients with, or at risk of, complete atrioventricular (AV) block, unless the patient has an implanted pacemaker.

NUEDEXTA causes dose-dependent QTc prolongation. When initiating NUEDEXTA in patients at risk of QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation of QT interval should be conducted at baseline and 3-4 hours after the first dose.

The most common adverse reactions in patients taking NUEDEXTA are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence.

NUEDEXTA may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls.

Patients should take NUEDEXTA exactly as prescribed. Patients should not take more than 2 capsules in a 24-hour period, make sure that there is an approximate 12-hour interval between doses, and not take a double dose after they miss a dose.

These are not all the risks from use of NUEDEXTA. For additional important safety information about NUEDEXTA, please see the full Prescribing Information at www.NUEDEXTA.com.

Please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. NUEDEXTA Prescribing Information, Avanir Pharmaceuticals. **2.** Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol.* 2010;68(5):693-702. **3.** Data on file, Avanir Pharmaceuticals, Inc.

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NUEDEXTA™ (dextromethorphan HBr and quinidine sulfate) Capsules

Brief Summary of Prescribing Information
See package insert for full Prescribing Information

INDICATIONS AND USAGE
NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA). PBA occurs secondary to a variety of otherwise unrelated neurological conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. Studies to support the effectiveness of NUEDEXTA were performed in patients with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). NUEDEXTA has not been shown to be safe and effective in other types of emotional lability that can commonly occur, for example, in Alzheimer's disease and other dementias.

DOSAGE AND ADMINISTRATION
The recommended starting dose of NUEDEXTA (20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate) is one capsule daily by mouth for the initial seven days of therapy. On the eighth day of therapy and thereafter, the daily dose should be a total of two capsules a day, given as one capsule every 12 hours. The need for continued treatment should be reassessed periodically, as spontaneous improvement of PBA occurs in some patients.

CONTRAINDICATIONS
Quinidine and related drugs: NUEDEXTA contains quinidine, and should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine. **Hypersensitivity:** NUEDEXTA is contraindicated in patients with a history of NUEDEXTA, quinine, mefloquine or quinidine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome; also in patients with known hypersensitivity to dextromethorphan *[see Warnings and Precautions (5.1 in full PI)]*. **MAOIs:** NUEDEXTA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Allow at least 14 days after stopping NUEDEXTA before starting an MAOI *[see Drug Interactions (7.1 in full PI)]*. **Cardiovascular:** NUEDEXTA is contraindicated in patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes, and in patients with heart failure *[see Warnings and Precautions (5.3 in full PI)]*. NUEDEXTA is contraindicated in patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide), as effects on QT interval may be increased *[see Drug Interactions (7.2 in full PI)]*. NUEDEXTA is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block.

