PRODUCT MONOGRAPH

Pr OLEPTRO™

Trazodone Hydrochloride Extended-Release Caplets

150 and 300 mg

Antidepressant

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Date of Preparation:
October 7, 2014

Submission Control No: 177639

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OLEPTRO™

Trazodone Hydrochloride Extended-Release Caplets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Extended-Release Caplets / 150 mg, 300 mg	Hydroxypropyl distarch phosphate (Contramid®), hypromellose, sodium stearyl fumarate, colloidal silicon dioxide, iron oxide yellow (CI number 77492), iron oxide red (CI number 77491), talc, polyethylene glycol 3350, polyvinyl alcohol, titanium dioxide (CI number 77891), iron oxide black (CI number 77499), shellac glaze, ethanol, isopropyl alcohol, N-butyl alcohol, propylene glycol, ammonium hydroxide

INDICATIONS AND CLINICAL USE

OLEPTRO™ (trazodone hydrochloride) is indicated for the symptomatic relief of major depressive disorder (MDD).

The short-term efficacy of OLEPTRO™ has been demonstrated for up to 8 weeks in a placebo-controlled trial with MDD patients (see **CLINICAL TRIALS**).

Geriatrics (> 65 years of age):
OLEPTRO™ should be used with caution in geriatric patients (see **WARNINGS AND PRECAUTIONS: Special Populations**, **and DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age):
Safety and efficacy in the pediatric population have not been established. OLEPTRO™ is not indicated for use in patients below the age of 18 years (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Long-Term Use of OLEPTRO™
The effectiveness of OLEPTRO™ in long-term use (i.e., more than 8 weeks) has not been established in controlled trials. The physician who elects to use OLEPTRO™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for individual patients (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

OLEPTRO™ (trazodone hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or the other components of the product (see **DOSAGE FORMS: COMPOSITION AND PACKAGING**).

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among the drugs in the class.**

Adult and Pediatrics: Additional data

- **There are clinical trial and postmarketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia/psychomotor restlessness, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional or behavioural changes.

Discontinuation Symptoms

Patients currently taking OLEPTRO™ should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended (see WARNINGS AND PRECAUTIONS: Dependence/Tolerance, and DOSAGE AND ADMINISTRATION: Discontinuation of treatment).

General

QT Prolongation and Risk of Arrhythmias and Sudden Death

OLEPTRO™ 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.

QT Prolongation: OLEPTRO™ is associated with QT/QTc interval prolongation (see **ADVERSE REACTIONS: Electrocardiography, and DRUG INTERACTIONS**). Although torsade 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. Events of torsade de pointes, ventricular tachycardia, and sudden death have been reported with the immediate-release form of trazodone during postmarketing use.

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering OLEPTRO™ to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QT/QTc-prolonging drug.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: Female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia); bradycardia (<50 beats per minute); acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); nutritional deficits (e.g., eating disorders, extreme diets); diabetes mellitus; autonomic neuropathy.

The concomitant use of OLEPTRO™ with drugs known to prolong the QT interval should be avoided (see **DRUG INTERACTIONS**).

Concomitant administration of CYP3A4 inhibitors may increase trazodone plasma levels (see **WARNINGS AND PRECAUTIONS: Interactions with Medications that Alter CYP3A4 Metabolism**). The concomitant use of potent CYP3A4 inhibitors with OLEPTRO™ is discouraged. If used, a lower dose of OLEPTRO™ should be considered (see **DRUG INTERACTIONS**).

When drugs that prolong the QT/QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Cardiac Disease: Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, and short episodes of ventricular tachycardia (3-4 beats). There have also been several postmarketing reports of arrhythmias in trazodone-treated patients who have pre-existing cardiac disease and in some patients who did not have pre-existing cardiac disease [(1)].

Psychomotor Impairment

OLEPTRO™ may impair the mental and/or physical abilities required for performance of potentially hazardous tasks, such as operating an automobile or machinery. Patients should be cautioned not to engage in such activities until they are reasonably certain that OLEPTRO™ therapy does not affect them adversely.

Priapism

Rare cases of priapism (painful erections greater than 4 hours in duration) were reported in patients receiving trazodone. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.

Although priapism 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 [(4)].

Trazodone should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** for animal data.

Cardiovascular

OLEPTRO™ is associated with QT/QTc interval prolongation (see **WARNINGS AND PRECAUTIONS: QT Prolongation and Risk of Arrhythmias and Sudden Death**).

OLEPTRO™ 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.

Hypotension: OLEPTRO™ may cause hypotension including orthostatic hypotension and syncope; caution is required if it is given to patients receiving antihypertensive drugs and an adjustment in the dose of the antihypertensive medication may be required [(1)].

Dependence/Tolerance

Although trazodone has not been systematically studied for its potential for abuse, there is no indication of drug-seeking behaviour in clinical trials with OLEPTRO™. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of trazodone.

Discontinuation 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 (see **WARNINGS AND PRECAUTIONS: Discontinuation Symptoms**).

Interactions with Medications that Alter CYP3A4 Metabolism

Concomitant use of OLEPTRO™ with CYP3A4 inhibitors may increase trazodone plasma levels (see **WARNINGS AND PRECAUTIONS: QT Prolongation and Risk of Arrhythmias and Sudden Death, and DRUG INTERACTIONS**). The concomitant use of potent CYP3A4 inhibitors with OLEPTRO™ is discouraged. If used, a lower dose of OLEPTRO™ should be considered (see **DRUG INTERACTIONS**).

In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with CYP3A4 inhibitors. Ritonavir, a potent CYP3A4 inhibitor, increased the C_{max}, AUC, and elimination half-life, and decreased clearance of trazodone after administration of ritonavir twice daily for 2 days. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered (see **DRUG INTERACTIONS**). It is likely that ketoconazole, indinavir and other CYP3A4 inhibitors such as itraconazole may lead to substantial increases in trazodone plasma concentrations with a potential for adverse effects. If OLEPTRO™ is used with a potent CYP3A4 inhibitor, a lower dose of OLEPTRO™ should be considered.

Carbamazepine, a CYP3A4 inducer, reduced plasma concentrations of trazodone when co-administered. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs (see **DRUG INTERACTIONS**).

Endocrine and Metabolism

Hyperprolactinemia and Breast Tumours: There is sufficient experimental evidence to conclude that chronic administration of psychotropic drugs, which increase prolactin secretion (e.g., trazodone), have the potential to induce mammary neoplasms in rodents. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels or increased secretion and turnover is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of psychotropic drugs and mammary tumorigenesis; available evidence is considered too limited to be conclusive at this time (see **TOXICOLOGY**) [(1)].

Genitourinary

See **WARNINGS AND PRECAUTIONS: Priapism**.

Hematologic

See **Monitoring and Laboratory Tests**.

Abnormal Bleeding: Postmarketing data have shown an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal 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.

Hepatic/Biliary/Pancreatic

OLEPTRO™ has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population.

Neurologic

Serotonin Syndrome: On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with trazodone treatment, particularly when given in combination with other serotonergic and/or neuroleptic/antipsychotic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with OLEPTRO™ should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma, and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic

syndrome or neuroleptic malignant syndrome, OLEPTRO™ should not be used in combination with MAO inhibitors or serotonin precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (e.g., triptans, lithium, tramadol, St. John's Wort, SSRIs, most tricyclic antidepressants) or neuroleptics/antipsychotics (see **DRUG INTERACTIONS**).

CNS Depressants: Trazodone may enhance the response to alcohol and the effects of barbiturates and other CNS depressants and patients should be cautioned accordingly [(1)].

Seizure Disorder: Episodes of grand mal seizures have been reported in a small number of patients. The majority of these patients were already receiving anticonvulsant therapy for a previously diagnosed seizure disorder [(1)].

Psychiatric

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder (MDD) and may persist until significant remission occurs. Close supervision of patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization of high risk patients. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen.

The risk of suicide attempt must be considered, especially in depressed patients; the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose with this drug (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

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 OLEPTRO™ is not approved for use in treating bipolar depression.

