Professional Information for TREZOT

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TREZOT 50 hard capsules

TREZOT 100 hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TREZOT 50: Each capsule contains 50 mg trazodone hydrochloride.

TREZOT 100: Each capsule contains 100 mg trazodone hydrochloride.

Excipient with known effect:

Contains sugar.

TREZOT 50: Each capsule contains 81,2 mg lactose monohydrate.

TREZOT 100: Each capsule contains 162,4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.

TREZOT 50: White to off white powder filled in size ’3’ hard gelatine capsule with yellow coloured cap and yellow coloured body.

TREZOT 100: White to off white powder filled in size ’2’ hard gelatine capsule with dark brown coloured cap and dark brown coloured body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TREZOT is indicated for the treatment of depression and mixed anxiety and depression.

4.2 Posology and method of administration

The dosage is dependent upon the diagnosis, 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.

Children and adolescents under 18 years of age

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

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.

4.3 Contraindications

- Known hypersensitivity to trazodone or to any of the excipients of TREZOT listed in section 6.1.
- Alcohol intoxication and intoxication with hypnotics.
- Acute myocardial infarction (see section 4.4).
- 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 TREZOT. (See section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18

TREZOT 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 TREZOT 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 medicines 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 TREZOT 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 TREZOT 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. (See section 4.5).
- 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 or in the immediate recovery phase following myocardial infarction. (See section 4.3).
- Hyperthyroidism.
- Micturition disorders (such as prostate hypertrophy), although problems would not be anticipated as the anticholinergic effect of TREZOT 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 TREZOT.

Should jaundice or signs of hepatic dysfunction or blood dyscrasias occur in a patient, TREZOT therapy must be withdrawn.

TREZOT undergoes extensive hepatic metabolism (see section 5.2) and has also been associated with hepatotoxicity. Severe hepatic disorders with potentially 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 doctor or health care provider. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately, and withdrawal of TREZOT therapy be considered.

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.

No dosage adjustment is usually necessary, but caution should be exercised when prescribing for patients with severe renal impairment (see section 5.2).

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 TREZOT a depressive phase can change from a manic – depressive psychosis into a manic phase. In that case TREZOT 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, selective serotonin reuptake inhibitores (SSRI's), seretonin and

norepinephrine (noradrenaline) reuptake inhibitors (SNRI's) and monoamine oxidase inhibitors (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 medicine 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 TREZOT. Concomitant administration of antihypertensive therapy with TREZOT may require a reduction in the dose of the antihypertensive medicine.

Elderly patients are more sensitive to andidepressant medicines and may more often experience orthostatic hypotension, somnolence and other anticholinergic effects of TREZOT. Careful consideration should be given to the potential for additive effects with concomitant medication use such as with other psychotropic- or antihypertensive medicines or in the presence of risk factors such as comorbid disease, which may exacerbate these reactions. It is recommended that the patient/caretaker 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. Combined use with other psychotropic medicines should only be undertaken with due recognition of the possibility of potentiation (see section 4.5).

Following therapy with TREZOT, particularly for a prolonged period, an incremental dosage reduction to withdrawal is recommended, to minimise the occurrence of withdrawal syptoms, characterised by nausea, headache, and malaise.

There is no evidence that TREZOT possesses any addictive properties.

Cases of QT interval prolongation have been reported with TREZOT less frequently. Caution is advised when prescribing TREZOT with medicines known to prolong the QT interval. TREZOT should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval (see section 4.5).

Potent cytochrome P3A4 (CYP3A4) inhibitors may lead to increases in TREZOT serum levels (see section 4.5).

TREZOT has less frequently been associated with priapism. This may be treated with an intracavernosum injection of an alpha-adrenergic medicine, such as epinephrine (adrenaline). However, there are reports of TREZOT-induced priapism which have required surgical intervention or led to permanent sexual dysfunction. Patients developing inappropriate or prolonged penile erections should stop the use of TREZOT immediately.