WARNINGS AND PRECAUTIONS
Thrombocytopenia and Other Hypersensitivity Reactions: Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. NUEDEXTA should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is not drug-related, as continued use increases the risk for fatal hemorrhage. Likewise, NUEDEXTA should not be restarted in sensitized patients, because of the risk of more rapid and more severe thrombocytopenia. NUEDEXTA should not be used if immune-mediated thrombocytopenia from structurally related drugs including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually resolves within a few days of discontinuation of the sensitizing drug. Quinidine has also been associated with a lupus-like syndrome involving polyarthritis, sometimes with a positive ANA. Other associations include rash, bronchospasm, adenopathy, hemolytic anemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevated serum levels of skeletal muscle enzymes, and pneumonitis. **Hepatotoxicity:** Hepatitis has been reported in patients receiving quinidine, generally during the first few weeks of therapy. **Cardiac Effects:** NUEDEXTA causes dose-dependent QTc prolongation *[see Clinical Pharmacology (12.2 in full PI)]*. QT prolongation can cause torsades de pointes-type ventricular tachycardia, with the risk increasing as prolongation increases. When initiating NUEDEXTA in at risk patients, ECG evaluation of QT interval should be done at baseline and 3-4 hours after the first dose. This includes patients concomitantly taking drugs that prolong the QT interval or that are strong or moderate CYP3A4 inhibitors, and patients with left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease, or history of stroke. LVH and LVD can be diagnosed utilizing echocardiography or another suitable cardiac imaging modality. Reevaluate ECG if risk factors for arrhythmia change during the course of treatment. Risk factors include concomitant use of drugs associated with QT prolongation, electrolyte abnormality (hypokalemia, hypomagnesemia), bradycardia, and family history of QT abnormality. Hypokalemia and hypomagnesemia should be corrected prior to initiation of therapy with NUEDEXTA, and should be monitored during treatment. If patients experience symptoms that could indicate cardiac arrhythmias, e.g., syncope or palpitations, NUEDEXTA should be discontinued and the patient further evaluated. **Concomitant use of CYP2D6 Substrates:** The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited *[see CYP2D6 Poor Metabolizers (5.8 in full PI), Pharmacokinetics (12.3 in full PI), Pharmacogenomics (12.5 in full PI)]*. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 *[see Drug Interactions (7.5 in full PI)]*. **Dizziness:** In a controlled trial of NUEDEXTA, 10% of patients on NUEDEXTA and 5% on placebo experienced dizziness. **Serotonin Syndrome:** When used with SSRIs or tricyclic antidepressants, NUEDEXTA may cause serotonin syndrome, including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor *[see Drug Interactions (7.4 in full PI), Overdosage (10 in full PI)]*. **Anticholinergic Effects of Quinidine:** Monitor for worsening clinical condition in diseases that may be adversely affected by anticholinergic effects. **CYP2D6 Poor Metabolizers:** The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone *[see Concomitant use of CYP2D6 substrates (5.4 in full PI), Pharmacokinetics (12.3 in full PI), Pharmacogenomics (12.5 in full PI)]*. Approximately 7-10% of Caucasians and 3-8% of African Americans are poor metabolizers (PMs) lacking capacity to metabolize CYP2D6. In patients who may be at risk of significant toxicity due to quinidine, consider genotyping to determine if they are PMs prior to treating with NUEDEXTA.

ADVERSE REACTIONS
A total of 946 patients participated in four Phase 3 controlled and uncontrolled PBA studies and received at least one dose of the combination product of dextromethorphan hydrobromide/quinidine sulfate in various strengths at the recommended or higher than the recommended dose. In a 12-week, placebo-controlled study (N=326), the most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) that led to discontinuation were muscle spasticity (3%), respiratory failure (1%), abdominal pain (2%), asthenia (2%), dizziness (2%), fall (1%), and muscle spasms (2%). The most common adverse reactions (≥ 3% and ≥ 2X placebo) were diarrhea (13%), dizziness (10%), cough (5%), vomiting (5%), asthenia (5%), edema (5%), urinary tract infection (4%), influenza (4%), flatulence (3%) and increased GGT (3%). 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 the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. **Safety Experience of Individual Components:** *Dextromethorphan:* Drowsiness, dizziness, nervousness or restlessness, nausea, vomiting, and stomach pain. *Quinidine:* Cinchonism (nausea, vomiting, diarrhea, headache, tinnitus, hearing loss, vertigo, blurred vision, diplopia, photophobia, confusion, and delirium) is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose of several hundred milligrams. Other adverse reactions occasionally reported with quinidine therapy include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, keratopathy, and abnormalities of skin pigmentation.

DRUG INTERACTIONS
MAOIs: Do not use NUEDEXTA with monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days *[see Contraindications (4.3 in full PI)]*. **Drugs that Prolong QT and are Metabolized by CYP2D6:** Do not use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide) *[see Contraindications (4.4 in full PI)]*. **Drugs that Prolong QT and Concomitant CYP3A4 Inhibitors:** Recommend ECG in these patients who are taking NUEDEXTA *[see Warnings and Precautions (5.3 in full PI)]*. **SSRIs and Tricyclic Antidepressants:** Use of NUEDEXTA with SSRIs or tricyclic antidepressants increases the risk of serotonin syndrome *[see Warnings and Precautions (5.6 in full PI)]*. **CYP2D6 Substrate:** The co-administration of NUEDEXTA with drugs that undergo extensive CYP2D6 metabolism may result in altered drug effects *[see Warnings and Precautions (5.4 in full PI)]*. ***Desipramine (CYP2D6 substrate):*** This tricyclic antidepressant is metabolized primarily by CYP2D6. A drug interaction study was conducted between a higher combination dose of dextromethorphan (dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg) and desipramine 25 mg. This dose increased steady state desipramine levels approximately 8-fold. If NUEDEXTA and desipramine are prescribed concomitantly, the initial dose of desipramine should be markedly reduced. The dose of desipramine can then be adjusted based on response, but a dose above 40 mg/day is not recommended. ***Paroxetine (CYP2D6 inhibitor and substrate):*** When the combination dose of dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg was added to paroxetine at steady state, paroxetine exposure ($AUC_{0\text{-}24}$) increased by 1.7 fold and C_{max} increased by 1.5 fold. Consider initiating treatment with a lower dose of paroxetine if given with NUEDEXTA. The dose of paroxetine can then be adjusted based on response, but dosage above 35 mg/day is not recommended. **Digoxin:** Quinidine is an inhibitor of P-glycoprotein. Prescribing quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. **Alcohol:** As with any other CNS drug, caution should be used when NUEDEXTA is taken in combination with other centrally acting drugs and alcohol.