Renal

Hyponatremia: Hyponatremia has been reported with the use of antidepressants, some possibly due to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted may be at greater risk of developing hyponatremia. Cases of hyponatremia have been reported with the use of trazodone, including overdoses.

Renal Impairment: OLEPTRO™ has not been studied in patients with renal impairment. Trazodone should be used with caution in this population.

Sexual Function/Reproduction

See **WARNINGS AND PRECAUTIONS: Genitourinary**.

Special Populations

Pregnant Women: In two studies using the rat, trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus 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 not be used in women of childbearing potential unless, in the opinion of the physician, the expected benefits justify the potential risk to the fetus.

OLEPTRO™ Treatment during Pregnancy – Effects on Newborns
Postmarketing reports indicate that some neonates exposed to trazodone, SSRIs or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. When treating a pregnant woman with OLEPTRO™ during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Nursing Women: Since trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk, it should not be administered to nursing mothers unless the potential benefits justify the possible risks to the child.

Pediatrics (<18 years of age): The safety and effectiveness of OLEPTRO™ in children below the age of 18 have not been established. OLEPTRO™ should not be used in children or adolescents (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Geriatrics (>65 years of age): Trazodone should be used with caution in geriatric patients. In a clinical trial with 406 patients with major depressive disorder, 9 out of 202 patients treated with OLEPTRO™ and 13 out of 204 patients treated with placebo were 65 years of age or older. Experience with OLEPTRO™ in geriatric patients is therefore limited. OLEPTRO™ should be

used with caution in geriatric patients and lower initial and maintenance doses should be considered (see **DOSAGE AND ADMINISTRATION**).

Elderly patients receiving antidepressants may be at increased risk of clinically significant hyponatremia (see **WARNINGS AND PRECAUTIONS: Renal**, **Hyponatremia**).

Monitoring and Laboratory Tests

Self-harm: Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Screening Patients for Bipolar Disorder: See **WARNINGS AND PRECAUTIONS: Psychiatric**.

Laboratory Tests: It is recommended that white blood cell and differential counts be performed in patients who develop sore throat, fever or other signs of infection or blood dyscrasia, and OLEPTRO™ should be discontinued if the white blood cell or absolute neutrophil count falls below normal (1).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of OLEPTRO™ in MDD was evaluated 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 67.5% of patients in the active-treated group had at least one previous episode of depression in the last 24 months. Of the 202 patients treated with OLEPTRO™, there were 9 patients older than 65 years. In individual patients, doses were flexible (forced titration) and ranged from 150 to 375 mg/day. The mean daily dose during the 6-week treatment period for patients in the active-treated group was 310 mg. The caplets were administered orally and were given once a day for a total duration of 8 weeks, including the titration period (see **CLINICAL TRIALS**).

Three patients treated with OLEPTRO™ experienced a serious adverse drug reaction (staphylococcal sepsis, viral pericarditis, pulmonary embolism). These events were considered "not related" to the study medication. All 3 patients were discontinued from the trial. There were no serious adverse events that were considered related to treatment (4).

The most commonly observed adverse reactions (incidence of 5% or greater in the OLEPTRO™ group) were headache, somnolence, dry mouth, dizziness, nausea, sedation, fatigue, diarrhea, constipation, back pain and blurred vision.

In the study, 12% of patients treated with OLEPTRO™ discontinued due to an adverse reaction. Adverse reactions that led to discontinuation of 2 or more patients were dizziness, sedation, somnolence, confusional state, coordination abnormal, headache, nausea, and balance disorder/gait disturbance.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below reflects exposure of 202 MDD patients to OLEPTRO™ in a Phase III clinical trial (see **CLINICAL TRIALS**).

Electrocardiography

In the Phase III clinical trial, OLEPTRO™ was associated with a mean +7 ms increase in the QTc interval from baseline to week 8 (placebo-adjusted). The ECG recordings were performed at unspecified time points in relation to dosing. Due to the low ECG sampling frequency, these data are not expected to reflect the maximum effect of the drug on the QTc interval (see **WARNINGS AND PRECAUTIONS: QT Prolongation And Risk of Arrhythmias and Sudden Death, and DRUG INTERACTIONS**).

Vital Signs and Weight:
In the Phase III clinical trial, mean decreases in systolic and diastolic blood pressure were observed in the OLEPTRO™ group (-3.3 mmHg systolic and -2.0 mmHg diastolic) and in the placebo group (-0.7 mmHg systolic and -0.3 mmHg diastolic); mean decreases in heart rate were observed in the OLEPTRO™ group (-0.9 bpm) and in the placebo group (-0.1 bpm). Orthostatic hypotension and hypotension were reported for 3 patients (1.5%) and 1 patient (0.5%), respectively, in the OLEPTRO™ group, and no patient in the placebo group. Hypertension was reported for 3 patients (1.5%) in the placebo group, and no patient in the OLEPTRO™ group. No notable changes in weight were observed in either treatment group.

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, erectile dysfunction in 1.0% and abnormal orgasm in < 1% of patients.

Anxiety and Agitation:
Anxiety was observed infrequently (<1%) while agitation was observed frequently (≥ 1% to <5%) with OLEPTRO™. One patient treated with OLEPTRO™ reported anxiety during the study compared with five receiving placebo (OLEPTRO™: 1/202, 0.5%; placebo: 5/204, 2.5%).

Agitation/restlessness was reported by 4 patients of 202 (2.0%) treated with OLEPTRO™ and 1 patient of 204 (0.5%) receiving placebo.

Adverse Events:
Table 1 presents the summary of all Adverse Events (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 1. Most Common Treatment Emergent Adverse Events (≥ 5% of Patients in the OLEPTRO™ Group) – Phase III – Safety Population

	OLEPTRO™ n= 202 (%)	Placebo n= 204 (%)
Nervous System Disorders		
Headache	67 (33.2%)	55 (27.0%)
Somnolence	63 (31.2%)	32 (15.7%)
Dizziness	50 (24.8%)	25 (12.3%)
Sedation	34 (16.8%)	7 (3.4%)
Gastrointestinal Disorders		
Dry mouth	51 (25.2%)	26 (12.7%)
Nausea	42 (20.8%)	26 (12.7%)
Diarrhea	19 (9.4%)	23 (11.3%)
Constipation	16 (7.9%)	4 (2.0%)
General Disorders and Administration Site Conditions		
Fatigue	30 (14.9%)	17 (8.3%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	11 (5.4%)	7 (3.4%)
Eye Disorders		
Vision blurred	11 (5.4%)	-

OLEPTRO™ was generally well-tolerated. The majority of adverse events were mild to moderate in intensity and transient in nature. The median duration was 9 days for somnolence, 4 days for dizziness and 12.5 days for sedation. Three patients (1.5%) discontinued due to somnolence, 7 patients (3.5%) due to dizziness and 5 patients (2.5%) due to sedation.

In addition to the AEs enumerated above, the following were reported with an incidence of ≥ 1% to < 5% in the OLEPTRO™ group, and more frequently than in the placebo group (whether considered by the clinical investigator to be related to the study drug or not) (Table 2).

