# PRODUCT MONOGRAPH

## PrTEVA-TRAZODONE

(Trazodone Hydrochloride)

50 mg, 100 mg and 150 mg Tablets

USP

Antidepressant

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## PHARMACOLOGICAL CLASSIFICATION

Antidepressant

## ACTION

The mechanism of action of trazodone hydrochloride, a psychoactive compound with sedative and antidepressant properties, is unclear in humans.

After oral administration, trazodone hydrochloride is well absorbed, with plasma levels peaking within one-half to two hours after ingestion. Food enhances, although delays somewhat, absorption. For the period from 3 to 10 hours after dosing, the mean plasma elimination half-life is 4.4 hours; and for the period from 10 to 34 hours after dosing, it is *7* to 8 hours. Metabolism of the drug is extensive, with 3 or 4 major metabolites having been identified in man. Approximately 60-70% of 14C-labelled trazodone appeared in the urine within 2 days, whereas only 9-29% was excreted in the feces over 60-100 hours. At concentrations attained with therapeutic doses, trazodone is 89-95% protein bound.

A comparative, randomized, two-way, crossover, bioavailability study of two 100 mg trazodone hydrochloride tablet products (Teva-Trazodone and Desyrel®) was performed in healthy adult males. The pharmacokinetic data are tabulated below:

| | Geometric Mean Arithmetic Mean (C.V.) | | |
|---|---|---|---|
| | Teva-Trazodone (1 x 100mg) | DESYREL® (1 x 100mg) | Percentage of DESYREL® |
| $AUC_T$ (ng•h/mL) | 6502<br>6990 (41) | 5884<br>6287 (39) | 111 |
| $AUC_I$ (ng•h/mL) | 6905<br>7470 ( 45) | 6374<br>6884 (44) | 108 |
| $C_{max}$ (ng/mL) | 992<br>1042 (32) | 907<br>944 (32) | 109 |
| $T_{max*}$ (h) | 1.32 (1.17) | 1.26 (0.78) | - |
| $T_{1/2*}$ | 6.95 (3.41) | 7.32 (3.76) | - |

* These are arithmetic means (standard deviation)

A two-way, single dose bioavailability study of two 150 mg trazodone hydrochloride tablet products (Teva-Trazodone and Desyrel®) conducted in normal healthy male volunteers. The pharmacokinetic data are tabulated below:

| | Geometric Mean Arithmetic Mean (C.V.) | | |
|---|---|---|---|
| | Teva-Trazodone (2/3 x 150mg) | DESYREL® (2/3 x 150mg) | Percentage of DESYREL® |
| $AUC_T$ | 10938 | 10721 | 102 |
| (ng•h/mL) | 11192 (25) | 11117 (29) | |
| $AUC_I$ | 11384 | 11159 | 102 |
| (ng•h/mL) | 11763 ( 30) | 11619 (32) | |
| $C_{max}$ | 1510 | 1556 | 97 |
| (ng/mL) | 1522 (15) | 1599 (26) | |
| $T_{max*}$ | 1.09 (0.62) | 1.91 (0.89) | - |
| (h) | | | |
| $T_{1/2*}$ | 7.83 (2.37) | 7.51 (1.95) | - |

* These are arithmetic means (standard deviation)

## INDICATIONS AND CLINICAL USE

TEVA-TRAZODONE (trazodone hydrochloride) is of value in the symptomatic relief of depressive illness.

## CONTRAINDICATIONS

TEVA-TRAZODONE (trazodone hydrochloride) is contraindicated in patients with a known hypersensitivity to trazodone.

## WARNINGS

Priapism has occurred with the use of trazodone. Surgical intervention was required in approximately 1/3 of the cases reported, and permanent impairment of erectile function or impotence resulted in a portion of these cases. Male patients should immediately discontinue the drug and consult their physician if prolonged or inappropriate erections occur. It would be advisable for the treating physician to consult a urologist or appropriate specialist if the condition persists for more than 24 hours in order to decide on a management approach.

