SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trazodone 150 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Trazodone 150 mg
Each tablet contains trazodone as 150 mg trazodone hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Trazodone 150 mg: White to off white, 16.90 mm in length, 8.40 mm in width, oval, flat faced bevelled edge, uncoated tablets, with score line, engraved “IT” bisect “III” on one side and plain on the other side.

The tablet can be divided into equal doses.

4.1 Therapeutic indications

Major depressive episodes in adults.

4.2 Posology and method of administration

Posology
Adults:

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

This may be increased gradually, e.g. every 3-4 days by steps of 50 mg, up to a maximum of 300mg/day in a single or divided doses. The major portion of a divided dose to be taken on retiring. The dose may be further increased to 600mg/day in divided doses in hospitalised patients.

After reaching an effective dose, clinical response is usually evident within two to four weeks.

In the case of non-responders the dose may be increased to the maximimum recommended. If, following this, there is no response after two to four weeks, therapy should be discontinued.

After reaching a satisfactory clinical response, the dose should be maintained for a minimum of four weeks. Following this period, generally the dose can be incrementally decreased, depending on therapeutic response. 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.

Special populations

Elderly:

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

Hepatic Impairment:
Trazodone 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 dose adjustment is usually necessary, but caution should be exercised when prescribing for patients with severe renal impairment (see also sections 4.4 and 5.2).

Paediatric population
Trazodone should not be used in children and adolescents below the age of 18 years as safety and efficacy have not been established in this patient group (see section 4.4).

Method of administration
Oral use.

A decrease in undesirable effects can be reached by taking Trazodone after a

meal.

Trazodone should be taken together with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance or 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

Elderly
Elderly patients may more often experience orthostatic hypotension, somnolence and other anticholinergic effects of trazodone.

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 medicinal products 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-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 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 dose 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. Trazodone should be used with particular caution in these patients
- Patients with hypokalaemia or hypomagneseia. These electrolyte-disturbances increase the risk for malignant arrhythmias and should be corrected before treatment with trazodone is started.
- Hyperthyroidism
- Micturition disorders, such as prostate hypertrophy, although problems would not be anticipated as the anticholinergic effect of trazodone 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.

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 tradozone therapy be considered. Should jaundice occur in a patient, Trazodone 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 a depressive phase can change from a manic – depressive psychosis into a manic phase. In that case Trazodone must be stopped.

Interactions in terms of serotonin syndrome/malignant neuroleptic 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. Malignant neuroleptic 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 for further information. Treatment with trazodone must be stopped immediately and supportive symptomatic treatment should be initiated.

Concomitant administration of Trazodone and buprenorphine or a combination of buprenorphine/naloxone may result in serotonin syndrome, a potentially life-threatening condition (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.

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. Concomitant administration of antihypertensive therapy with Trazodone may require a reduction in the dose of the antihypertensive medicinal product.

Trazodone is a sedative antidepressant and causes drowsiness, especially at the beginning of treatment (see Sections 4.7 and 4.8).

Careful consideration should be given to the potential for additive effects with concomitant medicinal product 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, particularly for a prolonged period, an incremental dose reduction to withdrawal is recommended, to minimise the occurrence of withdrawal symptoms, characterised by agitation, sleep disturbances nausea, headache, and malaise.

Cases of QT interval prolongation have been reported with trazodone (see section 4.8). Caution is advised when prescribing Trazodone 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 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.

Trazodone has been associated with priapism. This may be treated with an intracavernosum injection of an alpha-adrenergic medicinal product 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

General: The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, and antihistaminic medicinal products may be intensified; dose 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 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. It has been confirmed in in- vivo-studies in healthy volunteers, that a ritonavir dose of 200 mg twice daily increased the plasma levels of trazodone by greater than twofold, leading to nausea, syncope and hypotension. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered. However, co-administration of trazodone 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 and its active metabolite m-chlorophenylpiperazine of 76% and 60%, respectively. Patients should be closely monitored to ascertain if an increased trazodone dose is required.

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

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.

Monoamine oxidase inhibitors: Possible interactions with monoamine oxidase inhibitors have occasionally been reported. Although some clinicians do give both concurrently, use of trazodone 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 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 may enhance the effects of muscle relaxants and volatile anaesthetics, and caution should be exercised in such instances.

Alcohol: Trazodone intensifies the sedative effects of alcohol. Alcohol should be avoided during trazodone therapy.

Levodopa: Antidepressants can accelerate the metabolism of levodopa.

Other: Concomitant use of trazodone with medicinal products known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Caution should be used when these medicinal products are co-administered 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 medicinal products, 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*.