Table 2. Treatment Emergent Adverse Events With an Incidence ≥ 1% and < 5% of Patients in the OLEPTRO™ Group – Phase III – Safety Population

	OLEPTRO™ N= 202 (%)	Placebo N= 204 (%)
Cardiac Disorders		
Palpitations	8 (4.0%)	5 (2.5%)
Ear and Labyrinth Disorders		
Hypoacusis	2 (1.0%)	-
Tinnitus	3 (1.5%)	1 (0.5%)
Eye Disorders		
Eye swelling	2 (1.0%)	-
Visual disturbance	3 (1.5%)	-
Gastrointestinal Disorders		
Abdominal discomfort	3 (1.5%)	-
Abdominal distension	6 (3.0%)	1 (0.5%)
Abdominal pain	4 (2.0%)	3 (1.5%)
Stomach discomfort	6 (3.0%)	1 (0.5%)
General Disorders and Administration Site Conditions		
Chest discomfort	2 (1.0%)	-
Edema peripheral	7 (3.5%)	2 (1.0%)
Pain	5 (2.5%)	4 (2.0%)
Immune System Disorders		
Seasonal allergy	2 (1.0%)	1 (0.5%)
Infections and Infestations		
Bronchitis	2 (1.0%)	-
Sinusitis	4 (2.0%)	3 (1.5%)
Urinary tract infection	4 (2.0%)	2 (1.0%)
Injury, Poisoning and Procedural Complications		
Foot fracture	2 (1.0%)	-
Procedural pain	2 (1.0%)	-
Investigations		
Semen volume decreased	2 (1.0%)	-
Musculoskeletal and Connective Tissue Disorders		
Joint stiffness	2 (1.0%)	-
Joint swelling	2 (1.0%)	-
Muscle tightness	2 (1.0%)	-
Musculoskeletal stiffness	5 (2.5%)	-
Myalgia	6 (3.0%)	4 (2.0%)
Sensation of heaviness	3 (1.5%)	1 (0.5%)
Nervous System Disorders		
Balance disorder	3 (1.5%)	-
Coordination abnormal	3 (1.5%)	-
Disturbance in attention	7 (3.5%)	3 (1.5%)
Dysgeusia (decreased sense of taste)	4 (2.0%)	1 (0.5%)
Memory impairment	2 (1.0%)	-

Table 2. Treatment Emergent Adverse Events With an Incidence ≥ 1% and < 5% of Patients in the OLEPTRO™ Group – Phase III – Safety Population

	OLEPTRO™ N= 202 (%)	Placebo N= 204 (%)
Migraine	3 (1.5%)	2 (1.0%)
Paresthesia	2 (1.0%)	1 (0.5%)
Restless legs syndrome	2 (1.0%)	1 (0.5%)
Tremor	6 (3.0%)	4 (2.0%)
Psychiatric Disorders		
Agitation	3 (1.5%)	1 (0.5%)
Confusional state	5 (2.5%)	-
Disorientation	2 (1.0%)	-
Libido decreased	3 (1.5%)	2 (1.0%)
Renal and Urinary Disorders		
Micturition urgency	2 (1.0%)	-
Pollakiuria (excessive frequent urination)	7 (3.5%)	2 (1.0%)
Reproductive System and Breast Disorders		
Dysmenorrhea	3 (1.5%)	2 (1.0%)
Ejaculation delayed	2 (1.0%)	-
Erectile dysfunction	2 (1.0%)	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	3 (1.5%)	2 (1.0%)
Dyspnea	2 (1.0%)	1 (0.5%)
Nasal congestion	8 (4.0%)	3 (1.5%)
Sinus congestion	4 (2.0%)	3 (1.5%)
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	2 (1.0%)	1 (0.5%)
Night sweats	3 (1.5%)	1 (0.5%)
Rash	3 (1.5%)	1 (0.5%)
Skin burning sensation	3 (1.5%)	-
Vascular Disorders		
Orthostatic hypotension	3 (1.5%)	-

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following AEs have been reported with an incidence of < 1% (whether considered by the clinical investigator to be related to the study drug or not):

Blood and Lymphatic System Disorders: lymphadenopathy

Cardiac Disorders: cardiomegaly, left ventricular dysfunction

Ear and Labyrinth Disorders: auricular swelling, vertigo

Endocrine Disorders: hyperthyroidism, hypothyroidism

Eye Disorders: conjunctivitis, dry eye, eye pain, ocular hyperaemia, photophobia, vitreous floaters

Gastrointestinal Disorders: abdominal lower pain, gastroesophageal reflux disease, reflux esophagitis

General Disorders and Administration Site Conditions: chest pain, irritability, chills, edema, energy increased, feeling jittery, gait disturbance, injection site swelling, non-cardiac chest pain, sluggishness

Hepatobiliary Disorders: hepatic pain

Immune System Disorders: hypersensitivity

Infections and Infestations: diarrhea infectious, endocarditis, fungal skin infection, gastroenteritis viral, herpes simplex, onychomycosis, pharyngitis streptococcal, rhinitis, skin infection, staphylococcal sepsis, vaginitis bacterial, viral pericarditis

Injury, Poisoning and Procedural Complications: contusion, fall, heat exhaustion, joint sprain, laceration, mouth injury, muscle strain, neck injury, scratch, skin laceration

Investigations: blood glucose increased, blood pressure decreased, blood pressure increased, blood pressure systolic increased, weight decreased, weight increased

Metabolism and Nutrition Disorders: anorexia, hyperphosphatemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, arthropathy, muscle twitching, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, osteoarthritis

Nervous System Disorders: amnesia, aphasia, head discomfort, hypoesthesia, hypogeusia, lethargy, sinus headache, speech disorder, syncope

Psychiatric Disorders: anxiety, illusion, nightmare, orgasm abnormal, panic attack, restlessness

Renal and Urinary Disorders: bladder pain, renal failure acute, renal pain, urinary incontinence

Reproductive System and Breast Disorders: ejaculation disorder, sexual dysfunction

Respiratory, Thoracic and Mediastinal Disorders: dry throat, respiratory tract congestion, sinus disorder, pleuritic pain, productive cough, pulmonary embolism, wheezing

Skin and Subcutaneous Tissue Disorder: acne, ecchymosis, hyperhidrosis, hypoesthesia facial, photosensitivity reaction, pruritus, rash maculo-papular, rash papular, swelling face

Vascular Disorders: flushing, hot flush, hypotension

Abnormal Hematologic and Clinical Chemistry Findings

None reported as clinically significant.

Post-Market Adverse Drug Reactions

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: Priapism**), pruritus, psoriasis, psychosis, rash, stupor, syndrome of inappropriate ADH secretion, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: torsade de pointes, atrioventricular block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation, and sudden death.

DRUG INTERACTIONS

Overview

In vitro drug metabolism studies reveal that trazodone is a substrate of the cytochrome P450 3A4 (CYP3A4) enzyme and trazodone metabolism can be inhibited by the CYP3A4 inhibitors ketoconazole, ritonavir and indinavir. 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 C_{max} 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.

Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg/day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone (as well as mCPP) by 76 and 60%, respectively, compared to pre-carbamazepine values (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

Trazodone is metabolized by CYP3A4 to produce the active metabolite m-chlorophenylpiperazine (mCPP). mCPP is itself metabolized to p-hydroxy-mCPP (OH-mCPP) by CYP2D6. Thioridazine increased plasma concentrations of both trazodone and mCPP in a small study in depressed patients.

Drug-Drug Interactions

Interactions with potential to increase the risk of QTc prolongation/arrhythmias (see **WARNINGS AND PRECAUTIONS: QT Prolongation and Risk of Arrhythmias and Sudden Death**): The concomitant use of OLEPTRO™ with another QT/QTc-prolonging drug is discouraged. If used concomitantly with these drugs, OLEPTRO™ should be started at a low dose and patients monitored closely. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide); Class 1C antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); pentamidine; antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., dolasetron, ondansetron); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

OLEPTRO™ is a substrate for cytochrome P450 3A4 (CYP3A4). Plasma levels of trazodone can be increased by inhibitors of CYP3A4. Prolongation of the QT/QTc interval by OLEPTRO™ is anticipated to be increased in the presence of CYP3A4 inhibitors. Drugs that inhibit CYP3A4 include ketoconazole, itraconazole, voriconazole, clarithromycin, erythromycin, telithromycin, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, and amiodarone. The concomitant use of these drugs with OLEPTRO™ is discouraged. If used concomitantly with a CYP3A4 inhibitor, OLEPTRO™ should be started at a low dose and patients monitored closely.

The use of OLEPTRO™ is discouraged with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids. If used concomitantly with these drugs, OLEPTRO™ should be started at a low dose and patients monitored closely.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval, inhibit CYP3A4, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Drugs affected by concomitant trazodone: Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving trazodone concurrently with either of these drugs.