Recent clinical studies have shown that trazodone hydrochloride may be arrhythmogenic in some patients with pre-existing cardiac disease. Isolated PVC's, ventricular couplets, and in two patients, short episodes (3-4 beats) of ventricular tachycardia are the identified arrhythmias. Several post-marketing reports of arrhythmias exist in trazodone-treated patients; in both those patients with preexisting cardiac disease and in some patients who did not have pre-existing cardiac disease. Therefore, patients with preexisting cardiac disease should be closely monitored, particularly for cardiac arrhythmias, until the results of

prospective studies are available. TEVA-TRAZODONE (trazodone hydrochloride) is not recommended for use during the initial recovery phase of myocardial infarction.

**Angle-Closure Glaucoma**
As with other antidepressants, TEVA-TRAZODONE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

## PRECAUTIONS

General: As the possibility of suicide in depressed patients remains during treatment and until significant remission occurs, patients with suicide ideation should never have access to large quantities of trazodone; therefore, the number of tablets prescribed at any one time should take this possibility into account.

In a small number of patients, episodes of grand ma1 seizures have been reported. Most of these patients were already receiving anticonvulsant therapy for a previously diagnosed seizure disorder.

Safety of Driving: TEVA-TRAZODONE (trazodone hydrochloride) may impair the mental and/or physical abilities required for performance of potentially hazardous tasks, such as operating an automobile or dangerous machinery. Therefore, the patient should be cautioned against engaging in such activities while impaired.

Interactions: The response to alcohol and the effects of barbiturates and other
CNS depressants may be enhanced by trazodone; patients should be cautioned accordingly.

Serum phenytoin and digoxin levels have been reportedly increased in patients receiving trazodone concurrently with either of these two drugs. TEVA-TRAZODONE should be discontinued for as long as clinically feasible prior to elective surgery since little is known about the interaction between trazodone and general anesthetics.

Administration of TEVA-TRAZODONE should be initiated very cautiously with gradual increase in dosage as required if an MAO inhibitor is given concomitantly or has been discontinued shortly before medication with TEVA-TRAZODONE is instituted, because it is not known whether an interaction will occur between TEVA-TRAZODONE and MAO inhibitors.

Caution is required if TEVA-TRAZODONE is given to patients receiving antihypertensive drugs, and an adjustment in the dose of antihypertensive medication may be required since trazodone may cause hypotension, including orthostatic hypotension and syncope.

Concurrent administration of electroshock therapy should be avoided because of the absence of experience.

Use in Pregnancy and Nursing Mothers: TEVA-TRAZODONE 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, because the safety and use of trazodone in pregnant women have not been established. Unless the potential benefits justify the possible risks to the child, TEVA-TRAZODONE should not be

administered to nursing mothers since trazodone and/or its metabolites have been detected in the milk of lactating animals.

Use in Children: In children below the age of 18, the safety and effectiveness of trazodone have not been established.

Laboratory Tests: In patients who develop sore throat, fever or other signs of infection or blood dyscrasia, it is recommended that white blood cell and differential counts be performed. If the white blood cell or absolute neutrophil count falls below normal, TEVA-TRAZODONE should be discontinued.

Hyperprolactinemia and Breast Tumours: Sufficient experimental evidence exists to conclude that the chronic administration of those psychotropic drugs, such as trazodone, which increase prolactin secretion has the potential to induce mammary neoplasms in rodents under appropriate conditions. It is indicated in tissue culture experiments that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer.

Disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, but the clinical significance of elevated serum prolactin levels or increased secretion and turnover are unknown for most patients. An association between the chronic administration of these drugs and mammary tumourigenesis has not been found in clinical studies or epidemiologic studies conducted to date. The available evidence is considered too limited to be conclusive at this time (see TOXICOLOGY).

