SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trazodone hydrochloride 50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg trazodone hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Trazodone hydrochloride 50 mg: White to off white, round, biconvex, uncoated tablets 7.14 mm in diameter, engraved ‘IT’ bisect ‘I’ on one side and plain on the other side.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trazodone hydrochloride tablet is indicated for major depressive episodes.

4.2 Posology and method of administration

Posology

a) Adults:

Initially 150mg/day in divided doses after food or as a single dose on retiring.

The dose will be increased every 3 to 4 days by 50 mg a day (preferably upon retiring) until an optimal therapeutic effect is achieved. This may be increased up to a dose of 300 mg a day, administered in divided doses after food, or as a single dose upon retiring. In administering divided doses the major part of the divided dose should be taken upon retiring.

In hospitalised patients, the maximum daily dose may be incrementally increased to a maximum of 600 mg per day, administered as divided doses.

After reaching an effective dose, clinical response is usually evident within two to four weeks. In the case of non – responders the dosage may be increased to the maximum recommended. If, following this, there is no response after two to four weeks, therapy should be discontinued.

Patients should be maintained on the lowest effective dose and be periodically reassessed to determine the continued need for maintenance treatment. In general, it is preferable to continue therapy with an antidepressant until the patient has been symptomless for four to six months.

In order to avoid withdrawal symptoms abrupt discontinuation of treatment should be avoided. At the end of treatment, the dose should be gradually decreased.

b) Elderly:

For elderly or frail patients the recommended initial starting dose is reduced to 100mg/day given in divided doses or as a single night-time dose (see section 4.4). This may be incrementally increased, under supervision, according to efficacy and tolerance. In general, single doses above 100 mg should be avoided in these patients. It is unlikely that 300mg/day will be exceeded.

Paediatric population:

The safety and efficacy of Trazodone hydrochloride tablet in children below the age of 18 years has not yet been established therefore Trazodone hydrochloride tablet is not recommended for use in this age group.

Hepatic Impairment:

Trazodone hydrochloride tablet undergoes extensive hepatic metabolism (see section 5.2) and has also been associated with hepatotoxicity (see sections 4.4 and 4.8). Therefore caution should be exercised when prescribing for patients with hepatic impairment, particularly in cases of severe hepatic impairment. Periodic monitoring of liver function may be considered.

Renal Impairment:

No dosage adjustment is usually necessary, but caution should be exercised when prescribing for patients with severe renal impairment (see also section 4.4 and 5.2).

Method of administration

For oral use.

A decrease of the side-effects (increase of the resorption and decrease of the peak plasma concentration) can be reached by taking Trazodone hydrochloride tablets after a meal.

Trazodone hydrochloride tablets should be taken together with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substanceor to any of the excipients listed in section 6.1.

- Alcohol intoxication and intoxication with hypnotics.
- Acute myocardial infarction.

4.4 Special warnings and precautions for use

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 behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

To minimise the potential risk of suicide attempts, particularly at therapy initiation, only restricted quantities of Trazodone hydrochloride tablets should be prescribed at each occasion.

It is recommended that careful dosing and regular monitoring is adopted in patients with the following conditions:

- Epilepsy, specifically abrupt increases or decreases of dosage should be avoided
- Patients with hepatic or renal impairment, particularly if severe
- Patients with cardiac and vascular disease, such as cardiovascular insufficiency, angina pectoris, conduction disorders or AV blocks of different degree, arrhythmias, recent myocardial infarction, congenital long QT syndrome or bradycardia.
- Hyperthyroidism
- Micturition disorders, such as prostate hypertrophy, although problems would not be anticipated as the anticholinergic effect of Trazodone hydrochloride tablet is only minor
- Acute narrow angle glaucoma, raised intra-ocular pressure, although major changes would not be anticipated due to the minor anticholinergic effect of Trazodone hydrochloride tablet.

