HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Oleptro safely and effectively. See full prescribing information for Oleptro.

OLEPTRO (trazodone hydrochloride) extended-release tablets
Initial U.S. Approval: 1981

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
See full prescribing information for complete boxed warning.

Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Oleptro is not approved for use in pediatric patients (5.1).

----------INDICATIONS AND USAGE----------
Oleptro is indicated for the treatment of major depressive disorder (1).
- Efficacy was established in one 8-week trial of Oleptro as well as in trials of trazodone immediate release formulation in patients with major depressive disorder (14).

----------DOSAGE AND ADMINISTRATION----------
- Starting dose: 150 mg once daily. May be increased by 75 mg per day every three days. Maximum dose: 375 mg per day (2).
- Dosing at the same time every day in the late evening, preferably at bedtime, on an empty stomach (2).
- Tablets should be swallowed whole or broken in half along the score line, and should not be chewed or crushed (2).
- When discontinued, gradual dose reduction is recommended (2).

----------DOSAGE FORMS AND STRENGTHS----------
Bisectable tablets of 150 mg or 300 mg (3).

----------CONTRAINDICATIONS----------
None (4).

----------WARNINGS AND PRECAUTIONS----------
- Clinical Worsening/Suicide Risk: Monitor for clinical worsening and suicidal thinking and behavior (5.1).
- Serotonin Syndrome or Neuroleptic Malignant Syndrome-like Reactions: Have been reported with antidepressants. Discontinue Oleptro and initiate supportive treatment (5.2).
- Activation of Mania/Hypomania: Screen for bipolar disorder and monitor for mania/hypomania (5.3).
- QT Prolongation: Increases the QT interval. Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval (5.4).
- Use in Patients with Heart Disease: Use with caution in patients with cardiac disease (5.5).
- Orthostatic Hypotension and Syncope: Have occurred. Warn patients of risk and symptoms of hypotension (5.6).
- Abnormal Bleeding: May increase the risk of bleeding. Use with NSAIDs, aspirin, or other drugs that affect coagulation may compound this risk (5.7).
- Interaction with MAOIs: Do not use concomitantly or within 14 days of monoamine oxidase inhibitors (5.8).
- Priapism: Has occurred. Warn male patients of this risk and how/when to seek medical attention (5.9).
- Hyponatremia: Can occur in association with SIADH (5.10).
- Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Advise patients to use caution when operating machinery (5.11).
- Discontinuation Symptoms: May occur with abrupt discontinuation and include anxiety and sleep disturbance. Upon discontinuation, taper Oleptro and monitor for symptoms (5.12).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and twice that of placebo) are: somnolence/sedation, dizziness, constipation, vision blurred (6).

To report SUSPECTED ADVERSE REACTIONS, contact Angelini Labopharm at 1-877-345-6177 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Monoamine Oxidase Inhibitors: Should not be used concomitantly with Oleptro (5.8, 7).
- CNS Depressants: Trazodone may enhance effects of alcohol, barbiturates, or other CNS depressants (7).
- CYP3A4 Inhibitors: May necessitate lower dose of Oleptro (7).
- CYP3A4 Inducers (e.g., carbamazepine): May necessitate higher dose of Oleptro (7).
- Digoxin or Phenytoin: Monitor for increased serum levels (7).
- Warfarin: Monitor for increased or decreased prothrombin time (7).
- Serotonergic Medications: Serotonin syndrome has been reported (5.2, 7).
- NSAIDs, Aspirin or other Anticoagulants: Potential for increased risk of bleeding (5.7, 7).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: Use with caution (8.3).
- Pediatric Patients: Oleptro is not approved in pediatric patients (8.4).
- Renal or Hepatic Impairment: Use with caution (8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION as well as MEDICATION GUIDE.
Revised: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***** Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL 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 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 (5.1) and Patient Counseling Information (17.1)]*.

1 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 (14)]*.

2 DOSAGE AND ADMINISTRATION

Dose Selection

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

- Oleptro tablets should be taken orally at the same time every day, in the late evening preferably at bedtime, on an empty stomach.
- Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.
- Patients should be monitored for withdrawal symptoms when discontinuing treatment with trazodone hydrochloride. The dose should be gradually reduced whenever possible *[see Warnings and Precautions (5.12)]*.

Maintenance Treatment

The efficacy of Oleptro for the maintenance treatment of MDD has not been evaluated. While there is no body of evidence available to answer the question of how long a patient treated with Oleptro should continue the drug, it is generally recommended that treatment be continued for several months after an initial response. Patients should be maintained on the lowest effective dose and be periodically reassessed to determine the continued need for maintenance treatment.