Serotonergic drugs: Based on the mechanism of action of trazodone and the potential for serotonin syndrome, OLEPTRO™ should not be used in combination with a MAO inhibitor or

within 14 days of discontinuing treatment with a MAO inhibitor; similarly, at least 14 days should be allowed after stopping OLEPTRO™ before starting treatment with a MAO inhibitor. Caution is advised when OLEPTRO™ is co-administered with other drugs that may affect neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, fentanyl, tramadol, or St. John's Wort (see **WARNINGS AND PRECAUTIONS: Serotonin Syndrome**).

Drugs that affect coagulation or bleeding: Due to a possible association between serotonin modulating drugs and gastrointestinal bleeding, 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 (see **WARNINGS AND PRECAUTIONS: Abnormal Bleeding**).

There have been reports of increased and decreased prothrombin time occurring in warfarinized patients who take trazodone.

CNS depressants: Trazodone may enhance the response to alcohol and the effects of barbiturates and other CNS depressants and patients should be cautioned accordingly.

Little is known about the interaction between trazodone and general anesthetics; therefore prior to elective surgery, OLEPTRO™ should be discontinued for as long as clinically feasible [(1)].

Drug-Non-drug Therapy Interactions

Electroconvulsive Therapy (ECT): The efficacy and safety of the concurrent use of OLEPTRO™ and ECT have not been studied.

Drug-Food Interactions

When OLEPTRO™ 300 mg caplets are taken shortly after ingestion of a high-fat meal, the rate of exposure as measured by C_{max} is increased by 86% (relative to when taken in the fasted state). However, the extent of exposure ($AUC_{0-\infty}$) and the time to reach maximum drug concentration in blood plasma (T_{max}) are not affected by food. OLEPTRO™ should be taken on an empty stomach.

Grapefruit, grapefruit juice, and products containing grapefruit extract should not be used during treatment with OLEPTRO™ because of the potential to inhibit CYP3A4 and increase plasma levels of trazodone.

Drug-Herb Interactions

In common with SSRIs, pharmacodynamic interactions between trazodone and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects (see **WARNINGS AND PRECAUTIONS: Serotonin Syndrome**).

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Trazodone may enhance response to alcohol and other CNS depressants. Concomitant use with alcohol should be avoided.

DOSAGE AND ADMINISTRATION

Dosing Considerations

OLEPTRO™ caplets are an extended-release dosage form containing Contramid® hydroxypropyl distarch phosphate. OLEPTRO™ caplets are designed to release trazodone hydrochloride over a 24-hour period and are intended for once-a-day dosing. Administration of OLEPTRO™ following a high fat meal increased the C_{max} by 86%. OLEPTRO™ should be taken on an empty stomach.

OLEPTRO™ should be swallowed whole or broken in half along the score line. In order to maintain controlled-release properties, **OLEPTRO™ caplets should not be chewed or crushed**. In a single dose study, the dose-adjusted trazodone bioavailability of the 150 mg, 300 mg, half 150 mg and half 300 mg caplets were equivalent, confirming a linear pharmacokinetic response over this range of strengths. Dose proportionality of the 150 mg and 300 mg and caplets broken in half has been demonstrated.

In order to break the caplets accurately and easily, the caplet should be held between the thumbs and index fingers close to the caplet score. Then, while facing the caplet score, pressure should be applied and the caplet segments snapped apart.

The uniformity of dosage units of the manually split caplets halves was demonstrated.

Recommended Dose and Dosage Adjustment

Adults:

OLEPTRO™ caplets should be taken orally at the same time every day, in the late evening, on an empty stomach.

The recommended starting dose of OLEPTRO™ is 150 mg/day. The dose may be increased by 75 mg/day every three days (i.e., start 225 mg/day on Day 4 of therapy). The maximum dose should not exceed 375 mg/day.

Maintenance/Continuation/Extended Treatment
There has been no systematic evaluation of the efficacy of OLEPTRO™ beyond 8 weeks. It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy beyond the response to the acute episode. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, and patients should be periodically reassessed to determine the need for continued treatment.

Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

Discontinuation of Treatment with OLEPTRO™
Patients should be monitored for discontinuation symptoms when discontinuing treatment with OLEPTRO™. The dose should be gradually reduced whenever possible.

Geriatrics (>65 years of age):
OLEPTRO™ should be used with caution in elderly patients. Limited clinical experience suggests that lower initial and maintenance doses should be used (see **WARNINGS AND PRECAUTIONS: Special Populations**, **Geriatrics**).

Pediatrics:
OLEPTRO™ is not indicated for use in children under 18 years of age (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Missed Dose

Patients should be cautioned against taking two doses concomitantly. If a dose is missed, it should not be compensated for by doubling the next dose. Patients should be advised not to take the missed dose the next morning. The next dose should be taken as scheduled.

OVERDOSAGE

Death from overdose has occurred predominantly in patients ingesting trazodone and other CNS depressant drugs concurrently (namely, 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, coma, seizures, and ECG changes, including QT prolongation and torsade de pointes, and death. The reactions reported most frequently have been drowsiness and vomiting. Also reported were bradycardia, transient first-degree heart block, ataxia and hyponatremia. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions.

Treatment of Overdosage:
There is no specific antidote for trazodone overdose. Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation. Ensure adequate airway, oxygenation and ventilation. Continuous ECG and vital signs monitoring are recommended. Monitor fluids and electrolyte status in symptomatic patients. Induction of emesis is not recommended. Any patient suspected of having taken a potentially life-threatening overdose should have the stomach emptied by gastric lavage, with appropriate airway protection, if it can be performed soon after ingestion. Forced diuresis may be useful in facilitating elimination of the drug.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Trazodone's antidepressant mechanism of action in man is not fully understood, but is thought to be related to its potentiation of serotonergic activity in the CNS. It is also called a Serotonin 2A/2C Antagonist and Serotonin Reuptake Inhibitor (SARI).

Preclinical studies have shown that trazodone functions as an antagonist at 5-HT2A and 5-HT2C receptors and as a weak inhibitor of serotonin reuptake.

Trazodone's active metabolite, m-chlorophenylpiperazine (mCPP) functions as a potent 5-HT2C agonist and as a partial agonist at several of the other subtypes of serotonin receptors.

Pharmacodynamics

Trazodone is a potent α1-adrenergic receptor antagonist with relatively weak α2-adrenergic receptor activity and its main actions at adrenergic receptors are dominated by antagonism of α1-adrenergic receptor subtypes. Trazodone has weak action at a variety of other neurotransmitter receptors, ion channels and transporters.

Cardiac conduction effects of trazodone in the anesthetized dog are qualitatively dissimilar and quantitatively less pronounced than those seen with tricyclic antidepressants. Trazodone is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

Pharmacokinetics

Administration of 300 mg OLEPTRO™ provides equivalent steady-state exposure to 100 mg immediate-release trazodone administered three times a day, with a 42% lower mean maximum plasma concentration (1812 vs 3118 ng/mL).

Steady-state pharmacokinetic parameter values following multiple-dose administration of OLEPTRO™ 300 mg caplets are presented in Table 3.

Table 3. Mean ± SD Steady-state Pharmacokinetic Parameters Following Multiple-dose Administration of OLEPTRO™ 300 mg Caplets

Parameter	300 mg Caplets
AUC_{ss} (ng·h/mL)	29131 ± 9931
C_{max} (ng/mL)	1812 ± 621
T_{max} (h)*	8 (3 – 16)

* Median and range are presented.

Absorption: In humans, trazodone is well absorbed after oral administration, without selective localization in any tissue. Following single-dose administration of OLEPTRO™ 300 mg caplets under fasting conditions, a mean peak trazodone plasma concentration (C_{max}) of 1188 ± 362 ng/mL was reported at a median T_{max} of 9 hours post-dose. When OLEPTRO™ 300 mg caplets are taken shortly after ingestion of a high-fat meal, the rate of exposure, as measured by C_{max}, is increased by 86% (relative to when taken in the fasted state). However, the extent of exposure ($AUC_{0-\infty}$) and the time to reach maximum drug concentration in blood plasma (T_{max}) are not affected by food.

Distribution: Trazodone is 89 to 95% protein bound *in vitro* at concentrations attained with therapeutic doses in humans.

