

caution is advised when Olepro 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. Olepro 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 Olepro 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)*]. Olepro should not be used in children or adolescents.

8.5 Geriatric Use

Of 202 patients treated with Olepro 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 Olepro 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

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

8.7 Hepatic Impairment

Olepro 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

Olepro 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 Olepro. 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 Olepro 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

5

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Absorption

Trazodone is well absorbed after oral administration, without selective localization in any tissue. Following single-dose administration of Olepro 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 Olepro 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-∞} and T_{max} are not significantly affected by food.

Olepro 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 Olepro 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 Olepro 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 Olepro and placebo in the treatment of unipolar major depressive disorder.

The Olepro 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 Olepro (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 Olepro group and the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Olepro 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

Olepro 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 – 30°C) in tight, light-resistant containers.

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 Olepro 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.

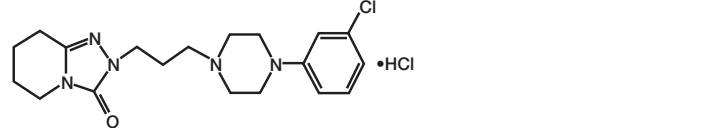
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

11 DESCRIPTION

Olepro (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: C₁₈H₂₂ClN₆O · HCl

Molecular Weight: 408.32

Olepro 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 amphetamin-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_{0-∞} = 33058 ± 8006 ng•h/mL) and Olepro 300 mg once daily (mean ± SD AUC_{0-∞} = 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 Olepro 300 mg once daily (mean ± SD C_{max,ss} = 1812 ± 621 ng/mL, C_{min,ss} = 674 ± 355 ng/mL) for one week.

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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 Olepro 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:

- Olepro 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 Olepro, since use in pregnant and nursing women is not recommended.

Important Administration Instructions:

- Olepro 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.
- Olepro should be taken at the same time every day, in the late evening preferably at bedtime, on an empty stomach.

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U.S. Patent 6,607,748
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17.2

Medication Guide Olepro™ (Oh-LEP-troe) (trazodone hydrochloride) extended-release tablets

Read the Medication Guide that comes with Olepro before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk to your healthcare provider or pharmacist if there is something you do not understand or you want to learn about Olepro.

What is the most important information I should know about Olepro?

Antidepressant medicines, depression or other serious mental illnesses, and suicidal thoughts or actions:

Talk to your healthcare provider about:

- All risks and benefits of treatment with antidepressant medicines
- All treatment choices for depression or other serious mental illnesses

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a higher risk of having suicidal thoughts or actions. These include people who have or have a family history of bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions?

- Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Call a healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Trouble sleeping (insomnia)

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Using Olepro with certain other medicines can affect each other causing serious side effects.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Olepro?

- Take Olepro exactly as your healthcare provider tells you.
- Olepro should be taken 1 time a day.
- Olepro should be taken at the same time each day in the late evening, if possible at bedtime, on an empty stomach.
- Do not stop taking Olepro without talking to your healthcare provider.
- Olepro should be swallowed whole or broken in half along the score line. Do not chew or crush Olepro. Tell your healthcare provider if you cannot swallow Olepro either whole or as a half tablet

What should I avoid while taking Olepro?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how Olepro affects you. Olepro can slow your thinking and motor skills.
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking Olepro until you talk with your healthcare provider. Olepro may make your sleepiness or dizziness worse if you take it with alcohol or other medicines that cause sleepiness or dizziness.

What are the possible side effects of Olepro?

Olepro can cause serious side effects or death. See “What is the most important information I should know about Olepro?”

Serious side effects include:

- Serotonin syndrome. Symptoms of serotonin syndrome include: agitation, hallucinations, problems with coordination, fast heartbeat, tight muscles, trouble walking, nausea, vomiting, diarrhea.
- Feeling high or in a very good mood, then becoming irritable, or having too much energy, feeling like you have to keep talking or do not sleep (Mania).
- Irregular or fast heartbeat or faint (QT prolongation).
- Low blood pressure. You feel dizzy or faint when you change positions (go from sitting to standing).
- Unusual bruising or bleeding.
- Erection lasting for more than 6 hours (Priapism).
- Low sodium in your blood (Hyponatremia). Symptoms of hyponatremia include: headache, feeling weak, feeling confused, trouble concentrating, memory problems and feeling unsteady when you walk.

Get medical help right away, if you have any of the symptoms listed above.

- New or worse irritability
- Acting aggressive, being angry or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking (mania)
- Other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

- Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

- Antidepressant medicines have other side effects.** Talk to your healthcare provider about the side effects of your medicines.

- Antidepressant medicines can interact with other medicines.** Know all of the medicines that you take. Keep a list of all medicines to show your healthcare provider. Do not start new medicines without first checking with your healthcare provider.

4. Olepro is not approved for use in children.

Talk to your healthcare provider for more information.

What is Olepro?

Olepro is a prescription medicine taken 1 time a day to treat major depressive disorder in adults.

What should I tell my healthcare provider before taking Olepro?

Before you take Olepro, tell your healthcare provider if you:

- Have heart problems, including QT prolongation or a family history of it
- Have ever had a heart attack
- Have bipolar disorder
- Have liver or kidney problems
- Have other serious medical conditions
- Are pregnant or plan to become pregnant. Olepro may harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed. It is not known if Olepro passes into your breast milk. You and your healthcare provider should decide if you will take Olepro or breastfeed.
- Have taken a Monoamine Oxidase Inhibitor (MAOI) or if you have stopped taking an MAOI in the last 2 weeks.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

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The most common side effects of Olepro include:

- Sleepiness
- Dizziness
- Constipation
- Blurry vision

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Olepro. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Olepro?

- Store Olepro between 59°F to 86°F (15°C to 30°C)
- Keep in tight container
- Keep out of the light

Keep Olepro and all medicines out of the reach of children. General information about Olepro.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Olepro for a condition for which it was not prescribed. Do not give Olepro to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Olepro. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Olepro that is written for health professionals.

For more information, go to www.olepro.com or call 1-877-345-6177.

What are the ingredients in Olepro?

Active ingredient: trazodone hydrochloride

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).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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