

1. NAME OF THE MEDICINAL PRODUCT

Trazodone 50mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsule containing 50mg of Trazodone Hydrochloride.

For excipients see 6.1

3. PHARMACEUTICAL FORM

Capsule, hard

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Relief of symptoms in all types of depression including depression accompanied by anxiety.

4.2. Posology and method of administration

Route of administration: Oral.

Adults:

Starting dose 150mg/day in divided doses. This may be increased to 300mg/day in a single dose or divided doses.

Elderly or Frail:

Starting dose 100mg/day in divided doses or as a single dose. This may be increased, under supervision, according to efficacy and tolerance. Doses above 300mg/day are unlikely to be required.

Children:

There are insufficient data to recommend the use of trazodone in children.

Trazodone controlled release capsules should be swallowed whole and not chewed. Tolerability may be improved by taking trazodone after food.

4.3 Contraindications

- Known hypersensitivity to trazodone and to any of the excipients.
- Alcohol intoxication and intoxication with hypnotics.
- Acute myocardial infarction.

4.4 Special warning and precautions for use

Trazodone should be administered with caution in patients of thyroid disease, psychosis/mania, the elderly, close angle glaucoma, anaesthesia, porphyria and urinary retention.

Suicide/suicidal thoughts or clinical worsening:

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

Other psychiatric conditions for which Trazodone is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Care should be exercised when administering trazodone to patients suffering epilepsy, avoiding in particular, abrupt increases or decreases in dosage.

Trazodone should be administered with care in patients with severe hepatic, renal or cardiac disease.

Potent CYP3A4 inhibitors may lead to increases in trazodone serum levels. See section 4.5 for further information.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

General: The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, and antihistaminic drugs may be intensified; dosage reduction is recommended in such instances.

The metabolism of antidepressants is accelerated due to hepatic effects by oral contraceptives, phenytoin, carbamazepine and barbiturates. The metabolism of antidepressants is inhibited by cimetidine and some other antipsychotics.

In vitro drug metabolism studies suggest that there is a potential for drug interactions when Trazodone is given with potent CYP3A4 inhibitors such as erythromycin, ketoconazole, itraconazole, ritonavir, indinavir, and nefazodone. It is likely that potent CYP3A4 inhibitors may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. Exposure to ritonavir during initiation or resumption of treatment in patients receiving Trazodone will increase the potential for excessive sedation, cardiovascular, and gastrointestinal effects. It has been confirmed in in- vivo-studies in healthy volunteers, that a ritonavir dose of 200 mg BID increased the plasma levels of Trazodone by greater than two-fold, leading to nausea, syncope and hypotension. If Trazodone is used with a potent CYP3A4 inhibitor, a lower dose of Trazodone should be considered. However, the co-administration of Trazodone and potent CYP3A4 inhibitors should be avoided where possible.

Carbamazepine reduced plasma concentrations of trazodone when coadministered. Concomitant use of carbamazepine 400 mg daily led to a decrease of plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine of 76 % and 60 %, respectively. Patients should be closely monitored to see if there is a need for an increased dose of Trazodone when taken with carbamazepine.

Trazodone may enhance the effects of muscle relaxants and volatile anaesthetics, and caution should be exercised in such instances. Similar considerations apply to combined administration with sedative and anti-depressant drugs, including alcohol. Trazodone intensifies the sedative effects of alcohol. Alcohol should be avoided during Trazodone therapy.

Trazodone has been well tolerated in depressed schizophrenic patients receiving standard phenothiazine therapy and also in depressed parkinsonian patients receiving therapy with levodopa. Antidepressants can accelerate the metabolism of levodopa.

Tricyclic antidepressants: Concurrent administration should be avoided due to the risk of interaction. Serotonin syndrome and cardiovascular side effects should be bewareed.

Fluoxetine: Rare cases have been reported of elevated Trazodone plasma levels and adverse effects when Trazodone had been combined with fluoxetine, a CYP1A2/2D6 inhibitor. The mechanism underlying a pharmacokinetic interaction is not fully understood. A pharmacodynamic interaction (serotonin syndrome) could not be excluded.