Metabolism: *In vitro* studies in human liver microsomes show that trazodone is metabolized, via oxidative cleavage, to an active metabolite, m-chlorophenylpiperazine (mCPP), by cytochrome P450 3A4 (CYP3A4). mCPP is itself metabolized to p-hydroxy-mCPP (OH-mCPP) by CYP2D6. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized. Trazodone is extensively metabolized; less than 1% of an oral dose is excreted unchanged in the urine [(2)].

Excretion: Elimination is predominantly renal with 70 to 75% of an oral dose being recovered in the urine within the first 72 hours of ingestion [(3)]. Following single-dose administration of OLEPTRO™ 300 mg caplets, a mean apparent terminal half-life of 10 hours was reported.

Special Populations and Conditions

Pediatrics (< 18 years of age): Safety and effectiveness in the pediatric population have not been established. OLEPTRO™ should not be used in children or adolescents (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Geriatrics (> 65 years of age): OLEPTRO™ should be used with caution in geriatric patients (see **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: OLEPTRO™ has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population.

Renal Insufficiency: OLEPTRO™ has not been studied in patients with renal impairment. Trazodone should be used with caution in this population.

STORAGE AND STABILITY

Store at room temperature (15 – 30ºC) in tight, light-resistant containers.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OLEPTRO™ (trazodone hydrochloride) caplets are an extended-release dosage form consisting of a single matrix containing Contramid® hydroxypropyl distarch phosphate and trazodone. OLEPTRO™ caplets are available in 150 mg and 300 mg strengths.

150 mg: The 150 mg caplets are scored on both sides and coated with a non-functional yellowish-beige coating. The bisectable coated caplets are printed with a logo on one side.

300 mg: The 300 mg caplets are scored on both sides and coated with a non-functional beige-orange coating. The bisectable coated caplets are printed with a logo on one side.

Both strengths are available in bottles of 30, 90 and 500 caplets and in blister packs of 4, 7, 10, 11 and 30 caplets. The 150 mg strength is also available in bottles of 10 caplets.

Composition:

Medicinal Ingredients:

Trazodone Hydrochloride

Nonmedicinal Ingredients:

Hydroxypropyl distarch phosphate (Contramid®), hypromellose, sodium stearyl fumarate, colloidal silicon dioxide, iron oxide yellow (CI number 77492), iron oxide red (CI number 77491), talc, polyethylene glycol 3350, polyvinyl alcohol, titanium dioxide (CI number 77891), iron oxide black (CI number 77499), shellac glaze, ethanol, isopropyl alcohol, N-butyl alcohol, propylene glycol, ammonium hydroxide.

Contramid is a registered trademark of Labopharm Inc.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

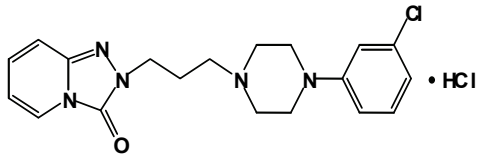
Proper name: Trazodone Hydrochloride

Chemical name: trazodone hydrochloride {2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride}

Molecular formula: $C_{19}H_{22}ClN_5O \cdot HCl$

Molecular mass: 408.33 (salt)
371.88 (base)

Structural formula:



Physicochemical properties:

Physical description: white to almost white crystalline powder

Solubility (at room temperature):

Solvent	Solubility (g/100 mL)
Water	About 1.8
95% ethanol	About 1.6
Methanol	About 2.5
Chloroform	About 3.6
Benzene	Practically insoluble
Ethyl ether	Practically insoluble
Octanol	Less than 0.1
Olive oil	Less than 0.1

pH and pKA values: The reported pKa in 50% ethanol is 6.14 (potentiometric determination using a glass-calomel electrode). The pH of a 1% (w/v) aqueous solution is 3.90 – 4.50.

Melting point: Trazodone hydrochloride melts with decomposition between 231ºC and 234ºC according to USP <741> class Ia testing under reduced pressure.

CLINICAL TRIALS

Study Demographics and Trial Design

The efficacy and safety of OLEPTRO™ for the treatment of unipolar major depressive disorder (MDD) were established in a multicentre, parallel-design, placebo-controlled study. The study consisted of a baseline phase (screening and washout) and a double-blind randomized phase. The total study duration, including washout of prohibited medications, was approximately 11 weeks; the duration of the randomized phase was 8 weeks (titration: 2 weeks and treatment: 6 weeks). Rescue medication for MDD was not allowed.

In the study, outpatients meeting DSM-IV criteria for major depressive disorder received either OLEPTRO™ (n = 202) or placebo (n = 204) at a dose of 150 – 375 mg once-daily at bedtime, without regard to meals. Patients had to increase their doses according to the titration schedule (every 4th or 5th day) up to 375 mg/day over 2 weeks, unless a decrease was necessary to improve tolerability. The doses could be adjusted during the Treatment Period for efficacy or tolerability reasons. Eligible patients were between 18 – 80 years of age. The mean age of the population was 44 years, 64% were female, and the race distribution was 69% Caucasian, 21% Black, 2% Asian, and 9% other. There were a total of 25 patients aged 65 or older (16 in the placebo group and 9 in the OLEPTRO™ group). Among those, a total of 7 patients were aged 75 or older (5 in the placebo group and 2 in the OLEPTRO™ group). The mean total Hamilton Depression Scale (HAMD-17) score at baseline was 23.2 and 22.4 for patients randomized to OLEPTRO™ and placebo, respectively.

Efficacy and safety evaluations occurred at baseline (Visit 2), 7 days post-randomization (Day 7; Visit 3), Day 14 (Visit 4), Day 21 (Visit 5), Day 28 (Visit 6), Day 42 (Visit 7), and Day 56 (Visit 8). The primary efficacy endpoint in this study was change from baseline to the last study visit in HAMD-17 total score.

Study Results

The mean dose received by patients during the 6-week treatment period was 310 mg for the OLEPTRO™ group and 355 mg for the placebo group (note that doses had to be increased to 375 mg/day during the titration period unless a decrease was necessary to improve tolerability). At the end of the study (Day 56), the active group demonstrated a statistically significant greater improvement in the HAMD-17 score compared with the placebo group (-11.4 vs -9.3, $p = 0.0119$). The primary outcome was also supported by some of the secondary outcomes.

At study endpoint, the patient group receiving OLEPTRO™ had a higher percentage of HAMD-17 responders (defined as patients with a decrease of ≥50% from baseline to Day 56 in HAMD-17 total score) vs placebo (54.0% vs 41.2%, respectively).

Patients in the OLEPTRO™ group also demonstrated a greater decrease than the placebo group in change from baseline in MADRS total score at week 8 (-16.6 vs -14.1, respectively).

Comparative Bioavailability Studies

Single-dose Study:

A single-centre, randomized, open-label, 2-way crossover study was conducted to assess the comparative bioavailability of OLEPTRO™ (trazodone hydrochloride) 300 mg extended-release caplets administered as a single dose, and Desyrel® (trazodone hydrochloride, Bristol-Myers Squibb, Canada) 100 mg immediate-release tablets administered as three doses, 8 hours apart, under fasting conditions (n=19). Twenty-four healthy male and female subjects were enrolled. The study consisted of two treatment phases of 72 hours each. Doses of study medication between periods were separated by a washout period of 7 calendar days.

The mean pharmacokinetic parameters are summarized below. The mean trazodone plasma concentration-time profiles are illustrated in Figure 1.

