

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Trazodone Hydrochloride Azure 50 mg Hard Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg trazodone hydrochloride.

Excipient(s) with known effect: Each capsule contains 73.75 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsule.

Hard gelatin capsule of size '3' with blue/opaque cap marked 'THC' with black colour and green opaque body marked '50' with black colour containing white to off white powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Anxiety, depression, mixed anxiety and depression.

### 4.2 Posology and method of administration

#### Posology

#### Depression:

##### *Adults:*

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

This may be increased up to 300 mg/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 600 mg/day in divided doses in hospitalised patients.

##### *Elderly:*

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. It is unlikely that 300 mg/day will be exceeded.

##### *Children:*

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

#### Depression accompanied by anxiety:

As for depression.

#### Anxiety:

75 mg/day increasing to 300 mg/day as necessary.

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.

#### *Hepatic Impairment:*

Trazodone hydrochloride 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 administration.

### 4.3 Contraindications

- Hypersensitivity to trazodone 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

*Use in children and adolescents under 18:*

Trazodone hydrochloride should not be used in children and adolescents under 18 years old. Suicidal behaviour (suicidal attempt and suicidal planning) and hostility (essentially aggressiveness, opposing behavior 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 behavioral 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 hydrochloride 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 hydrochloride 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 hydrochloride 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.

Should jaundice occur in a patient, Trazodone hydrochloride 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 hydrochloride a depressive phase can change from a manic – depressive psychosis into a manic phase. In that case Trazodone hydrochloride 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 and MAO-inhibitors) 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 hydrochloride. Concomitant administration of antihypertensive therapy with Trazodone hydrochloride 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 hydrochloride, 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 hydrochloride very rarely. Caution is advised when prescribing Trazodone hydrochloride with medicinal products known to prolong QT interval. 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.

As with other drugs with alpha-adrenolytic activity, Trazodone hydrochloride 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 hydrochloride immediately.

### **Important information regarding the ingredients of this medicine**

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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

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

In vitro drug metabolism studies suggest that there is a potential for drug interactions when Trazodone hydrochloride 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 hydrochloride 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 hydrochloride by greater than two fold, leading to nausea, syncope and hypotension. If Trazodone hydrochloride is used with a potent CYP3A4 inhibitor, a lower dose of Trazodone hydrochloride should be considered. However, the co-administration of Trazodone hydrochloride 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 Trazodone hydrochloride 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 hydrochloride when taken with carbamazepine.

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

Since Trazodone hydrochloride is only a very weak inhibitor of noradrenaline reuptake 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 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 hydrochloride is administered together with preparations containing *Hypericum perforatum* (*St John's Wort*). There have been reports of changes in prothrombin time in patients concomitantly receiving trazodone and warfarin.

Concurrent use with Trazodone hydrochloride 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 hydrochloride on pregnancy or on the health of the foetus/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/foetal development, parturition or postnatal development at therapeutic doses. On basic principles, therefore, its use during the first trimester should be avoided.

Caution should be exercised when prescribing to pregnant women. When Trazodone 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 must be made whether to discontinue breast-feeding or to discontinue/abstain from Trazodone hydrochloride therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

##### *Fertility:*

There is no data available regarding the effect of Trazodone on fertility.

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

Trazodone hydrochloride has had no effect on arterial blood pCO<sub>2</sub> or pO<sub>2</sub> levels in patients with severe respiratory insufficiency due to chronic bronchial or pulmonary disease.

The following symptoms, some of which are commonly reported in cases of untreated depression, have also been recorded in patients receiving Trazodone hydrochloride 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 <sup>1</sup> , weight loss, anorexia, increased appetite,
Psychiatric disorders	Suicidal ideation or suicidal behaviours <sup>2</sup> , 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 <sup>3</sup> , restlessness, decreased alertness, tremor, blurred vision, memory disturbance, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered
Cardiac disorders	Cardiac arrhythmias <sup>4</sup> (including Torsade de Pointes, palpitations,

	premature ventricular contractions, ventricular couplets, ventricular tachycardia), bradycardia, tachycardia, ECG abnormalities (QT prolongation) <sup>2</sup>
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	Hepatic function abnormalities (including jaundice and hepatocellular damage) <sup>5</sup> , 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 <sup>6</sup>
General disorders and administration site conditions	Weakness, oedema, influenza-like symptoms, fatigue, chest pain, fever
Investigations	Elevated liver enzymes

<sup>1</sup>Fluid and electrolyte status should be monitored in symptomatic patients.

<sup>2</sup> See also Section 4.4.

<sup>3</sup>Trazodone is a sedative antidepressant and drowsiness, sometimes experienced during the first days of treatment, usually disappears on continued therapy.

<sup>4</sup>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.

<sup>5</sup>Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur, trazodone should be immediately discontinued.

<sup>6</sup>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 HPRC Pharmacovigilance Website: [www.hpra.ie](http://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, eg dopamine or dobutamine.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06A X05.

Trazodone Hydrochloride 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. It has negligible effect on noradrenaline reuptake mechanisms. Whilst the mode of action of Trazodone Hydrochloride is not known precisely, its antidepressant activity may concern noradrenergic potentiation by mechanisms other than uptake blockade. A central antiserotonin effect may account for the drug's anxiety reducing properties.

### 5.2 Pharmacokinetic properties

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

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

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

### 5.3 Preclinical safety data

None stated.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate  
Magnesium stearate

#### *Capsule body and shell:*

Brilliant Blue (E133)  
Titanium dioxide (E171)  
Iron oxide yellow (E172)  
Patent Blue V (E131)  
Gelatin

#### *Printing ink:*

Shellac (E904)  
Propylene glycol (E 1520)  
Black iron oxide (E172)  
Potassium hydroxide (E525)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

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3 years

#### **6.4 Special precautions for storage**

Store below 30°C

#### **6.5 Nature and contents of container**

Alu-PVC/PVdC blister pack of 14, 28, 56, 84 and 100 capsules.

HDPE bottle packs of 500 and 1000 capsules.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

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

### **7 MARKETING AUTHORISATION HOLDER**

Azure Pharmaceuticals Ltd

12 Hamilton Drive

The Rock Road

Blackrock

Co. Louth

A91 T997

Ireland

### **8 MARKETING AUTHORISATION NUMBER**

PA22871/018/001

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30<sup>th</sup> September 2022

### **10 DATE OF REVISION OF THE TEXT**