## ADVERSE REACTIONS

Drowsiness, nausea/vomiting, headache and dry mouth are the most common adverse reactions encountered. Adverse reactions reported include the following:

Behavioral: drowsiness, fatigue, lethargy, retardation, lightheadedness, dizziness, difficulty in concentration, confusion, impaired memory, disorientation, excitement, agitation, anxiety, tension, nervousness, restlessness, insomnia, nightmares, anger, hostility and, rarely, hypomania, visual distortions, hallucinations, delusions and paranoia.

Neurologic: tremor, headache, ataxia, akathisia, muscle stiffness, slurred speech, retarded speech, vertigo, tinnitus, tingling of extremities, paresthesia, weakness, grand mal seizures (see PRECAUTIONS) and, rarely, impaired speech, muscle twitching, numbness, dystonia and involuntary movements.

Autonomic: dry mouth, blurred vision, diplopia, miosis, nasal congestion, constipation, sweating, urinary retention, increased urinary frequency and incontinence.

Cardiovascular: orthostatic hypotension, hypertension, tachycardia, palpitations, shortness of breath, apnea, syncope, arrhythmias, prolonged PR interval, atrial fibrillation, bradycardia, ventricular ectopic activity (including ventricular tachycardia), myocardial infarction and cardiac arrest.

Gastrointestinal: nausea, vomiting, diarrhea, gastrointestinal discomfort, anorexia and increased appetite.

Endocrine: priapism (see WARNINGS), decrease and, more rarely, increase in libido, weight gain and loss and, rarely, menstrual irregularities, retrograde ejaculation and inhibition of ejaculation.

Allergic or Toxic: skin rash, itching, edema and, rarely, hemolytic anemia, rnethemoglobinemia, liver enzyme alterations and obstructive jaundice, leukocytoblastic vasculitis, purpuric maculopapular eruptions, photosensitivity and fever.

Miscellaneous: aching joints and muscles, peculiar taste, hypersalivation, chest pain, hematuria, red, tired and itchy eyes.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

TEVA-TRAZODONE (trazodone hydrochloride) overdosage may cause an increase in the incidence or severity of any of the reported adverse reactions, e.g., hypotension and excessive sedation. In one known suicide attempt, symptoms of drowsiness and weakness were apparent 3 hours after the ingestion of 7.5 grams (12.5 times the maximum daily dose) of trazodone hydrochloride. This patient recovered uneventfully. To date, there have been no reports of death by deliberate or accidental overdosage with trazodone alone.

As no specific antidote for trazodone hydrochloride exists, management of overdosage should be symptomatic and supportive.

A patient should be admitted to the hospital as soon as possible and the stomach emptied by gastric lavage if ingestion of an overdosage is suspected. In facilitating elimination of the drug, forced diuresis may be useful.

## DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually. The clinical response and any evidence of intolerability should be carefully noted. It should be kept in mind that there may be a lag in therapeutic response and that increasing the dosage rapidly does not normally shorten this latent period but may increase the incidence of side effects.

Usual Adult Dosage: The recommended initial dose is 150-200 mg a day, in two or three divided doses. In order to reduce the incidence of adverse reactions, TEVA-TRAZODONE (trazodone hydrochloride) should be taken shortly after a meal or light snack. The initial dose may be increased by increments of 50 mg, usually up to 300 mg daily in divided doses, according to tolerance and response. Doses up to 400 mg daily and, rarely, up to 600 mg daily in hospitalized patients may be required in some patients. The administration of a major portion of the daily dose at bedtime or a reduction of dosage may be required in the event that drowsiness occurs.

The dosage may be gradually reduced once an adequate response has been\ achieved, with adjustment depending on therapeutic response. The dosage should be kept at the lowest effective level during prolonged maintenance therapy.

Use in the Elderly: Doses not exceeding half of the recommended adult dosage should be used in the elderly, with adjustments made depending on tolerance and response.