Trazodone HCl

[1 x 300 mg (Test); 1 x 100 mg *tid* q8h (Reference)]

From measured data

uncorrected for potency

Geometric Mean

Arithmetic Mean (CV %)

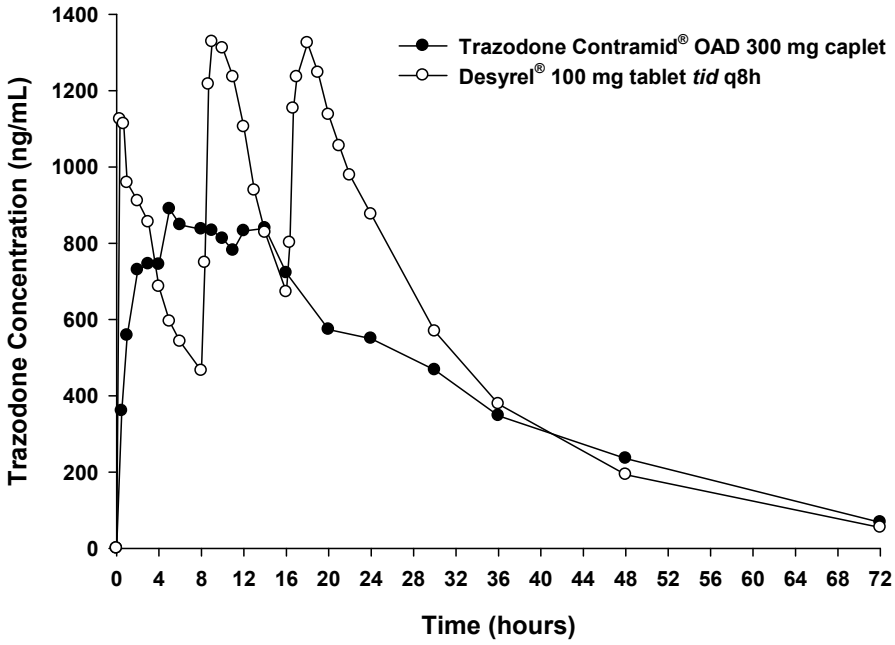
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	27656 29748 (35.4)	34808 36533 (26.3)	79.46	70.00 – 90.19
AUC_I (ng·h/mL)	29071 31554 (37.6)	35879 37853 (28.3)	81.03	70.99 – 92.48
C_{MAX} (ng/mL)	1025 1063 (35.4)	1746 1764 (26.8)	58.72	49.72 – 69.35
T_{MAX}§ (h)	6.00 (1.05-24.0)	9.00 (0.33-21.0)		
$T_{½}$‖ (h)	14.5 (30.1)	12.3 (29.2)		

* OLEPTRO™ 300 mg extended-release caplet

† Desyrel®, Bristol-Myers Squibb, Canada

§ Expressed as median (range)

Figure 1. Mean Plasma Trazodone Concentrations Following Administration of a 300 mg Daily Dose of OLEPTRO™ Extended-Release Caplets and 100 mg Desyrel® Immediate-Release Tablets under Fasting Conditions in Healthy Volunteers (n=19)



DETAILED PHARMACOLOGY

ANIMAL

Mechanism of Action

Trazodone, or 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,5-a]pyridin-3-one, has been known to have antidepressant actions since 1971. Trazodone hydrochloride is chemically unrelated to other known antidepressants. The pharmacological profile of trazodone differs significantly from that of other known psychopharmacological agents (e.g., Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs).

Trazodone's antidepressant mechanism of action in man is not fully understood. It is also called a Serotonin 2A/2C Antagonist and Serotonin Reuptake Inhibitor (SARI). Trazodone has a complex mechanism of action in which is thought to be predominated by 5-HT2A/2C serotonin receptor antagonism. Trazodone's main active metabolite, m-chlorophenylpiperazine (mCPP), functions as a potent 5-HT2C agonist and as a weak partial agonist at several 5-HT receptors. Trazodone has weak off-target actions at a variety of neurotransmitter receptors, ion channels and transporters, and it is likely that these actions contribute to both the known side effects and beneficial actions of trazodone.

Pharmacodynamics

Trazodone impedes the membrane uptake of serotonin. Small doses of the drug impede the depletion of brain serotonin by fenfluramine but doses of 50 mg/kg do not affect the concentration of serotonin in the rat brain. In experimental studies, trazodone is a weak inhibitor of noradrenalin reuptake but is practically inactive against 1-dopa, histamine and acetylcholine. It has no known monoamine oxidase inhibiting activity. Trazodone exhibits CNS depressant properties, causing decreased motor activity in cats, rats and mice and increasing the hexobarbital-induced sleeping time in mice. It also inhibits conditioned avoidance responding in rats at doses which do not influence the unconditioned response (ED_{50}=19.5 mg/kg p.o.). Trazodone has no anticonvulsant, anti-reserpine or cataleptogenic effects and its muscle relaxant activity is very weak.

In mice, responses to painful stimuli are suppressed by doses at which motor activity is unaffected (10 mg/kg p.o.), and oxotremorine-, clonidine- and nicotine-induced tremors are significantly inhibited by 12.5 mg/kg i.p. Trazodone protects grouped mice against amphetamine-induced toxicity, but does not inhibit the stereotyped behaviour due to amphetamine or apomorphine.

In rats, infusion of trazodone produces a fall in mean blood pressure, followed by ECG changes only as a consequence of the produced hypotension. In anesthetized dogs, graded doses between 1 and 30 mg/kg i.v. demonstrated no effect on His bundle conduction and no evidence of heart block or rhythm disturbance other than the slowing of normal sinus rhythm, while 0.5 to 5 mg/kg imipramine slowed impulse conduction as well as atrial transmission. The effect of trazodone on the sleep-wakefulness cycle in rats was comparable to that of similar doses of imipramine. 10 mg/kg p.o. reduced and 160 mg/kg completely suppressed REM sleep.

Pharmacokinetics

The absorption, distribution, metabolism and excretion of trazodone, and its metabolite mCPP (m-chlorophenylpiperazine), has been studied in rats and dogs.

Trazodone administration in rats displays a similar pharmacokinetic profile in both blood and brain tissues, which is possibly the result of a 2-compartmental elimination phase, however, C_{max} is higher when it is administered by intraperitoneal injection compared to oral intake. The pharmacokinetics of trazodone in the plasma of rats and dogs through oral and intravenous administrations of the drug was studied. Trazodone is rapidly absorbed from the intestinal tract in both rats and dogs; plasma concentrations reached maximum levels at 5 and 30 minutes after every dose in each species, respectively. Following intravenous administration, elimination from the plasma appeared to be biexponential, with $t_{1/2}$ being similar between the two species in the first phase (0.14 - 0.15 h), and different in the second phase (0.6 h and 2.5 h for rats and dogs, respectively). Elimination appears to be biphasic and may be due to differences in affinity to different tissues.

Pharmacokinetic analysis of levels of trazodone in the brain and blood of rats after acute or chronic treatment were also assessed. Trazodone given acutely displayed similar time course

levels in the brain and blood (T_{max} = 15 minutes) after i.p. and p.o. administration. However, the C_{max} for trazodone levels after i.p. injection was double that of p.o. administration. Trazodone was eliminated from the blood and brain in a biphasic manner, regardless of the route of administration. This consisted of a phase of slow disposition followed by a phase of rapid disposition. After chronic treatment, the T_{max}, C_{max}, $t_{1/2}$ and rate of elimination were similar to that after acute treatment. Distribution of trazodone following i.p. administration in decreasing order of levels detected were lungs>kidney>liver>spleen>brain>plasma. Blood and brain displayed similar affinities for trazodone while other tissues like lung and kidney exhibited greater trazodone affinities. These different "compartments" may explain the biphasic nature of trazodone elimination.

The levels of trazodone and its metabolite mCPP in the rat brain were tested after single and multiple administrations of trazodone i.p. or p.o. After acute i.p. administration of trazodone in rats, trazodone was found to be rapidly metabolized to mCPP with rapid distribution of the metabolite to the brain. In fact, 40 minutes after trazodone treatment, the level of mCPP in the brain exceeded that of trazodone. This difference increased with time, and 4 hours post-treatment, the level of mCPP was 3 times that of trazodone. Elimination rates of the two compounds from the brain were also different with trazodone being eliminated very rapidly and mCPP being eliminated slowly. The AUC for trazodone and mCPP for the first 4 hours post-treatment was similar.

Pharmacokinetic analysis after chronic administration of trazodone to female pregnant and non pregnant rats was also evaluated. There were no differences in the mean steady-state plasma concentrations of the compounds that could be attributable to sex or pregnancy. Both compounds were found in fetal and placental tissue, however, the steady state concentrations of trazodone were much lower in fetal tissue than in the maternal plasma. Only trace amounts of mCPP were present in the fetus compared to trazodone.