USE IN SPECIFIC POPULATIONS
Pregnancy Category C: There are no adequate studies of NUEDEXTA in pregnant women. **Labor and Delivery:** The effects of NUEDEXTA on labor and delivery are unknown. **Nursing Mothers:** It is not known whether dextromethorphan and/or quinidine are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NUEDEXTA is given to a nursing mother. **Pediatric and Geriatric Use:** The safety and effectiveness of NUEDEXTA in these populations has not been determined. **Renal and Hepatic Impairment:** Dose adjustment of NUEDEXTA is not required in patients with mild to moderate renal or hepatic impairment. Increases in dextromethorphan and/or quinidine levels are likely to be observed in patients with severe renal or hepatic impairment.

DRUG ABUSE AND DEPENDENCE
NUEDEXTA contains dextromethorphan, and dextromethorphan abuse has been reported, predominately in adolescents. These observations were not systematic and it is not possible to predict on the basis of this experience the extent to which NUEDEXTA will be misused once marketed. Therefore, patients with a history of drug abuse should be observed closely.

OVERDOSAGE
Evaluation and treatment of NUEDEXTA overdose is based on experience with the individual components. Treatment of dextromethorphan overdosage should be directed at symptomatic and supportive measures. Treatment of quinidine overdosage requires monitoring the QTc interval and should involve a healthcare provider experienced in cardiac arrhythmia prevention and treatment and α-blockade-induced hypotension. Because of the theoretical possibility of QT prolongation that might be additive to those of quinidine, antiarrhythmics with Class I (procainamide) or Class III activities should (if possible) be avoided.

PATIENT COUNSELING INFORMATION
Physicians should discuss the following topics with patients when prescribing NUEDEXTA: **Hypersensitivity:** *[see Contraindications (4.2 in full PI), Warnings and Precautions (5.1 in full PI)]*. **Cardiac effects:** Consult their healthcare provider immediately if they feel faint or lose consciousness. Inform their healthcare provider if they have any personal or family history of QTc prolongation *[see Contraindications (4.4 in full PI), Warnings and Precautions (5.3 in full PI) Drug Interactions (7 in full PI)]*. **Dizziness:** *[see Warnings and Precautions (5.5 in full PI), Adverse Reactions (6.1 in full PI)]*. **Drug Interactions:** *[see Drug Interactions (7 in full PI)]*. **Dosing:** Instruct patients to take NUEDEXTA exactly as prescribed, not to take more than 2 capsules in a 24-hour period, to be sure that there is an approximate 12-hour interval between doses, and not to take a double dose after a missed dose. **General:** Contact their healthcare provider if their PBA symptoms persist or worsen. Advise patients to keep this and all medications out of reach of children and pets.

Marketed by Avanir™ Pharmaceuticals, Inc., Aliso Viejo, CA 92656
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www.NUEDEXTA.com

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NUE-0153-ADV-0112

Cymbalta is indicated in adults for:

- The treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in 4 short-term trials and 1 maintenance trial.
- The treatment of general anxiety disorder (GAD). The efficacy of Cymbalta was established in 3 short-term trials and 1 maintenance trial.
- The management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic pain due to osteoarthritis (OA).
- The management of diabetic peripheral neuropathic pain (DPNP).
- The management of fibromyalgia (FM).