TEVA-TRAZODONE is not recommended for use in the pediatric age group because safety and effectiveness in children have not been established.

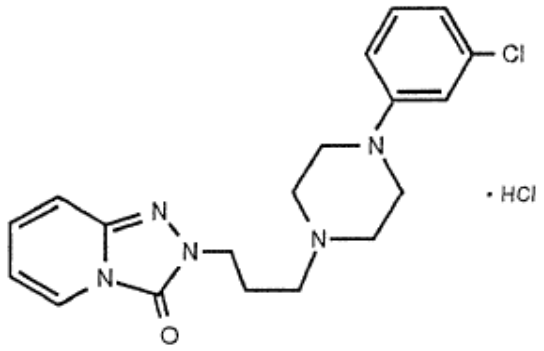
## PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Trazodone Hydrochloride

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

Structural Formula:




Molecular Formula: $C_{19}H_{22}ClN_5O$•HCl Molecular Weight: 408.33

Description: White to off-white crystalline powder. Soluble in chloroform and sparingly soluble in water. Melts between 231º and 234º when the melting point determination is carried out in an evacuated capillary tube; otherwise melts with decomposition over a broad range below 230º.

STABILITY AND STORAGE RECOMMENDATIONS: Store between 15 - 30°C and protect from light. Unit dose strips should be stored between 15 - 25°C and protected from light and high humidity.

AVAILABILITY

TEVA-TRAZODONE (trazodone hydrochloride) Tablets 50 mg are light orange, round, single-scored, standard convex, film coated tablets, engraved with **'50'** above scoreline on one side and **'novo'** on the other side. Available in bottles of 100, 500 and 1000 and unit dose strips of 100.

TEVA-TRAZODONE (trazodone hydrochloride) Tablets 100 mg are white, round, single-scored, standard convex, film coated tablets, engraved with **'100'** above scoreline on one side and **'novo'** on the other side. Available in bottles of 100, 500 and 1000 and unit dose strips of 100.

TEVA-TRAZODONE (trazodone hydrochloride) Tablets 150 mg are light orange coloured, rectangular-shaped, compressed tablets, engraved **'novo'** on one side and trisected with **50|50|50** including partial bisect on the other side of each trisect. Available in bottles of 100, 500 and 1000.

## PHARMACOLOGY

Trazodone differs significantly from other known psychopharmacological agents in pharmacological profile.

Trazodone impedes the uptake of serotonin by the membrane. The depletion of brain serotonin by fenfluramine is impeded with small doses of the drug, but doses of 50 mg/kg do not affect the concentration of serotonin in the rat brain. Trazodone is a weak inhibitor of noradrenaline re-uptake in experimental studies but is practically inactive against I-dopa, histamine and acetylcholine. It is not known to inhibit monoamine oxidase.

Trazodone exhibits CNS depressant activities, with motor activity being decreased in cats, rats and mice, and hexobarbital-induced sleeping time being increased in mice. At doses which do not influence the unconditioned response ($ED_{50}$ = 19.5 mg/kg p.o.), trazodone also inhibits conditioned avoidance responding in rats. Trazodone has very weak muscle relaxant activity, but has no anticonvulsant, anti-reserpine or cataleptogenic effects.

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

The infusion of trazodone in rats produces first a fall in mean blood pressure, followed by ECG changes only as a consequence of the hypotension produced. There was no effect on His bundle conduction nor evidence of heart block or rhythm disturbance other than the slowing of normal sinus rhythm when anesthetized dogs were administered graded doses of trazodone between 1 and 30 mg/kg i.v. Doses of 0.5 to 5 mg/kg imipramine, however, slowed impulse conduction as well as atrial transmission. Similar doses of trazodone and imipramine had comparable effects on the sleep-wakefulness cycle in rats; REM sleep was reduced with 10 mg/kg p.o. and completely suppressed with 160 mg/kg.

