Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trazodone Hydrochloride 50 mg/5 ml Oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 50 mg of Trazodone hydrochloride.
Each 5 ml contains 1 g of glycerol, 1.4 g of sorbitol and 5 mg benzoic acid.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.

Clear, colourless solution with a pungent taste and orange flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Symptoms of depression likely to respond in the first week of treatment include depressed mood, insomnia, anxiety, somatic symptoms and hypochondriasis.

4.2 Posology and method of administration

Posology

Adults
Starting dose is 150 mg/day in divided doses after food or as a single dose before retiring. This may be increased to 300 mg/day, the major portion of which is preferably taken on retiring. In hospitalised patients dosage may be further increased to 600 mg/day.

Paediatric population
There are insufficient data on safety to recommend the use of trazodone in children below the age of 18 years.

Older people
For very elderly or frail patients, the recommended initial starting dose is reduced to 100 mg/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. Doses above 300 mg/day are unlikely to be required.

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

In conformity with current psychiatric opinion, it is suggested that trazodone be continued for several months after remission. Cessation of trazodone treatment should be gradual.

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 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
Oral.

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

Paediatric Population
Trazodone should not be used in children and adolescents under 18 years old. Suicidal behaviour (suicidal attempt and suicidal planning) and hostility (essentially aggressiveness, opposing behaviour and anger) has been observed in a clinical study on children and adolescents treated with antidepressant more frequently than with placebo. Moreover, long-term safety data on children and adolescents regarding growth, maturation and cognitive and behavioural development are not available.

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.

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.

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 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 disease, such as angina pectoris, conduction disorders or AV blocks of different degree, recent myocardial infarction
- 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.

Should jaundice occur in a patient, trazodone therapy must be withdrawn.

Severe hepatic disorders with potential fatal outcome have been reported with trazodone use (see adverse reaction section). 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 therapy be considered.

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 serotonine 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 and MAOinhibitors) 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.

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 drug.

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, 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.

There is no evidence that trazodone hydrochloride possesses any addictive properties.

As with other antidepressant drugs, cases of QT interval prolongation have been reported with trazodone very rarely. Caution is advised when prescribing trazodone with medicinal products known to prolong QT interval. 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.

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.

Trazodone Hydrochloride Oral Solution contains sorbitol.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Trazodone Hydrochloride Oral Solution contains glycerol which may cause, headache, stomach upset and diarrhoea.

Trazodone Hydrochloride Oral Solution contains benzoic acid. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

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 co-administered. Concomitant use of carbamazepine 400 mg daily led to a decrease of plasma concentrations of trazadone 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 antidepressant 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 are possible.

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 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 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number (< 200) of exposed pregnancies indicate no adverse effects of Trazodone hydrochloride on pregnancy or on the health of the fetus/newborn child. To date, no other relevant epidemiological data are available. The safety of Trazodone hydrochloride in human pregnancy has not been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal 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 hydrochloride is used until delivery, newborns should be monitored for the occurrence of withdrawal symptoms.

Lactation

Limited data indicate that excretion of Trazodone hydrochloride 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 breastfeeding or to continue/discontinue therapy with Trazodone hydrochloride should be made taking into account the benefit of breast-feeding to the child and the benefit of Trazodone hydrochloride 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. As with all other drugs acting on the central nervous system, 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 following symptoms, some of which are commonly reported in cases of untreated depression, 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
Endocrine disorders	Syndrome of Inappropriate Antidiuretic Hormone Secretion
Metabolism and nutrition disorders	Hyponatraemia[1], weight loss, anorexia, increased appetite
Psychiatric disorders	Suicidal ideation or suicidal behaviours[2], 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[3], restlessness, decreased alertness, tremor, blurred vision, memory disturbance, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered
Cardiac disorders	Cardiac arrhythmias[4] (including Torsade de Pointes, palpitations, premature ventricular contractions, ventricular couplets, ventricular tachycardia), bradycardia, tachycardia, ECG abnormalities (QT prolongation)[2]
Vascular disorders	Orthostatic hypotension, hypertension, syncope
Respiratory, thoracic and	Nasal congestion, dyspnoea