Important Administration Instructions
Oleptro tablets are scored to provide flexibility in dosing.

Oleptro can be swallowed whole or administered as a half tablet by breaking the tablet along the score line. Breaking the tablet in half does not affect the controlled-release properties of the tablet.

In order to maintain its controlled-release properties, Oleptro should not be chewed or crushed.

3 DOSAGE FORMS AND STRENGTHS

Oleptro tablets are available in the following strengths:

- Oleptro bisectable tablets containing 150 mg of trazodone hydrochloride (yellowish-beige, capsule-shaped tablet, coated and scored on both sides with DDS 080 printed on one side)
- Oleptro bisectable tablets containing 300 mg of trazodone hydrochloride (beige-orange, capsule-shaped tablet, coated and scored on both sides with DDS 081 printed on one side)

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 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.

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.

5.2 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 (5.8) and Drug Interactions (7)]*.

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.

5.3 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.

5.4 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.

5.5 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 (5.4)]*. 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.

5.6 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.

5.7 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.

5.8 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.

5.9 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 (6.2) and Overdosage (10)]*.

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).

5.10 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.

5.11 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.

5.12 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.

6 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 (5.1)]*
- Serotonin Syndrome or NMS-like Reactions *[see Warnings and Precautions (5.2)]*
- QT Prolongation and Risk of Sudden Death *[see Warnings and Precautions (5.4)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.6)]*
- Abnormal bleeding events *[see Warnings and Precautions (5.7)]*
- Priapism *[see Warnings and Precautions (5.9)]*
- Hyponatremia *[see Warnings and Precautions (5.10)]*
- Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Discontinuation symptoms *[see Warnings and Precautions (5.12)]*

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: AEs 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%)

6.1 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

6.2 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 (5.9) and Patient Counseling Information (17.1)]*, 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 (5.4)]*.

7 DRUG INTERACTIONS

MAOIs
MAOIs should not be used within 14 days of Oleptro *[see Warnings and Precautions (5.8)]*.

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 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. 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 (5.4)]* 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-chlorophenylpiperazine (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 (5.2)]*.

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 (5.7)]*.

Warfarin

There have been reports of altered (either increased or decreased) prothrombin times in taking both warfarin and trazodone.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.3 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.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions (5.1)]*. Oleptro should not be used in children or adolescents.

8.5 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 (5.10)]*.

8.6 Renal Impairment

Oleptro has not been studied in patients with renal impairment. Trazodone should be used with caution in this population.

8.7 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Oleptro is not a controlled substance.

9.2 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).

10 OVERDOSAGE

10.1 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.

10.2 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.

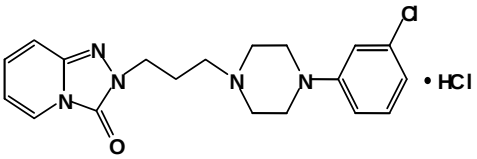
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

11 DESCRIPTION

Oleptro (trazodone hydrochloride) is a triazolopyridine. It is a white, odorless crystalline powder which is freely soluble in water.

Chemical Name: 2-[3-[4-(*m*-Chlorophenyl)-1-piperazinyl]propyl]-*s*-triazolo[4,3-*a*]pyridin-3(2*H*)-one monohydrochloride

Structural Formula:



Molecular Formula: $C_{19}H_{22}ClN_5O \cdot HCl$
Molecular Weight: 408.32

Oleptro tablets containing 150 mg or 300 mg of trazodone hydrochloride are designed to release their drug content over a 24-hour period and are intended for once-a-day dosing.

Inactive Ingredients:

Hydroxypropyl distarch phosphate (Contramid®)
Hypromellose
Sodium stearyl fumarate
Colloidal silicon dioxide
Iron Oxide Yellow
Iron Oxide Red
Talc
Polyethylene Glycol 3350
Titanium Dioxide
Polyvinyl Alcohol
Black ink (food grade)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of trazodone's antidepressant action is not fully understood, but is thought to be related to its potentiation of serotonergic activity in the CNS.

12.2 Pharmacodynamics

Preclinical studies have shown that trazodone selectively inhibits neuronal reuptake of serotonin and acts as an antagonist at 5-HT-2A/2C serotonin receptors.

Trazodone is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

Trazodone antagonizes alpha 1-adrenergic receptors, a property which may be associated with postural hypotension.