In vitro studies using human liver microsomes and cell lines have shown that trazodone is metabolized to produce mCPP through the action of the cytochrome P450 isoenzyme CYP3A4 and that mCPP is itself metabolized to p-hydroxy-mCPP through the action of CYP2D6.

TOXICOLOGY

Acute Toxicity

The acute toxicity of trazodone has been examined in the mouse, rat, rabbit and dog. Summarized LD_{50} values are presented in the following table.

LD_{50} in mg/kg (95% confidence limits)				
	Species			
Route	**Mouse**	**Rat**	**Rabbit**	**Dog**
Intravenous	91 (82 - 101)	91 (86 - 96)	52	40
Intraperitoneal	210 (189 - 233)	178 (162 - 196)	--	--
Oral	610 (540 - 689)	690 (616 - 733)	**560**	**500**

Signs of toxicity included dyspnea, salivation, ptosis, aggressivity, hypoactivity, prostration and clonic convulsions.

Subacute and Chronic Toxicity

In several subacute studies in rats, 100 to 450 mg/kg/day p.o. for one to four months produced a decrease in body weight gain and slight liver enlargement in males as the main toxic effects. The highest dose also caused some deaths. In dogs, 50 and 100 mg/kg/day p.o. for one month produced tremors, vomiting and clonic convulsions [(1)].

One of two dogs receiving 100 mg/kg died after 3 weeks. In a 6 month rat study, administration of approximately 250 mg/kg/day in the diet resulted in significantly greater liver weights than in control rats and in slightly lower weight gain in males. Dogs receiving 5 and 25 mg/kg/day for 6 months showed no toxic effects [(1)].

An eighteen month study was carried out in rats using doses of 0, 30, 100 and 300 mg/kg/day p.o. A decrease in body weight gain was seen in all treated groups, and males at the highest dose level showed significantly reduced food intake. No behavioural or pathologic effects were observed at the lowest dose level, while rats at the 100 mg/kg dose exhibited some lethargy and salivation immediately following dosing. At the highest dose level, there was excessive salivation and the animals became inactive, assuming a prone position for approximately 3 hours after dosing. Occasional body tremors were also seen. Tolerance developed to all these reactions within 30 weeks [(1)].

Beagle dogs were given oral doses of 0, 10 and 40 mg/kg/day for one year; however, after 8 weeks the highest dose was reduced to 30 mg/kg/day following the death of 3/10 animals in the group. No abnormal signs were observed at the 10 mg/kg level. In the 20 mg/kg group, one animal was found prostrate and panting on one occasion and another was unexpectedly found dead near the end of the study. 40 mg/kg produced occasional transient ataxia, excessive salivation and convulsions. Following the three deaths and the reduction of dosage to 30 mg/kg,

a fourth death occurred 16 weeks later, subsequent to convulsions. A fifth animal became hypersensitive to touch and aggressive during the final 6 months of the study [(1)].

Hematological and biochemical analyses were normal apart from one case of transient anemia in the 20 mg/kg group and slightly elevated SGPT values in 2/6 high dose dogs during the final 3 months [(1)].

Groups of 6 rhesus monkeys received 0, 20, 40, and 80 mg/kg/day of trazodone by gavage for one year. The only effects noted were a slight dose-related decrease in activity and tremors in 3 high-dose monkeys. Both effects decreased during the study [(1)].

Reproductive Studies

A number of reproductive studies were performed. Fertility and general reproductive performance of male and female rats were not affected by doses of up to 250 mg/kg/day.

At 300 mg/kg, the birth weight of pups was significantly reduced. In one rat study, 100 and 210 mg/kg/day p.o. was given during days 10 - 15 and 6 - 15 of gestation respectively, and in another study, 150 to 450 mg/kg/day p.o. was given during days 9 - 14 of gestation. At 100 mg/kg only a sedative effect on dams was noted. 150 mg/kg and higher doses produced increased sedation, decreased maternal and fetal weights, and retarded ossification. 300 and 450 mg/kg resulted in a significant increase in resorption and stillborn feti in addition to retarded fetal growth. Also noted were isolated cases of branched rib, separated thoracic arch, umbilical hernia, and exencephalia.

Peri- and postnatal effects of up to 300 mg/kg/day of trazodone were examined in rats. The only effects observed were reduced birth and weaning weights of offspring in the highest dosage group [(1)].

When doses approximately 30 – 50 times the proposed maximum human dose were administered to rats, trazodone was shown to cause increased fetal resorption and other adverse effects on the fetus. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15 – 50 times the maximum human dose [(1), (5)].

Carcinogenicity Studies

A two-year carcinogenicity study was performed in rats at dose levels of 0, 40 and 80 mg/kg/day. Larger numbers of female rats in both treatment groups died sooner than controls and most deaths were related to the presence of pituitary tumors. The incidence of palpable masses (mammary tumors, cysts, etc.) also was increased in both treatment groups at 12, 13, and 14 months. The observations may be related to the effects of trazodone on prolactin secretion. (Acute administration caused an increase in prolactin blood levels; chronic administration did not; however, turnover was not studied. A neuroleptic, used as a positive control, produced similar results.) The relative incidences of male rats with pituitary tumors were reversed; however, early deaths due to nephritis and other causes might have influenced these observations [(1)].

Toxicology of Contramid®

Contramid® hydroxypropyl distarch phosphate is chemically identical to modified starch for food use. This class of modified starches has been in widespread use for over 40 years. A review of published toxicity studies including this type of starch has shown no evidence of toxic effects.

To date, Contramid® has been administered in clinical studies to over 2,700 human subjects (as a component of the drug product being tested). Subjects were administered formulations containing between 117 and 364 mg Contramid® daily for periods up to one year. There was no association between reported adverse events and Contramid®.

REFERENCES

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(4) Sheehan DV, Croft HA, Gossen ER, Levitt RJ, Brullé C, Bouchard S, et al. Extended-release trazodone in major depressive disorder: a randomized double-blind, placebo-controlled study. Psychiatry. 2009; 6(5):20-33.

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PART III: CONSUMER INFORMATION

PrOLEPTRO™
Trazodone Hydrochloride Extended-Release Caplets

This leaflet is part III of a three-part "Product Monograph" published when OLEPTRO™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OLEPTRO™. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medication, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
OLEPTRO™ (trazodone hydrochloride extended-release caplets) is an antidepressant used to treat the symptoms of major depressive disorder (MDD) in adults over 18 years old.

What it does:
Depression is an illness that is believed to be caused by an imbalance of a chemical called serotonin. OLEPTRO™ belongs to a group of medicines called Serotonin 2A/2C Antagonist and Reuptake Inhibitors (SARIs). OLEPTRO™ is thought to work by increasing the levels of serotonin in your brain.

OLEPTRO™ is an extended-release formulation designed to work over a 24-hour period. It may take several weeks of treatment before you notice an improvement. It is important for you to continue therapy as directed by your doctor.

When it should not be used:
You should not use OLEPTRO™ if you are allergic to trazodone or any of the nonmedicinal ingredients in the product (see **What the nonmedicinal ingredients are**). Contact your doctor immediately if you experience an allergic reaction (e.g., skin rash, hives) or any severe or unusual side effects.

What the medicinal ingredient is:
Trazodone hydrochloride.

What the nonmedicinal ingredients are:
Hydroxypropyl distarch phosphate (Contramid®), hypromellose, sodium stearyl fumarate, colloidal silicon dioxide, iron oxide yellow (CI number 77492), iron oxide red (CI number 77491), talc, polyethylene glycol 3350, polyvinyl alcohol, titanium dioxide (CI number 77891), iron oxide black (CI number 77499), shellac glaze, ethanol, isopropyl alcohol, N-butyl alcohol, propylene glycol, ammonium hydroxide.

What dosage forms it comes in:
OLEPTRO™ caplets are extended-release caplets and are available in 150 mg and 300 mg strengths. Caplets are scored on both sides.

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

OLEPTRO™ is not for use in children under 18 years of age.

New or Worsened Emotional or Behavioural Problems

Particularly in the first weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Do not discontinue your medication on your own.