Patients with hypokalaemia or hypomagnesemia. These electrolyte-disturbances increase the risk for malignant arrhythmias and should be corrected before treatment with trazodone is started

Hepatic impairment

Severe hepatic disorders with potential fatal outcome have been reported with trazodone use (see section 4.8). Patients should be instructed to report immediately signs such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately, and withdrawal of Trazodone hydrochloride tablet therapy be considered. Should jaundice occur in a patient, Trazodone hydrochloride tablet therapy must be withdrawn.

Administration of antidepressants in patients with schizophrenia or other psychotic disorders may result in a possible worsening of psychotic symptoms. Paranoid thoughts may be intensified. During therapy with Trazodone hydrochloride tablet a depressive phase can change from a manic – depressive psychosis into a manic phase. In that case Trazodone hydrochloride tablet must be stopped.

Should jaundice occur in a patient, Trazodone hydrochloride tablets therapy must be withdrawn.

Serotonin syndrome

Interactions in terms of serotonin syndrome (a potentially life-threatening condition)/ neuroleptic malignant syndrome have been described in case of concomitant use of other serotonergically acting substances like other antidepressants (e.g. tricyclic antidepressants, SSRI's, SNRI's, tryptophan and MAO-inhibitors), triptans and neuroleptics. Neuroleptic malignant syndromes with fatal outcome have been reported in cases of co-administration with neuroleptics, for which this syndrome is a known possible adverse drug reaction (see sections 4.5 and 4.8). Treatment with trazodone must be stopped immediately and supportive symptomatic treatment should be initiated.

Concomitant administration of Trazodone hydrochloride tablets and **buprenorphine may result in serotonin syndrome, (see section 4.5).**

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Agranulocytosis

Since agranulocytosis may clinically reveal itself with influenza-like symptoms, sore throat, and fever, in these cases it is recommended to check haematology.

Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving Trazodone hydrochloride tablets. Concomitant administration of antihypertensive therapy with Trazodone hydrochloride tablets may require a reduction in the dose of the antihypertensive drug

Elderly

Elderly patients may more often experience orthostatic hypotension, somnolence, and other anticholinergic effects of trazodone. Careful consideration should be given to the potential for additive effects with concomitant medication use such as with other psychotropics or antihypertensives or in the presence of risk factors such as comorbid disease, which may exacerbate these reactions. It is recommended that the patient/carer is informed of the potential for these reactions and monitored closely for such effects following initiation of therapy, prior to and following upward dose titration.

Following therapy with Trazodone hydrochloride tablets, particularly for a prolonged period, an incremental dosage reduction to withdrawal is recommended, to minimise the occurrence of withdrawal symptoms, characterised by nausea, headache, and malaise.

QT prolongation

Cases of QT interval prolongation have been reported with Trazodone hydrochloride tablets (see section 4.8). Caution is advised when prescribing Trazodone hydrochloride tablets with medicinal products known to prolong QT interval such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine). Trazodone hydrochloride should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval.

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

Priapism

As with other drugs with alpha-adrenolytic activity, trazodone has 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 hydrochloride tablets immediately.

Undesirable effects may be more frequent when Trazodone hydrochloride tablet is administered together with preparations containing Hypericum perforatum.

Paediatric population

Trazodone should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Excipient(s) warning:

This medicinal product contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interactions 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.

CYP3A4 inhibitors:

Drug metabolism studies in vitro are indicative that there is a potential for drug interactions when Trazodone hydrochloride tablet 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. 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 hydrochloride tablets by greater than towfold, leading to nausea, syncope and hypotension. If Trazodone hydrochloride tablet is used with a potent CYP3A4 inhibitor, a lower dose of Trazodone hydrochloride tablets should be considered. However, co-administration of Trazodone hydrochloride tablets and potent CYP3A4 inhibitors should be avoided where possible.

Carbamazepine:

Co-administration results in reduced plasma concentrations of trazodone . Concomitant use of carbamazepine 400 mg daily led to a decrease of plasma concentrations of Trazodone hydrochloride tablets and its active metabolite m-chlorophenylpiperazine of 76% and 60%, respectively. Patients should be closely monitored to ascertain if an increased Trazodone hydrochloride tablets dosage is required.