# TOXICOLOGY

Acute Toxicity:

| | LD50 in mg/kg (95% Confidence Limits) | | | |
|---|---|---|---|---|
| Route | Species | | | |
| | 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, prostation and clonic convulsions.

Subacute and Chronic Toxicity:
Several subacute studies were conducted in rats using doses ranging from 100 to 450 mg/kg/day p.o. for one to four months. The main toxic effects observed were decreased body weight gain and slight liver enlargement in males. There were some deaths at the highest dose. Tremors, vomiting and clonic convulsions were produced in dogs given 50 and 100 mg/kg/day p.o. for one month.

Of two dogs receiving 100 mg/kg, one died after 3 weeks. Administration of approximately 250 mg/kg/day in the diet of rats for 6 months resulted in significantly greater liver weights than in control rats and slightly lower weight gain in males. No toxic effects were evident in dogs receiving 5 and 25 mg/kg/day for 6 months.

Rats were given doses of 0, 30, 100 and 300 mg/kg/day p.o. for 18 months. All treated groups demonstrated decreased body weight gain, and males in the highest dose group showed significantly reduced food intake. Rats at the 100 mg/kg dose exhibited some lethargy and salivation immediately following dosing, but at the lowest dose level, no behavioral or pathologic effects were observed. There was excessive salivation and the animals became inactive, assuming a prone position for approximately 3 hours after dosing with the highest dose. There were occasional body tremors also. Within 30 weeks, tolerance developed to all these reactions.

Oral doses of 0, 10, 20 and 40 mg/kg/day were given to beagle for one year. Following the death of 3/10 animals in the highest dose group, the dose was reduced to 30 mg/kg/day after 8 weeks. There were no abnormal signs at the 10 mg/kg level. One animal in the 20 mg/kg group was found prostate and panting on one occasion and another was unexpectantly found dead near the end of the study. Occasional transient

ataxia, excessive salivation and convulsions were produced with 40 mg/kg. Upon reducing the dosage to 30 mg/kg following the three deaths, a fourth death occurred 16 weeks later, subsequent to convulsions. During the final *6* months of the study, a fifth animal became hypersensitive to touch and aggressive. Apart from one case of transient anemia in the 20 mg/kg group and slightly elevated SGPT values in 2 of the high dose dogs during the final 3 months, hematological and biochemical analyses were normal.

Trazodone was administered in doses of 0, 20, 40 and 80 mg/kg/day by gavage for one year to groups of 6 rhesus monkeys. A slight, dose-related decrease in activity and tremors in 3 high dose monkeys were the only effects noted. Both these effects decreased during the study.

Reproductive Studies:
Fertility and general reproductive performance of male and female rats were unaffected by doses of up to 250 mg/kg/day. The birth weight of pups was significantly reduced at 300 mg/kg. Two rat studies were conducted: one in which rats were given 100 and 210 mg/kg/day p.o. during days 10-15 and 6-15 of gestation, respectively; and another in which doses of 150-450 mg/kg/day p.o. were given during days 9-14 of gestation. Only a sedative effect on dams was noted at 100 mg/kg. Increased sedation, decreased maternal and fetal weights and retarded ossification were produced at doses of 150 mg/kg and higher. A significant increase in resorptions and stillborn fetuses, in addition to retarded fetal growth, occurred with 300 and 450 mg/kg. Isolated cases of branched rib, separated thoracic arch, umbilical hernia and exencephalia were also noted.

The only peri- and postnatal effects of up to 300 mg/kg/day of trazodone in rats were reduced birth and weaning weights of offspring in the highest dosage group.