I Will:

Offer educational resources that may support your patients

Realize I'm not the most important person you'll see today

Remember that small talk is best in small doses

Cymbalta® DELAYED RELEASE CAPSULES
duloxetine HCl

I will support your goal of doing what's best for your patients.

We provide clinical and educational resources designed to help appropriate patients at the start of and throughout their treatment plan with Cymbalta. To find out more, speak with your Cymbalta sales representative or visit insidecymbalta.com.

Important Safety Information About Cymbalta

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 Cymbalta 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. Cymbalta is not approved for use in pediatric patients.

(cont.)

See Important Safety Information, including Boxed Warning, above and on next page, and Brief Summary of Prescribing Information on following pages.

Lilly

Important Safety Information About Cymbalta *(Cont.)*

Contraindications

- Concomitant use in patients taking Monoamine Oxidase Inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of 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 serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

  At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

- Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma.

Warnings and Precautions

- **Clinical Worsening and Suicide Risk**

  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 within 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 (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If discontinuing treatment, the medication should be tapered. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.**

- Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

- Because it is possible that Cymbalta and alcohol may interact to cause liver injury or that Cymbalta may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

- Orthostatic hypotension and syncope have been reported with therapeutic doses of Cymbalta. This tends to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.

- The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, 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. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. Concomitant use with serotonin precursors (e.g., tryptophan) is not recommended. Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

(cont.)

Cymbalta® DELAYED RELEASE CAPSULES
duloxetine HCl

Important Safety Information About Cymbalta *(Cont.)*

Warnings and Precautions *(Cont.)*

- SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- On abrupt or tapered discontinuation, spontaneous reports of adverse events, some of which may be serious, have been reported during the marketing of SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.
- Cymbalta should be used cautiously in patients with a history of mania or with a history of a seizure disorder.
- In clinical trials across indications relative to placebo, treatment with Cymbalta was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.
- Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.
- SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia that appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs.
- The effect that alterations in gastric motility may have on the stability of the enteric coating of Cymbalta is unknown. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).
- Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance <30 mL/min).
- As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases (up to 52 weeks) of the DPNP studies, an increase in HbA_{1c} in both the Cymbalta (0.5%) and the routine care groups (0.2%) was noted.
- Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

Use in Specific Populations

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child.

Most Common Adverse Events

- The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=6020 vs 3962) were: nausea (24% vs 8%), dry mouth (13% vs 5%), somnolence* (10% vs 3%), fatigue (10% vs 5%), constipation* (10% vs 4%), dizziness (10% vs 5%), decreased appetite* (8% vs 2%), and increased sweating (7% vs 2%).

  * Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies that did not have a placebo lead-in period or dose titration.

- In placebo-controlled clinical trials, the overall discontinuation rates due to adverse events were: **MDD:** 9% vs 5%; **GAD:** 15% vs 4%; **DPNP:** 13% vs 5%; **FM:** 20% vs 12%; **OA:** 16% vs 6%; **CLBP:** 17% vs 6%.

  The common adverse events reported as a reason for discontinuation and considered to be drug related were: **MDD:** nausea (1.3% vs 0.5%). **GAD:** nausea (3.7% vs 0.2%), vomiting (1.3% vs 0%), dizziness (1.0% vs 0.2%). **DPNP:** nausea (3.5% vs 0.7%), dizziness (1.2% vs 0.4%), somnolence (1.1% vs 0%). **FM:** nausea (1.9% vs 0.7%), somnolence (1.5% vs 0%), fatigue (1.3% vs 0.2%). **OA:** nausea (2.9% vs 0.8%), asthenia (1.3% vs 0%). **CLBP:** nausea (3.0% vs 0.7%), somnolence (1.0% vs 0%).

For more safety information, please see Brief Summary of Prescribing Information, including Boxed Warning, on following pages.

DD HCP ISI 4NOV10

Lilly

CYMBALTA (duloxetine hydrochloride) Delayed-Release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

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 Cymbalta 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. Cymbalta is not approved for use in pediatric patients. *[See Warnings and Precautions and Use in Specific Populations.]*

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in four short-term trials and one maintenance trial in adults.

Generalized Anxiety Disorder—Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in three short-term trials and one maintenance trial in adults.