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. 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 section 5.3). As a precautionary measure, it is preferable to avoid the use of Trazodone during the trimester of 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 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

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 therapy or early after treatment discontinuation (see section 4.4).

The most frequently reported adverse reactions are: somnolence, sedation, dizziness, dry mouth, gastrointestinal disorders, sleep disorders, headache, agitation, orthostatic hypotension.

The following symptoms have also been recorded in patients receiving trazodone therapy.

MedDRA System Organ Class	**Frequency not known (cannot be estimated from the available data)**
Blood and the lymphatic system disorders	Blood dyscrasias (including agranulocytosis, thrombocytopenia, eosinophilia, leucopenia and anaemia)
Immune system disorders	Allergic reactions, angioedema
Endocrine disorders	Syndrome of Inappropriate Antidiuretic Hormone Secretion

Metabolism and nutrition disorders	Hyponatraemia[4], weight loss, anorexia, increased appetite, weight gain
Psychiatric disorders	Suicidal ideation or suicidal behaviours[5], confusional state, insomnia, disorientation, mania, anxiety, nervousness, agitation (very occasionally exacerbating to delirium), delusion, aggressive reaction, hallucinations, nightmares, libido decreased, withdrawal syndrome
Nervous system disorders	Serotonin syndrome, convulsion, neuroleptic malignant syndrome, dizziness, vertigo, headache, drowsiness[6], somnolence, sedation, ataxia, restlessness, decreased alertness, tremor, blurred vision, memory disturbance, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered
Cardiac disorders	Cardiac arrhythmias[7] (including Torsade de Pointes, palpitations, premature ventricular contractions, ventricular couplets, ventricular tachycardia), bradycardia, tachycardia, ECG, abnormalities (QT prolongation)
Vascular disorders	Orthostatic hypotension, hypertension, syncope
Respiratory, thoracic and mediastinal disorders	Nasal congestion, dyspnoea
Gastrointestinal disorders	Nausea, vomiting, dry mouth, constipation, diarrhoea, dyspepsia, stomach pain, gastroenteritis, increased salivation, paralytic ileus
Hepato-biliary disorders	Severe hepatic disorders such as hepatitis/fulminant hepatitis, hepatic failure with potential fatal outcome. Hepatic function abnormalities (including jaundice and hepatocellular damage)[8], cholestasis intrahepatic.
Skin and subcutaneous tissue disorders	Skin rash, pruritus, hyperhidrosis
Musculoskeletal and connective tissue disorders	Pain in limb, back pain, myalgia, arthralgia
Renal and urinary disorders	Micturition disorder
Reproductive system and breast disorders	Priapism[9]
General disorders and administration site conditions	Weakness, oedema, influenza-like symptoms, fatigue, chest pain, fever
Investigations	Elevated liver enzymes

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

[5] See also Section 4.4.

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

[7] Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population.

[8] Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur, trazodone should be immediately discontinued.
[9] 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 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

Symptoms

The most frequently reported reaction 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.

Patients should be observed for at least 6 hours after ingestion (or 12 hours if a sustained release preparation has been taken). Blood pressure, pulse and Glasgow Coma Scale (GCS) should be monitored. Oxygen saturation should be monitored if GCS is reduced. Cardiac monitoring is appropriate in symptomatic patients.

Single brief convulsions do not require treatment. Frequent or prolonged convulsions should be controlled 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. Oxygen should be given and acid base and metabolic disturbances should be corrected as required.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nervous system; psychoanaleptics; antidepressants; other antidepressants,
ATC code: N06A X05

Trazodone is a sedative antidepressant with an anxiolytic effect. 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 active substance'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.

In vitro studies in human liver microsomes show that trazodone is mainly 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.

Special populations

Elderly
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.

Hepatic Impairment
As trazadone is extensively metabolized in liver, caution should be exercised when prescribing for patients with hepatic impairment, particularly in cases of severe hepatic impairment, (see sections 4.2, 4.4 and 4.8).

Renal Impairment
Trazodone is excreted in the urine. When prescribing for patients with severe renal impairment caution should be exercised (see also sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and carcinogenic potential.
No effects on the fertility of rats were noted up to daily doses of 300 mg/kg. In embryo-fetal development studies, increased embryolethality and fetal growth retardation (delayed ossification) were observed in rats and rabbits at maternally toxic doses of 150 mg/kg/day or above. In a peri-/postnatal development study in rats, the birth weight of the offspring was reduced at dose of 300 mg/kg/day.

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

2 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

Aluminium-Aluminium, PVC/PVdC-Aluminium and PVC-Aluminium blisters / perforated unit dose blisters.

Pack sizes:
14, 20, 28, 30, 50, 60 or 100 tablets in blister. Also available in 28 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

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HA3 0BU
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0230

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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