Carcinogenicity Studies:
Rats were used to conduct a two year carcinogenicity study at doses of 0, 40 and 80 mg/kg/day. In both treatment groups, larger numbers of female rats died sooner than controls; most deaths were related to the presence of pituitary tumours. In both treatment groups at 12, 13 and 14 months, the incidence of palpable masses (mammary tumours, cysts, etc.) was increased also. These observations may be related to trazodone's effects on prolactin secretion. (Acute administration caused an increase in prolactin blood levels whereas chronic administration did not. Turnover, however, was not studied. When a neuroleptic was used as a positive control, similar results were produced.) The relative incidences of male rats with pituitary tumours were reversed. These results may have been influenced by the early deaths due to nephritis and other causes, however.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**
**PATIENT MEDICATION INFORMATION**

# [Pr]TEVA-TRAZODONE
## trazodone hydrochloride tablets

Read this carefully before you start taking **TEVA-TRAZODONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-TRAZODONE**.

### What is TEVA-TRAZODONE used for?
TEVA-TRAZODONE has been prescribed for you by your healthcare professional to relieve your symptoms of depression which may include:

- feeling sad;
- loss of interest in usual activities;
- significant change in weight or appetite;
- change in sleeping habits;
- having a hard time concentrating;
- feeling tired;
- having suicidal thoughts.

### How does TEVA-TRAZODONE work?
TEVA-TRAZODONE is an antidepressant medication. It is thought to work by increasing the activity of serotonin in your brain. Serotonin is a brain chemical that helps to improve mood. It works at two different receptors in the brain.

### What are the ingredients in TEVA-TRAZODONE?
**Medicinal ingredients**: trazodone hydrochloride
**Non-medicinal ingredients**: Colloidal silicon dioxide (50 mg, 100 mg only), croscarmellose sodium (150 mg only), FD&C Yellow #6 Lake (50 mg, 150 mg only), lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry Clear YS-3-7413 (50 mg, 100 mg only), sodium starch glycolate (50 mg, 100 mg only) and starch.

### TEVA-TRAZODONE comes in the following dosage forms:
Tablets: 50 mg, 100 mg and 150 mg

### Do not use TEVA-TRAZODONE if you:

- are allergic to any of the ingredients in TEVA-TRAZODONE.
- take a Monoamine Oxidase Inhibitor (MAOI).
  - Ask your healthcare professional or pharmacist if you are not sure if you take a MAOI.
  - Examples of MAOIs include linezolid which is an antibiotic, methylene blue which is a dye used in certain surgeries.
  - If you stopped taking a MAOI within the last 14 days, only start TEVA-TRAZODONE if your healthcare professional tells you to.
  - Do not take a MAOI within 14 days of stopping TEVA-TRAZODONE unless directed to do so by your healthcare professional.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-TRAZODONE. Talk about any health conditions or problems you may have, including if you:**

- are taking or have recently taken a monoamine oxidase inhibitor (MAOI).
- have a history or a family history of heart problems, including: heart disease, heart attack, QT prolongation, and irregular heartbeats.
- have high blood pressure that is not controlled by your medication or any heart problems.
- have a history of drug abuse.
- have a bleeding disorder.
- take certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g., warfarin, dabigatran), acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (e.g., ibuprofen).
- have or had seizures or convulsions.
- take other medications that may increase your chance of a seizure, including drugs for depression and some antibiotics.
- have glaucoma or increased pressure in your eyes.
- have suicidal thoughts.
- have a family history of mania or bipolar disorder.
- have or have had an eating disorder, for example binge eating (bulimia) or anorexia nervosa.
- have liver problems.
- have kidney problems.
- have previous detected breast cancer.
- are pregnant or plan to become pregnant. It is not known if TEVA-TRAZODONE will harm your unborn baby. Talk to your healthcare professional about the benefits and risks of treating depression during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if TEVA-TRAZODONE passes into breast milk. You and your healthcare professional should decide if you should take TEVA-TRAZODONE while breastfeeding.
- have any other medical conditions.

**TEVA-TRAZODONE is not for use in children under 18 years of age.**

**Other warnings you should know about:**
It is important to talk to your healthcare professional about the risks of treating depression and also the risk of not treating it. You should discuss all treatment options with your healthcare professional.