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.

Fibromyalgia—Cymbalta is indicated for the management of fibromyalgia (FM).

Chronic Musculoskeletal Pain—Cymbalta is indicated for the management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic pain due to osteoarthritis.

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of 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 serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Warnings and Precautions].*

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[see Warnings and Precautions].*

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 major depressive disorder (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 4400 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 of 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 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	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.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms *[see Warnings and Precautions for descriptions of the risks of discontinuation of Cymbalta].*

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 healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder—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 above 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 Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

Hepatotoxicity—There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (89/29,435) of Cymbalta-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the upper limit of normal occurred in 1.37% (132/9611) of Cymbalta-treated patients compared to 0.49% (35/7182) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions and Drug Interactions]* and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

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 SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or

CYMBALTA® (duloxetine hydrochloride) PV 7213 AMP

with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, 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. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*.

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*.

Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine 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 (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. 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]*.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/10,524) of patients treated with duloxetine and 0.01% (1/7699) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta

CYP1A2 Inhibitors—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs

Drugs Metabolized by CYP2D6—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines, and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered *[see Drug Interactions]*.

Other Clinically Important Drug Interactions

Alcohol—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. 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 and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta 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 may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma *[see Contraindications]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta group and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

In postmarketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2489), GAD (N=910), OA (N=239), CLBP (N=600), DPNP (N=906), and FM (N=876). The population studied was 17 to 91 years of age; 65.5%, 62.5%, 61.5%, 42.9%, and 94.9% female; and 86.5%, 81.2%, 86.2%, 74.0%, and 88% Caucasian for MDD, GAD, OA and CLBP, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day *[see Clinical Studies (14)]*.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

CYMBALTA® (duloxetine hydrochloride) PV 7213 AMP

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.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), and vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain—Approximately 12.9% (117/906) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.5%, placebo 0.7%), dizziness (duloxetine 1.2%, placebo 0.4%), and somnolence (duloxetine 1.1%, placebo 0.0%).

Fibromyalgia—Approximately 19.6% (172/876) of the patients who received duloxetine in 3- to 6-month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 1.9%, placebo 0.7%), somnolence (duloxetine 1.5%, placebo 0.0%), and fatigue (duloxetine 1.3%, placebo 0.2%).

Chronic Pain due to Osteoarthritis—Approximately 16.3% (39/239) of the patients who received duloxetine in 13-week, placebo-controlled trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 5.6% (14/248) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 2.9%, placebo 0.8%) and asthenia (duloxetine 1.3%, placebo 0.0%).

Chronic Low Back Pain—Approximately 16.5% (99/600) of the patients who received duloxetine in 13-week, placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.0%, placebo 0.7%), and somnolence (duloxetine 1.0%, placebo 0.0%).

Most Common Adverse Reactions—Pooled Trials for all Approved Indications—The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis.

Diabetic Peripheral Neuropathic Pain—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth.

Fibromyalgia—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, dry mouth, constipation, somnolence, decreased appetite, hyperhidrosis, and agitation.

Chronic Pain due to Osteoarthritis—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, fatigue, and constipation.

Chronic Low Back Pain—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue.

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Table 2 in full PI gives the incidence of treatment-emergent adverse reactions in placebo-controlled trials (N=6020 Cymbalta; N=3962 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo. These adverse events were: nausea, headache, dry mouth, fatigue (includes asthenia), somnolence* (includes hypersomnia and sedation), insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), dizziness, constipation*, diarrhea, decreased appetite* (includes anorexia), and hyperhidrosis.

*Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials (N=2995 Cymbalta; N=1955 placebo) for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo. These adverse events were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Investigations—weight decreased*; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Nervous System Disorders—dizziness, somnolence (includes hypersomnia and sedation), tremor; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, libido decreased (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); Reproductive System and Breast Disorders—erectile dysfunction, ejaculation delayed*, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); Respiratory, Thoracic, and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flush.

*Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

DPNP, FM, OA, and CLBP—Table 4 in full PI gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta (determined prior to rounding) in the premarketing acute phase of DPNP, FM, OA, and CLBP placebo-controlled trials (N=2621 Cymbalta; N=1672 placebo) and with an incidence greater than placebo. These adverse events were: Gastrointestinal Disorders—nausea, dry mouth*, constipation*, diarrhea, abdominal pain (includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain), vomiting, dyspepsia (includes stomach discomfort); General Disorders and Administration Site Conditions—fatigue (includes asthenia); Infections and Infestations—nasopharyngitis, upper respiratory tract infection, influenza; Metabolism and Nutrition Disorders—decreased appetite*(includes anorexia); Musculoskeletal and Connective Tissue Disorders—musculoskeletal pain* (includes myalgia and neck pain), muscle spasm; Nervous System Disorders—headache, somnolence* (includes hypersomnia and sedation), dizziness, paraesthesia (includes hypoaesthesia, hypoaesthesia facial, and paraethesia oral), tremor*; Psychiatric Disorders—insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor hyperactivity); Reproductive System and Breast Disorders—erectile dysfunction*, ejaculation disorder; Respiratory, Thoracic, and Mediastinal Disorders—cough, oropharyngeal pain*; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—flushing (includes hot flush).

*Incidence of 120 mg/day is significantly greater than the incidence for 60 mg/day.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. (See *Table 5* in full PI for specific ASEX results.)

Vital Sign Changes—In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.07 mm Hg in systolic blood pressure and 0.62 mm Hg in diastolic blood pressure compared to mean decreases of 1.31 mm Hg systolic and 0.73 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions]*.

Duloxetine treatment, for up to 26 weeks in placebo-controlled trials across approved indications, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.40 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In studies of DPNP, FM, OA, and CLBP, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.6 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg. In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week, uncontrolled extension phase), duloxetine patients had a mean weight decrease of 0.6 kg in 13 weeks of acute phase compared to study entry, then a mean weight increase of 1.4 kg in 41 weeks of extension phase compared to end of acute phase.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials across approved indications, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients *[see Warnings and Precautions]*.

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 29,435 patients were treated with duloxetine. Of these, 30.4% (8953) took duloxetine for at least 6 months, and 14.7% (4317) for at least one year. The following listing is

CYMBALTA® (duloxetine hydrochloride) PV 7213 AMP

not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Cardiac Disorders**—*Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia. **Ear and Labyrinth Disorders**—*Frequent:* vertigo; *Infrequent:* ear pain and tinnitus. **Endocrine Disorders**—*Infrequent:* hypothyroidism. **Eye Disorders**—*Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance. **Gastrointestinal Disorders**—*Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena. **General Disorders and Administration Site Conditions**—*Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance. **Infections and Infestations**—*Infrequent:* gastroenteritis and laryngitis. **Investigations**—*Frequent:* weight increased; *Infrequent:* blood cholesterol increased. **Metabolism and Nutrition Disorders**—*Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia. **Musculoskeletal and Connective Tissue Disorders**—*Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching. **Nervous System Disorders**—*Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria. **Psychiatric Disorders**—*Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide. **Renal and Urinary Disorders**—*Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal. **Reproductive System and Breast Disorders**—*Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, and sexual dysfunction. **Respiratory, Thoracic and Mediastinal Disorders**—*Frequent:* yawning; *Infrequent:* throat tightness. **Skin and Subcutaneous Tissue Disorders**—*Infrequent:* cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis. **Vascular Disorders**—*Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these 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.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, galactorrhea, glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions].*

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) *[see Warnings and Precautions].*

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding 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 or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued *[see Warnings and Precautions].*

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq), or Cymbalta, with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption *[see Warnings and Precautions].*

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Warnings and Precautions].*

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—[*See Contraindications and Warnings and Precautions.]*
Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications and Warnings and Precautions].*

Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended *[see Warnings and Precautions].*

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions].*

Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen *[see Warnings and Precautions].*

CNS Drugs—*[See Warnings and Precautions.]*

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

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

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), 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

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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]*.

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Lilly maintains a pregnancy registry to monitor the pregnancy outcomes of women exposed to Cymbalta while pregnant. Healthcare providers are encouraged to register any patient who is exposed to Cymbalta during pregnancy by calling the Cymbalta Pregnancy Registry at 1-866-814-6975 or by visiting www.cymbaltapregnancyregistry.com.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics. (See *Nursing Mothers* section in full PI for additional information.)