12.3 Pharmacokinetics

Steady state AUC of Trazodone is equivalent after administration of Trazodone 100 mg immediate release (IR) three (3) times a day (mean ± SD AUC_{ss} = 33058 ± 8006 ng*h/mL) and Oleptro 300 mg once daily (mean ± SD AUC_{ss} = 29131 ± 9931 ng*h/mL) for one week. Steady State C_{max} and C_{min} of trazodone were not equivalent after administration of trazodone 100 mg IR 3 times a day (mean ± SD $C_{max,ss}$ = 3118 ± 758 ng/mL, $C_{min,ss}$ = 843 ± 274 ng/mL) and Oleptro 300 mg once daily (mean ± SD $C_{max,ss}$ = 1812 ± 621 ng/mL, $C_{min,ss}$ = 674 ± 355 ng/mL) for one week.

Absorption

Trazodone is well absorbed after oral administration, without selective localization in any tissue. Following single-dose administration of Oleptro 300 mg tablets 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 tablets are taken shortly after ingestion of a high-fat meal, C_{max} increases by about 86% compared to taking it under fasting conditions. However, $AUC_{0-\infty}$ and T_{max} are not significantly affected by food.

Oleptro tablets are dose proportional following single-dose administration of doses ranging from 75 mg to 375 mg as intact or bisected tablets.

Metabolism

In vitro studies in human liver microsomes show that trazodone is metabolized, via oxidative cleavage, to an active metabolite, m-chlorophenylpiperazine (mCPP) by CYP3A4. 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.

Elimination

Elimination is predominantly renal, with 70 to 75% of an oral dose being recovered in the urine within the first 72 hours of ingestion. Following single-dose administration of Oleptro 300 mg tablets, a mean apparent terminal half-life of 10 hours was reported.

Protein Binding

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving trazodone in daily oral doses up to 300 mg/kg for 18 months.

14 CLINICAL STUDIES

The efficacy and safety of Oleptro were established from trials of the immediate release formulation as well as a randomized, double-blind, two-arm study comparing the efficacy and safety of Oleptro and placebo in the treatment of unipolar major depressive disorder.

The Oleptro trial was a multi-center, parallel-design study of outpatients meeting DSM-IV criteria for major depressive disorder (MDD). This study consisted of a Baseline Phase (screening and washout) and a double-blind Randomized Phase (randomization to Oleptro (n=206) or placebo (n=206)). The total study duration, including washout of prohibited medications, was approximately 11 weeks; the total duration of the randomized treatment phase was 8 weeks (titration: 2 weeks and treatment: 6 weeks). Rescue medication for MDD was not allowed during the study.

Patients were between 18 and 80 years of age. Of this population, 25 patients were 65 years old or older. The mean age of the population was 44 years; 64% were female.

The primary efficacy endpoint in this study was change from baseline in HAMD-17 total score.

A statistically significant difference in the HAMD-17 score was demonstrated at 8 weeks between the Oleptro group and the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Oleptro 150 mg is a yellowish-beige, capsule-shaped extended-release tablet, coated and scored on both sides with DDS 080 printed on one side. It is supplied as follows:

Bottles of 30 tablets NDC 43595-080-03

Oleptro 300 mg is a beige-orange, capsule-shaped extended-release tablet, coated and scored on both sides with DDS 081 printed on one side. It is supplied as follows:

Bottles of 30 tablets NDC 43595-081-03

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

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Oleptro and should counsel them in its appropriate use.

Patients should be warned that:

- There is a potential for increased risk of suicidal thoughts especially in children, teenagers and young adults.

- The following symptoms should be reported to the physician: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania.
- They should inform their physician if they have a history of bipolar disorder, cardiac disease or myocardial infarction.
- Serotonin syndrome could occur and symptoms may include changes in mental status (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).
- Trazodone hydrochloride has been associated with the occurrence of priapism.
- There is a potential for hypotension, including orthostatic hypotension and syncope.
- There is a potential risk of bleeding (including life-threatening hemorrhages) and bleeding related events (including ecchymosis, hematoma, epistaxis, and petechiae) with the concomitant use of trazodone hydrochloride and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.
- Withdrawal symptoms including anxiety, agitation and sleep disturbances, have been reported with trazodone. Clinical experience suggests that the dose should be gradually reduced.

Patients should be counseled that:

- 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.
- Trazodone may enhance the response to alcohol, barbiturates, and other CNS depressants.
- Women who intend to become pregnant or who are breastfeeding should discuss with a physician whether they should continue to use Oleptro, since use in pregnant and nursing women is not recommended.

Important Administration Instructions:

- Oleptro should be swallowed whole or broken in half along the score line.
- In order to maintain its controlled-release properties, it should not be chewed or crushed.
- Oleptro should be taken at the same time every day, in the late evening preferably at bedtime, on an empty stomach.

Angelini Labopharm
Unit 5, The Seapoint Building
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U.S. Patent 6,607,748

Oleptro™ is a trademark of Labopharm Inc.
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