**New or worsened emotional or behaviour problems:**
Treatment with these types of medications is most safe and effective when you and your healthcare professional have good communication about how you are feeling. You may find it helpful to tell a relative or close friend that you are depressed. You might ask them to tell you if they think you are getting worse or if they are worried about changes in your behavior.

Some patients may feel worse instead of better when they first start taking drugs like TEVA-TRAZODONE or when changing the dose. You may have:

- new or worsened feelings of nervousness, tension, anger, agitation, or aggression.
- thoughts about suicide, hurting yourself or other people. Thoughts and actions about suicide can occur especially if you have had thoughts of hurting yourself in the past. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. **If this happens, seek immediate medical help.** Do NOT stop taking TEVA-TRAZODONE on your own.

**Effects on pregnancy and newborns:**
If you are pregnant or are planning to become pregnant while taking TEVA-TRAZODONE, talk to your healthcare professional about the risks and benefits of various treatment options. It is very important that you keep taking TEVA-TRAZODONE until your healthcare professional tells you to stop.

When pregnant women took drugs in the same group of medications as TEVA-TRAZODONE, some newborn babies had complications at birth. This happened especially when the medication was taken in the last three months of pregnancy. Some newborns:
- Required breathing support, tube feeding and a longer stay in the hospital.
- Had difficulty feeding or breathing, seizures, tense or overly relaxed muscles and were jittery and cried constantly.
- Had a serious condition called persistent pulmonary hypertension. This made the babies breathe faster and appear blue in color.

These symptoms normally go away over time. However, if your baby experiences any of these symptoms, consult your healthcare professional as soon as possible.

**Angle-closure Glaucoma**
TEVA-TRAZODONE can cause an acute attack of glaucoma. Get immediate medical help if you experience eye pain, changes in vision or swelling or redness in or around the eye.

**Risk of breaking a bone**
You should tell your healthcare professional if you:
- are elderly and had a recent bone fracture, or
- were told you have osteoporosis or risk factors for osteoporosis.

Taking TEVA-TRAZODONE may increase your risk of breaking a bone if you are elderly or have osteoporosis or have other major risk factors for breaking a bone. This is especially true when you first start taking TEVA-TRAZODONE and soon after you stop taking it. Take extra care to avoid falling, especially if you get dizzy or have low blood pressure.

**Effect on the hormones**
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 healthcare professional if you experience any of these symptoms.

**Discontinuation symptoms:**
If your healthcare professional recommends that you stop taking TEVA-TRAZODONE, they will gradually lower the dose of TEVA-TRAZODONE you are taking. This may help manage any symptoms of discontinuation, such as:

- dizziness, headache, ringing in the ears, seizures;
- nausea, diarrhea, vomiting;
- tingling, burning, or prickling sensation of your skin, excessive sweating;
- feeling nervous, confused, irritated, restless, or having an unstable mood;
- fatigue, insomnia (inability to sleep), nightmares.

These symptoms will usually disappear without needing treatment. Tell your healthcare professional immediately if you have these or any other symptoms. Your healthcare professional may adjust the dosage of TEVA-TRAZODONE to alleviate the symptoms.

**Driving and Using Machines:**
TEVA-TRAZODONE can make you feel sleepy or may affect your ability to think clearly, make decisions or react quickly. Wait until you know how you feel after you have taken TEVA-TRAZODONE before you drive or use heavy machines.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines, especially:**
- other antidepressants;
- other drugs that affect serotonin such as lithium, linezolid, sibutramine, tryptophan, triptans, St. John's Wort;
- drugs used to treat schizophrenia (e.g. olanzapine, risperidone);
- medicines used to treat anxiety, such as clonazepam, alprazolam, lorazepam, diazepam or phenobarbital;
- certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g., warfarin, dabigatran), acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (e.g., ibuprofen);
- certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine;
- certain medicines used to treat cough, such as dextromethorphan;
- when taking certain medicines such as antifungals (e.g. ketoconazole); antibiotics (e.g. erythromycin) or medicines used to treat seizures (carbamazepine). Your healthcare professional may adjust your dose of TEVA-TRAZODONE when taking these medicines.
- mephenytoin;
- diuretics

You should avoid drinking alcohol while taking TEVA-TRAZODONE.