Possible interactions with monoamine oxidase inhibitors have occasionally been reported. Although some clinicians do give both concurrently, use of Trazodone with MAOIs, or within two weeks of stopping treatment with these compounds is not recommended. The giving of MAOIs within one week of stopping Trazodone is also not recommended.

Phenothiazines: Severe orthostatic hypotension has been observed in case of concomitant use of phenothiazines, like e.g. chlorpromazine, fluphenazine, levomepromazine, perphenazine.

Other

Concomitant use of Trazodone with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Caution should be used when these drugs are coadministered with Trazodone.

Since Trazodone is only a very weak inhibitor of noradrenaline re-uptake and does not modify the blood pressure response to tyramine, interference with the hypotensive action of guanethidine-like compounds is unlikely. However, studies in laboratory animals suggest that Trazodone may inhibit most of the acute actions of clonidine. In the case of other types of antihypertensive drug, although no clinical interactions have been reported, the possibility of potentiation should be considered.

Undesirable effects may be more frequent when Trazodone is administered together with preparations containing *Hypericum perforatum* (St Johns wort).

There have been reports of changes in prothrombin time in patients concomitantly receiving trazodone and warfarin.

Concurrent use with trazodone may result in elevated serum levels of digoxin or phenytoin. Monitoring of serum levels should be considered in these patients.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Data on a limited number (< 200) of exposed pregnancies indicate no adverse effects of Trazodone on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. The safety of Trazodone in human pregnancy has not been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development at therapeutic doses. On basic principles, therefore, its use during the first trimester should be avoided.

Caution should be exercised when prescribing to pregnant women. When Trazodone is used until delivery, newborns should be monitored for the occurrence of withdrawal symptoms.

Lactation:

Limited data indicate that excretion of Trazodone in human breast milk is low, but levels of the active metabolite are not known. Due to the paucity of data, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trazodone should be made taking into account the benefit of breast-feeding to the child and the benefit of Trazodone therapy to the woman.

4.7. Effects on ability to drive and use machines

As with all other drugs acting on the central nervous system, patients should be warned against the risk of handling machinery and driving.

4.8. Undesirable effects

Trazodone is a sedative antidepressant and drowsiness, sometimes experienced during the first days of treatment, usually disappears on continued therapy.

Anticholinergic-like symptoms do occur but the incidence is similar to placebo.

The following symptoms, most of which are commonly reported in cases of untreated depression, have also been recorded in small numbers of patients receiving trazodone therapy: dizziness, headache, nausea and vomiting, weakness, decreased alertness, weight loss, tremor, dry mouth, bradycardia, tachycardia, postural hypotension, oedema, constipation, diarrhoea, blurred vision, restlessness, confusional states, insomnia and skin rash.

Blood dyscrasias, including agranulocytosis, thrombocytopenia and anaemia, have been reported on rare occasions. Adverse effects on hepatic function, including jaundice and hepatocellular damage, sometimes severe, have been rarely reported. Should such effects occur, trazodone should be discontinued immediately.

As with other drugs with alpha-adrenolytic activity, trazodone has very rarely been associated with priapism. This may be treated with an intracavernosum injection of an alpha-adrenergic agent such as adrenaline or metaraminol. However there are reports of trazodone-induced priapism which have required surgical intervention or led to permanent sexual dysfunction. Patients developing this suspected adverse reaction should cease trazodone immediately.

Cases of suicidal ideation and suicidal behaviors have been reported during trazodone therapy or early after treatment discontinuation (see section 4.4).

Studies in animals have shown that trazodone is less cardiotoxic than the tricyclic antidepressants, and clinical studies suggest that the drug may be less likely to cause cardiac arrhythmias in man. Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population.

Arrhythmias identified include isolated premature ventricular contractions, ventricular couplets, and short episodes (3-4 beats) of ventricular tachycardia.

Trazodone has had no effect on arterial blood pCO₂ or pO₂ levels in patients with severe respiratory insufficiency due to chronic bronchial or pulmonary disease.