BEFORE you use OLEPTRO™ talk to your doctor or pharmacist if you:

- have a history or a family history of heart problems, including: heart disease, heart attack, QT prolongation, arrhythmias (irregular heart beat), or a family history of sudden cardiac death at age younger than 50 years
- have liver problems
- have kidney problems
- have or have had fainting or dizziness
- have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- have an eating disorder or are following a strict diet
- have diabetes, especially with associated nerve disorders
- have or have had abnormal bleeding
- have bipolar disorder
- have blood pressure problems
- have had breast tumours
- have had pituitary tumours
- have conditions that might predispose you to priapism, (painful erections greater than 4 hours in duration) such as sickle cell anemia, multiple myeloma, or leukemia, or if you have any anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease)
- are taking or have recently taken any prescription, non-prescription, or natural/herbal medications (see Interactions with this Medication)
- are pregnant or thinking about becoming pregnant
- are breastfeeding
- are older than 65 years of age

Do not drive a vehicle or perform hazardous tasks while taking OLEPTRO™.

INTERACTIONS WITH THIS MEDICATION

There are medications that may cause OLEPTRO™ caplets to be less effective, or may cause you to have some side effects or drug reactions.

The following list includes some, but not all, of the drugs that may interact with OLEPTRO™.

Drugs (or therapies) that may interact with OLEPTRO™ include:

- Acetylsalicylic acid (ASA)
- Alcohol
- Anaesthetics for surgery
- Analgesics for pain (e.g., opioids)
- Antiarrythmics (for irregular heart rhythm)
- Antibiotics (e.g., erythromycin, clarithromycin, moxifloxacin, ciprofloxacin, etc.)
- Anticonvulsants (e.g., phenytoin)
- Antidepressants other than OLEPTRO
- Antifungals (e.g. ketoconazole, fluconazole, voriconazole)
- Antihypertensive drugs (for high blood pressure)
- Anti-infectives
- Antipsychotics
- Asthma drugs (e.g., formoterol, salmeterol)
- Barbiturates
- Coumarin
- Corticosteroids
- Digoxin or phenytoin
- Diuretics
- Drugs that alter CYP3A4 metabolism (e.g., ritonavir, ketoconazole, indinavir, itraconazole, carbamazepine),
- Drugs to treat nausea and vomiting (e.g., ondansetron, dolasetron, domperidone)
- Electroshock therapy
- Epilepsy drugs
- Laxatives or enemas
- Natural or herbal products (e.g., St. John's Wort)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Pentamidine
- Serotoninergic drugs (including SSRIs, SNRIs and triptans) and drugs that impair metabolism of serotonin (including MAOIs (e.g., phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegeline))
- Trazadone
- Warfarin

You should check with your doctor or pharmacist before taking any other medication with OLEPTRO™. Be sure to also talk to your doctor about any street drug consumption.

Consumption of grapefruit, grapefruit juice, or products containing grapefruit extract should be avoided while taking OLEPTRO™.

Do not drink alcohol while taking OLEPTRO™.

PROPER USE OF THIS MEDICATION

Usual adult dose:
OLEPTRO™ caplets are intended for a once-a-day treatment. The caplets should be taken orally at the same time every day, in the late evening on an empty stomach.

The recommended starting dose of OLEPTRO™ is 150 mg/day. Your doctor may recommend to increase the dose by 75 mg/day every three days (i.e., start 225 mg/day on Day 4 of therapy). The maximum dose should not exceed 375 mg/day.

OLEPTRO™ should be swallowed whole or broken in half along the score line. **OLEPTRO™ caplets should not be chewed or crushed**.

In order to break the caplets accurately and easily, hold the caplet between your thumbs and index fingers close to the caplet score. Then with the caplet score facing you, apply pressure and snap the caplet segments apart.

Dosage directions should be followed carefully. Never exceed the prescribed dose.

Discontinuing OLEPTRO™
It is very important that you do NOT stop taking OLEPTRO™ without first consulting your doctor. See the section **SIDE EFFECTS AND WHAT TO DO ABOUT THEM** for more information.

Elderly (65 years of age or older):
If you are older than 65 years of age, your doctor may recommend a lower dose.

Overdose:

In case of drug overdose, contact your regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Do not take more than one dose per day. If you miss a dose, do not double the next dose. Do not take the missed dose during the day; instead, the next dose should be taken as scheduled in the late evening.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, OLEPTRO™ can cause some side effects. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

The most common side effects of OLEPTRO™ are:

- Headache
- Drowsiness
- Dry mouth
- Dizziness (lightheadedness)
- Nausea
- Sedation
- Fatigue
- Diarrhea
- Constipation
- Back pain
- Blurred vision

This is not a complete list of side effects. For any unexpected effects while taking OLEPTRO™, contact your doctor or pharmacist.

Discontinuation Symptoms
Even if you have side effects, contact your doctor before stopping or reducing your dosage of OLEPTRO™. Discontinuation symptoms including anxiety, agitation and sleep disturbances, have been reported with trazodone. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of OLEPTRO™ to alleviate the symptoms.

Effect on the Hormone Prolactin
In women, medicines of this type may cause changes in the regularity of their monthly period or leakage of milk from the breast even if they are not pregnant. In some men, after prolonged treatment, there may be some diminished sexual function and breast enlargement may be experienced. Tell your doctor if you experience any of these symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

New or Worsened Emotional or Behavioural Problems
Particularly in the first weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, consult your doctor immediately. **Do not discontinue your medication on your own**. See also the **WARNINGS AND PRECAUTIONS** section.

Other effects may include the following:
Heart pounding, heart racing, ringing in the ears, vomiting, weakness, feeling jittery, disturbance in attention, tingling sensation, musculoskeletal stiffness, erectile dysfunction (in men), tremors, hot flashes, sore throat, changes in blood sugar, decreased appetite, changes in sense of taste, sweating, restlessness, nervousness, urinary urgency, excessively frequent urination, confusion, memory problems, painful menstrual periods.

Effects on Newborns

Some newborns whose mothers took certain antidepressants, such as OLEPTRO™, during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. In most cases, the antidepressant was taken during the third trimester of pregnancy. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek emergency medical attention
		Only if severe	In all cases	
Common	Low blood pressure: feeling dizzy, lightheaded		X	
Uncommon	Fainting			X
Rare	Painful erection lasting more than 4 hours			X
	Uncontrollable movements of the body or face		X	
See side effects and what to do about them	Allergic reactions (red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, skin rashes)			X*
Unknown	Bruising or unusual bleeding from the skin or other areas		X	
	Low sodium level in blood (symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles)		X	
	Mania/Hypomania (elevated or irritable mood, decreased need for sleep, racing thoughts)		X	
See warnings and precautions	New or worsened emotional or behavioural problems		X	
	Thoughts of death or suicide			X

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek emergency medical attention
		Only if severe	In all cases	
	Seizures (loss of consciousness with uncontrollable shaking 'fit')			**X***
	Serotonin Syndrome (a combination of most or all of the following: confusion, restlessness, sweating, shaking, sudden jerking of the muscles, hallucinations, fast heartbeat)			**X***
	Symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations or fast heart beat, fainting, or seizures			**X***
Unknown	**Inability to urinate**		**X**	
	Akathisia (feeling restless and unable to sit or stand still)		**X**	
	Tarry, dark-coloured stools		**X**	
See side effects and what to do about them	**Sore throat, fever, general feeling of being unwell**		**X**	

* Stop taking drug; do not take the next dose. Seek emergency medical attention.

HOW TO STORE IT

OLEPTRO™ should be stored at room temperature (15ºC to 30ºC). Keep it in a tight container and out of the light.

Do not use OLEPTRO™ caplets after the expiry date. All expired medications should be returned to your pharmacist.

Keep this and all medicines in a safe place away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.website.document
or by contacting the sponsor, Angelini Pharma Inc., at:
1-800-XXX-XXXX

This leaflet was prepared by Angelini Pharma Inc., 8322 Helgerman Court, Gaithersburg, MD 20877 USA.

Imported by:

Last revised: October 7, 2014