Pediatric Use—Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions]*. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1041 patients in CLBP premarketing studies, 21.2% (221) were 65 years of age or over. Of the 487 patients in OA premarketing studies, 40.5% (197) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta, 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]*. (See *Geriatric Use* section in full PI for additional information.)

Gender—Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—*[See Warnings and Precautions-Use in Patients with Concomitant Illness.]* (See *Use in Patients with Concomitant Illness-Hepatic Insufficiency* section in full PI for additional information.)

Severe Renal Impairment—*[See Warnings and Precautions-Use in Patients with Concomitant Illness.]* (See *Use in Patients with Concomitant Illness-Severe Renal Impairment* section in full PI for additional information.)

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. 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 Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. (See *Management of Overdose* section in full PI for additional information.)

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 20 mg/day on a mg/m^2 basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

Additional information can be found at www.Cymbalta.com

Literature revised: November 8, 2010

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Nomination Procedures:

APA members are asked to submit nominations by **July 1, 2011** to:

Council on Psychiatry and Law
American Psychiatric Association
c/o Lori Klinedinst, Staff Liaison
1000 Wilson Blvd., Suite 1825
Arlington, VA 22209
E-mail: advocacy@psych.org

The nomination letter should succinctly describe the contributions that are the basis for the nomination and be accompanied by a curriculum vitae of the nominee. The Council on Psychiatry and Law will serve as the award review panel in determining the recipients of this award. The recipients will receive a plaque which will be awarded during the Convocation at the APA's Annual Meeting in May.

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

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

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December 2009

Pfizer

FOR MAJOR DEPRESSIVE DISORDER

Help your patients

on a path forward with proven SNRI therapy

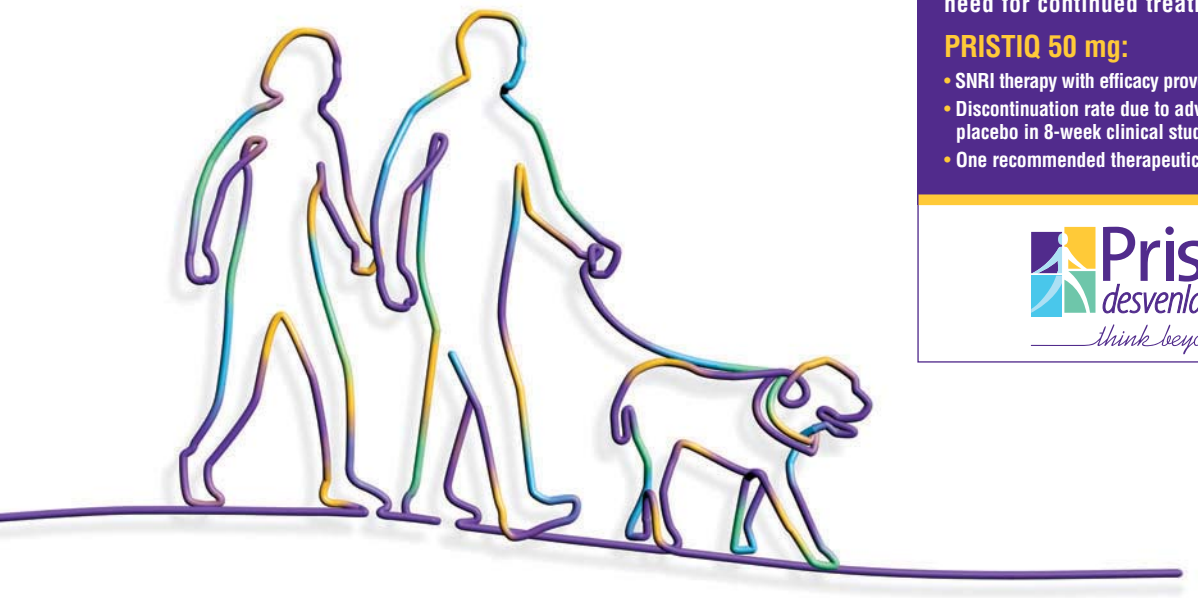
It's not just about starting your adult patients with MDD on therapy; it's about helping them toward their treatment goals. Patients should be periodically reassessed to determine the need for continued treatment.[1]

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