**How to take TEVA-TRAZODONE:**
It is important to take TEVA-TRAZODONE exactly as your healthcare professional has told you. Your healthcare professional may need to change the dose until it is right for you.
- Take your TEVA-TRAZODONE tablet at the same time each day. If you have any problems with your dosing routine, contact your doctor or pharmacist.
- TEVA-TRAZODONE should be taken shortly after a meal or light snack.

- Take only the recommended dose prescribed by your healthcare professional. Never increase the dose of TEVA-TRAZODONE you or those in your care are taking, unless your healthcare professional tells you to.
- The effects of your medication may not be noticeable in the first few days of treatment, and significant improvement may take several weeks. If you are concerned that your medicine is not working, discuss this with your healthcare professional.
- Even if you feel better, do not stop taking TEVA-TRAZODONE without talking to your healthcare professional.

**Usual dose:**
- The usual adult starting dose is 150 – 200 mg daily, in two or three divided doses.
- Your healthcare professional may increase your dose gradually by 50 mg each time up to 300 mg a day, in divided doses.

**Elderly (65 years of age or older):**
- The dose in elderly patients will be less than half the usual adult dose.

**Remember: The medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.**

**Overdose:**

If you think you have taken too much TEVA-TRAZODONE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed dose:**
If you miss a dose of TEVA-TRAZODONE, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of TEVA-TRAZODONE at the same time.

**What are possible side effects from using TEVA-TRAZODONE?**
These are not all the possible side effects you may feel when taking TEVA-TRAZODONE. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects in people who take TEVA-TRAZODONE include:
- headache
- dry mouth
- nausea/vomiting
- dizziness
- drowsiness, fatigue, weakness
- blurred vision

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Get immediate medical help |
| | Only if severe | In all cases | |
| **UNCOMMON**<br>**Mania/Hypomania**: elevated or irritated mood, decreased need for sleep, racing thoughts | | ✓ | |
| **Seizures:** loss of consciousness with uncontrollable shaking | | | ✓ |
| **RARE**<br>**Serotonin syndrome:** a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat | | | ✓ |
| **Glaucoma:** increased pressure in the eyes, eye pain and blurred vision | | ✓ | |
| **Low sodium level in blood:** tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles | | ✓ | |
| **Priapism:** painful, longer than normal erection of the penis | | | ✓ |
| **Bleeding in the gut:** vomiting blood or passing blood in stool | | | ✓ |
| **UNKNOWN**<br>**Allergic reaction:** red skin, hives, itching, swelling of the lips, face, tongue or throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes | | | ✓ |
| **Low platelets**: bruising or unusual bleeding from the skin or other areas | | ✓ | |
| **New or worsened emotional or behavioural problems:** feeling angry, aggressive, worried, agitated, hostile or impulsive. Feeling violent or suicidal. Thoughts of hurting yourself or other people. Feeling like you are | | | ✓ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Get immediate medical help |
| | Only if severe | In all cases | |
| not yourself or that you are less inhibited. | | | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report**:

- Online at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**
Store TEVA-TRAZODONE at room temperature (15-30°C) and protect from light. Unit dose strips should be stored between 15-25C and protected from light and high humidity.
Keep out of reach and sight of children.

**If you want more information about TEVA-TRAZODONE:**

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://www.hc-sc.gc.ca/); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 1255005 (English), 1-877-777-9117 (French); or email druginfo@tevacanada.com.

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