Approved Professional Information for Medicines for Human Use:

ZADOPAX 50 mg, 100 mg

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZADOPAX 50 mg Hard Gelatin Capsules

ZADOPAX 100 mg Hard Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZADOPAX 50 mg:

Each hard gelatin capsule contains 50 mg Trazodone Hydrochloride.

ZADOPAX 100 mg:

Each hard gelatin capsule contains 100 mg Trazodone Hydrochloride.

Contains sugar (Lactose monohydrate)

ZADOPAX 50 mg:

Each hard gelatin capsule contains 80 mg lactose monohydrate.

ZADOPAX 100 mg:

Each hard gelatin capsule contains 160 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

ZADOPAX 50 mg:

Size “3” opaque green body, printed “50” in black and violet cap.

ZADOPAX 100 mg:

Austell Pharmaceuticals, 540520-1, Zadopax 50, 100 mg Hard Gelatin Capsules

Size “2” light yellow body, printed “100” in black and violet cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZADOPAX is indicated in the treatment of depression and mixed anxiety and depression.

4.2 Posology and method of administration

The dosage is dependent upon the diagnosis and the severity of the condition and the individual patient’s response. The daily dosage is usually administered in three divided doses.

Adults:

Depression: The optimal dosage is between 300 - 400 mg/day. It is suggested that a starting dose of 150 mg/day is given for the first week, increasing to 300 mg/day – 400 mg/day according to the clinical response. The dose may be further increased to 600 mg/day in divided doses in hospitalised patients.

Mixed anxiety and depression: The recommended starting dose is between 100 – 150 mg/day. When depression is the predominant symptom, a dose of 300 – 400 mg daily may be required to obtain a satisfactory response.

Special populations

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. 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.

Paediatric population

Children and adolescents under 18 years of age:

ZADOPAX is not recommended for use in children and adolescents under 18 years of age

Method of administration

For oral use.

4.3 Contraindications

- Known hypersensitivity to trazodone or to any of the excipients listed in section 6.1.
- Combined use with other psychotropic medicines should only be undertaken with due recognition of the possibility of potentiation (see Interactions).
- Concurrent administration with monoamine oxidase inhibitors (MAOIs), or within two weeks of stopping treatment with these compounds. Administration of MAOIs within one week of stopping ZADOPAX.
- Alcohol intoxication and intoxication with hypnotics.
- Acute myocardial infarction (see section 4.4).

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.

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 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 medicinal product 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 ZADOPAX 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, ZADOPAX therapy must be withdrawn.

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 medical practitioner. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately, and withdrawal of ZADOPAX 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 ZADOPAX 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 medicinal product reaction, (see sections 4.5 and 4.8).

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 ZADOPAX may require a reduction in the dose of the antihypertensive medicinal product.

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 medicine 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 ZADOPAX, 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.

Cases of QT interval prolongation have been reported with trazodone. Caution is advised when prescribing ZADOPAX with medicinal products known to prolong QT interval. ZADOPAX 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.

Trazodone has been associated with priapism. This may be treated with an intracavernosum injection of an alpha-adrenergic medicine 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 ZADOPAX immediately.

Paediatric population

Use in children and adolescents under 18

ZADOPAX 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.

Excipients: lactose

ZADOPAX contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZADOPAX.

4.5 Interaction with other medicines and other forms of interaction

General: The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, and antihistaminic medicinal products 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 medicinal product metabolism studies suggest that there is a potential for medicinal product 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 ZADOPAX 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 ZADOPAX is used with a potent CYP3A4 inhibitor, a lower dose of ZADOPAX should be considered. However, the co-administration of ZADOPAX 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 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 ZADOPAX 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 medicinal products, including alcohol. Trazodone intensifies the sedative effects of alcohol. Alcohol should be avoided during ZADOPAX 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: Cases of elevated trazodone plasma levels and adverse effects have been reported when trazodone was 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. Use of ZADOPAX with MAOIs, or within two weeks of stopping treatment is contraindicated (see section 4.3). The giving of MAOIs within one week of stopping ZADOPAX is also contraindicated (see section 4.3).

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 medicinal products known to prolong the QT interval may increase the risk of ventricular dysrhythmias, including torsade de pointes. Caution should be used when these medicinal products are co-administered with ZADOPAX.

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 product, although no clinical interactions have been reported, the possibility of potentiation should be considered.

Undesirable effects may be more frequent when ZADOPAX is administered together with preparations containing Hypericum perforatum (St John's Wort).

Tryptophan: Since both ZADOPAX and tryptophan lead to an increase in 5-HT level at the synapse via different mechanisms of action, there is a possibility of a pharmacodynamic interaction which may lead to serotonin syndrome.

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

Concurrent use with ZADOPAX 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

The safety of Trazodone 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 is used until delivery, newborns should be monitored for the occurrence of withdrawal symptoms.

Lactation

ZADOPAX is excreted in the breastmilk and may have an effect on the breastfeeding infant. Mothers on treatment with ZADOPAX should not breastfeed their infants.

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

a) **Summary of the safety profile**

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

ZADOPAX has had no effect on arterial blood pCO2 or pO2 levels in patients with severe respiratory insufficiency due to chronic bronchial or pulmonary disease.

b) Tabulated summary of adverse reactions

The table below shows all adverse medicinal product reactions (ADRs) observed during clinical trials and post market spontaneous reports with Trazodone Hydrochloride.

