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

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 tabletsin children below the age of 18 years has not been established therefore Trazodone hydrochloride tablets 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 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

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, {Invented name} 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 tablet 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 (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 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 tablets 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 Interaction with other medicinal products and other forms of interaction

General:
The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, andantihistaminic 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 two-fold, 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 is required.

Tricyclic antidepressants:
Concurrent administration should be avoided due to the risk ofinteraction. Serotonin syndrome and cardiovascular side effects are possible.

Fluoxetine:

Rare cases have been reported of elevated Trazodone hydrochloride tabletplasma 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 useof 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 prolongthe 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 most frequently reported adverse reactions are: dizziness, drowsiness, fatigue, nervousness and dry mouth.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Some of the reported undesirable effects are themselves commonly reported symptoms in cases of untreated depression, e.g. inhibition, dry mouth, constipation, tremor and dizziness.
The frequency is defined as: very common (> 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**
Blood and the lymphatic system disorders	Rare: Blood dyscrasias including agranulocytosis, thrombocytopenia, eosinophilia, leucopenia and anaemia
Immune system disorders	Common: Allergic reactions
Endocrine disorders	Not known: Syndrome of Inappropriate Antidiuretic Hormone Secretion
Metabolism and nutrition disorders	Common: Weight gain, anorexia and increased hunger Uncommon: Weight loss Not known: Hyponatraemia[1]
Psychiatric disorders	Very common: Nervousness Common: Expressive aphasia, 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] Especially when associated with concomitant administration of other psychotropic drugs.
[5] Clinical studies involving patients with pre-existing cardiac disease suggest that trazodone may be arrhythmogenic in some patients in this population. Identified arrhythmias include isolated premature ventricular contraction, ventricular couplets, short episodes of ventricular tachycardia (3-4 beats).
[6] Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur trazodone should be immediately discontinued.

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 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 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.

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; 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: Other antidepressants, ATC code: N06A X05

Trazodone hydrochloride tablet is a sedative antidepressant with an anxiolytic effect. Trazodone hydrochloride tablet 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 hydrochloride tablet 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

Absorption
Following oral administration trazodone hydrochloride is rapidly absorbed from the gastrointestinal tract, with T^{max} of 0.5 to 2 hours, and it is approximately 65 % bioavailable. When trazodone is taken with food, there may be a slight increase (up to 20%) in the total amount of drug absorbed (AUC), whereas the rate of absorption is delayed (C_{max} is lower and T_{max} is later). Administration after food minimises the risk of side effects. Steady state plasma levels are achieved after about four days of drug administration.

Distribution
Trazodone does not appear to selectively accumulate, although concentrations may be higher in liver, bone marrow, and brain. It is 85 % – 95 % plasma protein bound, with a volume of distribution (V^d) following a single oral 100 mg dose of 0.84 ± 0.16 L / Kg,

Biotransformation
Following absorption trazodone undergoes extensive hepatic metabolism by oxidation and hydroxylation to yield a range of metabolites. About 10 % is formed into m – chlorophenylpiperazine, which is an active metabolite. Other metabolites are the N – oxide derivative, diol derivative, hydroxy derivative, and conjugated compounds, all of which are inactive.
Human liver microsome studies *in vitro* have shown that cyctochrome P450 3A4 is responsible for metabolism to m – chlorophenylpiperazine, and cytochrome P450 2D6 is also involved in the metabolism.

Elimination
Trazodone is excreted mainly by the renal route (70 %), mainly in the form of metabolites, (only 0.15% is excreted unchanged). Faecal excretion accounts for about 20 %. Trazodone is also excreted in breast milk. The elimination is biphasic, with a half life around 1 hour for the initial phase, and about 8 hours for the second phase, giving a terminal elimination half life of 5 – 13 hours.

Renal impairment
Trazodone is primarily eliminated via renal excretion in form of its inactive metabolites, and accumulation of the parent drug and active metabolite are therefore unlikely to occur in renal dysfunction. Dose adjustments may only be necessary in severe cases (see section 4.2 and 4.4). Dialysis does not significantly accelerate clearance of trazodone from the body.

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 (decreased 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

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:
50 mg: 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 Ireland Ltd.
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Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/122/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd June 2018
Date of last renewal: 4th April 2023

10 DATE OF REVISION OF THE TEXT

October 2023