Tricyclic antidepressants:

Concurrent administration should be avoided due to the risk of interaction. Serotonin syndrome and cardiovascular side effects are possible.

Fluoxetine:

Rare cases have been reported of elevated Trazodone hydrochloride tablet plasma levels and adverse effects when Trazodone hydrochloride tablet 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.

Monoamine oxidase inhibitors:

Possible interactions with monoamine oxidase inhibitors have occasionally been reported. Although some clinicians do give both concurrently, use of Trazodone hydrochloride tablet concomitantly with MAOIs, or within two weeks from discontinuation of these substances is not recommended. The administration of MAOIs within one week since discontinuation of Trazodone hydrochloride tablet treatment is not recommended either.

Phenothiazines:

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

Anaesthetics/muscle relaxants

Trazodone hydrochloride tablet may enhance the effects of muscle relaxants and volatile anaesthetics, and caution should be exercised in such instances.

Alcohol:

Trazodone hydrochloride tablet intensifies the sedative effects of alcohol. Alcohol should be avoided during Trazodone hydrochloride tablet therapy.

Levodopa:

Antidepressants can accelerate the metabolism of levodopa.

Buprenorphine/Naloxone: Trazodone hydrochloride tablets should be used cautiously when co-administered with buprenorphine or naloxone, as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Other:

Concomitant use of Trazodone hydrochloride tablet 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 co-administered with Trazodone hydrochloride tablet.

Antihypertensives:

Since Trazodone hydrochloride tablet 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 hydrochloride tablet 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

St. John's Wort:

Undesirable effects may be more frequent when Trazodone hydrochloride tablet is administered together with preparations containing *Hypericum perforatum*.

Warfarin:

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

Digoxin and phenytoin:

Concurrent use with Trazodone hydrochloride tablet 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

Trazadone should only be administered during pregnancy if considered essential by the physician.

Pregnancy

There are limited amounts of data (less than 200 pregnancy outcomes) from the use of trazodone in pregnant women. Data of exposed pregnancies indicate no adverse effects of trazodone on pregnancy or on the health of the foetus / newborn child. No other relevant epidemiological data are available. The safety of Trazodone hydrochloride tablet 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 (see also section 5.3). As a precautionary measure, it is preferable to avoid the use of trazodone during pregnancy.

When trazodone is used until delivery, newborns should be monitored for the occurrence of withdrawal symptoms.

Breast-feeding

Limited data indicate that excretion of Trazodone hydrochloride tablet 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 hydrochloride tablet should be made taking into account the benefit of breast-feeding to the child and the benefit of Trazodone hydrochloride tablet therapy to the woman.

Fertility

No fertility data are available in humans. In rats, effects of trazodone on fertility have been documented at high doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Trazodone has minor or moderate influence on the ability to drive and use machines. Patients should be cautioned against the risks of driving or operating machinery until they are sure they are not affected by drowsiness, sedation, dizziness, confusional states, or blurred vision.

4.8 Undesirable effects

Cases of suicidal ideation and suicidal behaviours have been reported during Trazodone hydrochloride tablet therapy or early after treatment discontinuation (see section 4.4).

The

following symptoms, some of which arecommonly reported in cases of untreated depression,.

MedDRA System Organ Class	**Frequency**
Blood and the lymphatic system disorders	Blood dyscrasias including agranulocytosis, thrombocytopenia, eosinophilia, leucopenia and anaemia
Immune system disorders	Allergic reactions
Endocrine disorders	Syndrome of Inappropriate Antidiuretic Hormone Secretion
Metabolism and nutrition disorders	Hyponatraemia1, weight loss anorexia and increased Uncommon: Weight loss Not known: Hyponatraemia[1]
Psychiatric disorders	, Suicidal ideation or suicidal confusional state, disorientation, mania, agitation (very occasionally exacerbating to delirium), aggressive reaction, hallucinations. Not known: Worsening delusions, inhibition, anxiety, suicidal ideation and suicidal behaviours[2], insomnia, nightmares, withdrawal syndrome.
Nervous system disorders	Very common: Dizziness, drowsiness[3] Common: Tinnitus, headache, tremor Uncommon: Serotonin syndrome[4], convulsions Rare: Myoclonus