Frequent (≥ 1/100)

Less frequent (< 1/100)

Not known (cannot be estimated from the available data)

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Blood and the lymphatic system disorders		Blood dyscrasias (including agranulocytosis, thrombocytopenia, anaemia) (see section 4.4)	Eosinophilia, leucopenia
Immune system disorders			Allergic reactions
Endocrine disorders			Syndrome of Inappropriate Antidiuretic Hormone Secretion
Metabolism and nutrition disorders			Hyponatraemia*, weight loss, anorexia, increased appetite
Psychiatric disorders	Confusional states		Suicidal ideation or suicidal behaviours (see section 4.4), insomnia, disorientation, mania, anxiety, nervousness, agitation (very occasionally exacerbating to delirium), delusion, aggressive reaction, hallucinations,

			nightmares, libido decreased, withdrawal syndrome
Nervous system disorders	Headache, dizziness, drowsiness, tremor, excitement		Serotonin syndrome, convulsion, neuroleptic malignant syndrome, vertigo, restlessness, decreased alertness, blurred vision, memory disturbance, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered, irritability
Eye disorders		Blurred vision	
Cardiac disorders		Bradycardia or tachycardia	Cardiac dysrhythmias~~4~~ (including Torsade de Pointes, palpitations, premature ventricular contractions, ventricular couplets, short episodes (3 – 4 beats) of ventricular tachycardia), ECG abnormalities

			(QT prolongation)) (see section 4.4)
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) (see section 4.4), cholestasis intrahepatic, severe hepatic disorders such as hepatitis/fulminant hepatitis and

			hepatic failure with potentially 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 (see section 4.4)	
General disorders and administration site conditions		Weakness	Oedema, influenza-like symptoms, fatigue, chest pain, fever
Investigations			Elevated liver enzymes

Description of selected adverse reactions

* Fluid and electrolyte status should be monitored in symptomatic patients.

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 dysrhythmias in man. Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be dysrhythmogenic in some patients in that population.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6,04 Adverse Medicinal product Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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. The stomach should be emptied as quickly as possible and symptomatic and supportive therapy is given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants.

ATC Code: N06A X05

Trazodone hydrochloride is a triazolopyridine derivative chemically unrelated to known tricyclic, tetracyclic and other antidepressant medicines. It has negligible effect on norepinephrine (noradrenaline) re-uptake mechanisms. Whilst the mode of action of ZADOPAX is not known precisely, its antidepressant activity may concern norepinephric potentiation by mechanisms other than uptake blockade. A central antiserotonin effect may account for the anxiety reducing properties of trazodone.

Trazodone hydrochloride is an anxiolytic/antidepressant, psychotropic medicine.

5.2 Pharmacokinetic properties

Absorption & Distribution

Trazodone is rapidly absorbed from the gastrointestinal tract and extensively metabolised in the liver.

Biotransformation

Paths of metabolism of trazodone include n-oxidation and hydroxylation. Trazodone is metabolised to its active metabolite m-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4.

Elimination

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 100 mg dose of trazodone. It was suggested that there is an age-related reduction in the hepatic metabolism of trazodone.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For Capsule Content:

Lactose monohydrate

Magnesium stearate

For Empty Hard Capsule Shells:

ZADOPAX 100 mg (Size of capsule is “2”)

Capsule cap (Colour description: Violet)

Brilliant Blue (E 133)

Erythrosine (E 127)

Iron oxide red (E 172)

Titanium dioxide (E 171)

Gelatin

Purified Water

Capsule body (Colour description: Light Yellow)

Iron Oxide Yellow (E172)

Erythrosine (E 127)

Iron oxide red (E 172)

Titanium dioxide (E171)

Gelatin

Purified Water

ZADOPAX 50 mg (Size of capsule is “3”)

Capsule cap (Colour description: Violet)

Brilliant Blue (E 133)

Erythrosine (E 127)

Iron oxide red (E 172)

Titanium dioxide (E 171)

Gelatin

Purified Water

Capsule body (Colour description: Opaque Green)

Brilliant Blue (E133)

Iron oxide yellow (E 172)

Iron oxide red (E 172)

Titanium dioxide (E171)

Gelatin

Purified Water

For Imprinted Ink:

For capsules shells used in ZADOPAX 50mg/100 mg Capsules

Imprinted ink: TekPrint™ SW-9008 Black Ink

Shellac (E 904)

Dehydrated Alcohol (E1510)

Isopropyl Alcohol

Butyl Alcohol

Propylene Glycol (E1520)

Strong Ammonia Solution (E527)

Potassium Hydroxide (E525)

Black Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 Months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in original packaging.

6.5 Nature and contents of container

ZADOPAX 50 mg and ZADOPAX 100 mg are available Alu-PVC/PVDC blister packs and Alu-PVC/PE/PVDC blister packs. The blister packs are packed into cardboard cartons in pack sizes of 5 x 10's and 10 x 10's respectively.

ZADOPAX 50 mg and ZADOPAX 100 mg are available in colourless, transparent polypropylene polymer plastic packs of 50's and 100's tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

ZADOPAX 50 mg: 54/1.2/0520

ZADOPAX 100 mg: 54/1.2/0521

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2023

10. DATE OF REVISION OF THE TEXT