There have been occasional reports of serotonin syndrome and convulsions associated with the use of Trazodone, especially when associated with other psychotropic drugs. Neuroleptic malignant syndrome may, very rarely, arise in the course of treatment with Trazodone.

Hyponatraemia has been reported in association with treatment with this product. Fluid and electrolyte status should be monitored in symptomatic patients.

4.9 Overdose

FEATURES OF TOXICITY:

The most frequently reported reactions to overdose have included drowsiness, dizziness, nausea and vomiting.

In more serious cases coma, tachycardia, hypotension, hyponatraemia, convulsions and respiratory failure have been reported. Cardiac features may include bradycardia, QT prolongation and torsade de pointes. Symptoms may appear 24 hours or more after overdose.

Overdoses of Trazodone in combination with other antidepressants may cause serotonin syndrome.

MANAGEMENT:

There is no specific antidote to trazodone. Activated charcoal should be considered in adults who have ingested more than 1 g trazodone, or in children who have ingested more than 150 mg trazodone within 1 hour of presentation. Alternatively, in adults, gastric lavage may be considered within 1 hour of ingestion of a potentially life threatening overdose.

Observe for at least 6 hours after ingestion (or 12 hours if a sustained release preparation has been taken). Monitor BP, pulse and GCS. Monitor oxygen saturation if GCS is reduced. Cardiac monitoring is appropriate in symptomatic patients.

Single brief convulsions do not require treatment. Control frequent or prolonged convulsions with intravenous diazepam (0.1-0.3 mg/kg body weight) or lorazepam (4 mg in an adult and 0.05 mg/kg in a child). If these measures do not control the fits, an intravenous infusion of phenytoin may be useful. Give oxygen and correct acid base and metabolic disturbances as required.

Treatment should be symptomatic and supportive in the case of hypotension and excessive sedation. If severe hypotension persists consider use of inotropes, e.g. dopamine or dobutamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N06A X05. Other antidepressants.

Trazodone is a potent antidepressant. It also has anxiety reducing activity. Trazodone is a triazolopyridine derivative chemically unrelated to known tricyclic, tetracyclic and other antidepressant agents. It has negligible effect on noradrenaline re-uptake mechanisms. Whilst the mode of action of trazodone is not known precisely, its antidepressant activity may concern noradrenergic potentiation by mechanisms other than uptake blockade. A central antiserotonin effect may account for the drug's anxiety reducing properties.

5.2. Pharmacokinetic properties

Trazodone is rapidly absorbed from the gastro-intestinal tract and extensively metabolised. Paths of metabolism of Trazodone include n-oxidation and hydroxylation. The metabolic m-chlorophenylpiperazine is active. Trazodone is excreted in the urine almost entirely in the form of its metabolites, either in free or in conjugated form. The elimination of Trazodone is biphasic, with a terminal elimination half-life of 5 to 13 hours. Trazodone is excreted in breast milk.

There was an approximate two-fold increase in terminal phase half-life and significantly higher plasma concentrations of Trazodone in 10 subjects aged 65 to 74 years compared with 12 subjects aged 23 to 30 years following a 100mg dose of Trazodone. It was suggested that there is an age-related reduction in the hepatic metabolism of Trazodone.

In vitro studies in human liver microsomes show that trazodone is metabolised by cytochrome P4503A4 (CYP3A4) to form m-chlorophenylpiperazine. Whilst significant, the role of this pathway in the total clearance of trazodone in vivo has not been fully determined.

5.3. Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate
Colloidal silica anhydrous
Magnesium Stearate

Capsule shell- Body composition

Titanium dioxide (E171)
Indigo Carmine (E132)
Yellow iron Oxide (E172)
Gelatin

Cap composition

Erythrosine (E 127)
Patent Blue V (E 131)
Titanium dioxide (E 171)
Gelatin

6.2. Incompatibilities

None stated.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Do not store above 25°C. Keep in the original packaging.

6.5. Nature and contents of container

Blister packs (PVC coated blisters backed by aluminium foil) available in pack sizes of 28, 56, 84 & 112 capsules.

6.6. Instructions for use and handling (, and disposal)

None.

7. MARKETING AUTHORISATION HOLDER

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30/01/2012