	Very rare: Neuroleptic malignant syndrome Not known: Vertigo, restlessness, decreased alertness, memory disturbance, paraesthesia, dystonia.
Eye disorders	Common: Accommodation and vision disorders, sometimes glaucoma, ocular pruritus, blurred vision
Cardiac disorders	Common: Palpitation[5], bradycardia, tachycardia Not known: Cardiac arrhythmias[5] (including Torsades de Pointes, premature ventricular couplets, ventricular tachycardia), ECG abnormalities (QT prolongation)
Vascular disorders	Common: Orthostatic hypotension, hypertension, syncope
Respiratory, thoracic and mediastinal disorders	Common: Nasal/sinus congestion Uncommon: Dyspnoea
Gastrointestinal disorders	Very common: Dry mouth Common: Taste changes, flatulence, nausea, vomiting, constipation and diarrhoea, dyspepsia, stomach pain, gastroenteritis. Not known: Intestinal perforation, paralytic ileus, gastrointestinal spasm, and hiatus hernia, increased salivation
Hepato-biliary disorders	Rare: Hepatic function abnormalities (including jaundice and hepatocellular damage)[6], severe hepatic disorders such as hepatitis/fulminant hepatitis, hepatic failure with potential fatal outcome. Not known: Intrahepatic cholestasis
Skin and subcutaneous tissue disorders	Common: Skin rash, pruritus Not known: Hyperhidrosis
Musculoskeletal and connective tissue disorders	Common: Asthenia, chest pain, limb pain, back pain Not known: Myalgia, arthralgia
Renal and urinary disorders	Not known: Urinary hesitancy, micturition disorders
Reproductive system and breast disorders	Uncommon: Decreased libido Very rare: Priapism[2]
General disorders and administration site conditions	Common: Perspiration, hot flushes, oedema, influenza-like symptoms Not known: Weakness, fatigue, fever
Investigations	Not known: Elevated liver enzymes

[1] Fluid and electrolyte status should be monitored in symptomatic patients.

[2] See also Section 4.4.

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

[4] Studies in animals have shown that Trazodone hydrochloride is less cardiotoxic than the tricyclic antidepressants, and clinical studies suggest that the drug may be less likely to cause cardiac arrhythmias in manClinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population. [6] Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur trazodone should be immediately discontinued.

See also Section 4.4

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 hydrochloride tablets 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 GCSMonitor 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/kgbody weight) or lorazepam (4 mg in an adult and 0.5 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

5.1 Pharmacodynamic properties

Trazodone hydrochloride tablet is a potent antidepressant It also has anxiety reducing activity Trazodone hydrochloride is a triazolopyridine derivative chemically unrelated to known tricyclic, tetracyclic and other antidepressant agents. The available data show that at sub-therapeutic doses, Trazodone hydrochloride acts as a 5-HT reuptake antagonist and at higher, therapeutic doses inhibits 5-HT reuptake. These effects and the effects of trazodone on noradrenergic transmission probably underlie the antidepressant actions of Trazodone hydrochloride. The importance of the effects of each transmitter is not known.

5.2 Pharmacokinetic properties

Trazodone hydrochloride is rapidly absorbed following oral administration, extensively metabolised and excreted almost entirely through the kidney with a T1/2 of 6-12 hours.

vitro studies in human liver microsomes show that Trazodone hydrochloride is mainly metabolised by cytochrome P4503A4 (CYP3A4).

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline

Sodium starch glycolate (Type A)

Starch, pregelatinised (maize)

Silica, colloidal anhydrous

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Tablets are available in OPA-Aluminium-PVC/Aluminium, PVC-PVdC/Aluminium and PVC/Aluminium blisters.

Pack sizes:

30 or 84 tablets in blister. Also available in 84 x 1 perforated unit dose blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0495

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/08/2022

10 DATE OF REVISION OF THE TEXT

01/03/2023