mediastinal disorders	
Gastrointestinal disorders	Nausea, vomiting, dry mouth, constipation, diarrhoea, dyspepsia, stomach pain, gastroenteritis, increased salivation, paralytic ileus
Hepato-biliary disorders	Hepatic function abnormalities (including jaundice and hepatocellular damage)[5], cholestasis intrahepatic, severe hepatic disorders such as hepatitis/fulminant hepatitis, hepatic failure with potential fatal outcome.
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[6]
General disorders and administration site conditions	Weakness, oedema, influenza-like symptoms, fatigue, chest pain, fever
Investigations	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 on continued therapy.
[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.
[5]Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur, trazodone should be immediately discontinued.
[6] See also section 4.4.

In contrast to the tricyclic antidepressants, trazodone is devoid of anticholinergic activity. Consequently, troublesome side effects such as dry mouth, blurred vision and urinary hesitancy have occurred no more frequently than in patients receiving placebo therapy. This may be of importance when treating depressed patients who are at risk from conditions such as glaucoma, urinary retention and prostatic hypertrophy.

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 national reporting system, HPRA Pharmacovigilance. Website: www.hpra.ie.

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 Glasgow Coma Scale (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 triazolopyridine derivative which differs chemically from other currently available antidepressants. Although Trazodone bears some resemblance to the benzodiazepines, phenothiazines and tricyclic antidepressants, its pharmacological profile differs from each of these classes of drugs. The basic idea for the development of Trazodone was the hypothesis that depression involves an imbalance of the mechanism responsible for the emotional integration of unpleasant experiences. Consequently, new animal models of depression consisting of responses to unpleasant or noxious stimuli, instead of the current tests related to the aminergic theory of depression, were used in studying the drug. Trazodone inhibits serotonin uptake into rat brain synaptosomes and by rat platelets at relatively high concentrations and inhibits brain uptake of noradrenaline in vitro only at very high concentrations. It possesses antiserotonin-adrenergic blocking and analgesic effects. The anticholinergic activity of Trazodone is less than that of the tricyclic antidepressants in animal studies and this has been confirmed in therapeutic trials in depressed patients.

The electroencephalographic profile of Trazodone in humans is distinct from that of the tricyclic antidepressants or the benzodiazepines, although bearing some resemblance to these agents in its effect in certain wavebands. Studies of the cardiovascular effects of Trazodone in humans, His bundle and surface electrocardiograms in dogs, and experience with overdosage in man indicate that Trazodone is less liable than imipramine to cause important adverse effects on the heart. However, studies in depressed patients with significant cardiac impairment suggest that Trazodone may aggravate existing ventricular arrhythmias in a small undefined subgroup of such patients.

5.2 Pharmacokinetic properties

Peak plasma concentrations are attained about 1.5 hours after oral administration of Trazodone. Absorption is delayed and somewhat enhanced by food. The area under the plasma concentration-time curve is directly proportional to dosage after oral administration of 25 to 100mg. Trazodone is extensively metabolised, less than 1% of an oral dose being excreted unchanged in the urine. The main route of elimination is via the kidneys with 70 to 75% of an oral dose being recovered in the urine within the first 72 hours of ingestion. The elimination half-life for unchanged drug has been reported to be about 7 hours.

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

Glycerol (E 422)
Sorbitol solution 70% non-crystallising (E 420)
Benzoic acid (E 210)
Saccharin sodium
Orange flavour
Sodium hydroxide solution (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25ºC. Keep the bottle in the outer carton in order to protect from light.
Once opened use within 1 month.

6.5 Nature and contents of container

Type III Ph. Eur., 125 ml amber glass bottle, sealed with a polyethylene screw cap with polypropylene child resistant cap, containing 120 ml of solution.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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