TREZOT contains sugar (lactose monohydrate)

TREZOT contains lactose and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

TREZOT contains the colourant sunset yellow which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

General

The sedative effects of antipsychotic, hypnotic, sedative, anxiolytic, and antihistaminic medicines 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

In vitro medicine metabolism studies suggest that there is a potential for medicine interactions when TREZOT is given with potent CYP3A4 inhibitors such as erythromycin, ketoconazole, itraconazole, ritonavir and indinavir. It is likely that potent CYP3A4 inhibitors may lead to substantial increases in TREZOT plasma concentrations with the potential for adverse effects. Exposure to ritonavir during initiation or resumption of treatment in patients receiving TREZOT 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 twice daily increased the plasma levels of TREZOT by greater than two-fold, leading to nausea, syncope and hypotension. If TREZOT is used with a potent CYP3A4 inhibitor, a lower dose of TREZOT should be considered. However, the co-administration of TREZOT and potent CYP3A4 inhibitors should be avoided where possible.

Carbamazepine

Carbamazepine reduced plasma concentrations of TREZOT 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 TREZOT when treated concomitantly with carbamazepine.

Anaesthetics/muscle relaxants

TREZOT 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 medicines, including alcohol. TREZOT intensifies the sedative effects of alcohol. Alcohol should be avoided during TREZOT therapy. (See section 4.3).

Levodopa

TREZOT has been well tolerated 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. (See section 4.4).

Fluoxetine and monoamine oxidase inhibitors

Less frequent cases have been reported of elevated TREZOT plasma levels and adverse effects when TREZOT 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 (MOAIs) have occasionally been reported. The use of TREZOT with MAOIs, or within two weeks of stopping treatment with these compounds is not recommended. The giving of MAOIs within one week of stopping TREZOT is also not recommended. (See section 4.3).

Phenothiazines

Severe orthostatic hypotension has been observed in case of concomitant use of phenothiazines, such as chlorpromazine or fluphenazine.

Other

Concomitant use of TREZOT with the antidisrhythmic medicine amiodarone or other medicines known to prolong the QT interval may increase the risk of ventricular disrhythmias, including torsades de pointes. Caution should be used when these medicines are co-administered with TREZOT.

Since TREZOT is only a very weak inhibitor of norepinephrine (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 TREZOT may inhibit most of the acute actions of clonidine. In the case of other types of antihypertensive medicine, although no clinical interactions have been reported, the possibility of potentiation should be considered.

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

Concomitant use of apraclonidine or brimonidine and TREZOT is not recommended.

Warfarin

There have been reports of changes in International Normalised Ratio (INR)/prothrombin time in patients concomitantly receiving TREZOT and warfarin. It is therefore prudent to monitor INR in patients taking warfarin, when treatment with TREZOT is started or stopped, and adjusting the warfarin dose if necessary.

Concurrent use with TREZOT may result in elevated serum levels of digoxin or phenytoin. Monitoring of serum levels should be considered in these patients. In general, antidepressants may antagonise the anticovulsant effect of antiepileptic medicines by lowering the seizure threshold. (See section 4.4).

Tryptophan

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of TREZOT in human pregnancy has not been established.

Data on a limited number (< 200) of exposed pregnancies indicate no adverse effects of TREZOT on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development at therapeutic doses.

Caution should be exercised when prescribing to pregnant women. When Trazodone is used until delivery, new-borns should be monitored for the occurrence of withdrawal symptoms.

Breastfeeding

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

Fertility

No data are available on the effects of TREZOT on human fertility.

4.7 Effects on ability to drive and use machines

TREZOT has minor or moderate influence on the ability to drive and use machines. Patients should be warned about the possibility of their judgement being impaired by drowsiness, sedation, dizziness, confusional states, or blurred vision when driving or operating machinery.

4.8 Undesirable effects

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

The following adverse reactions, some of which are frequently reported in cases of untreated depression, have been reported:

Blood and the lymphatic system disorders

Less frequent:	blood dyscrasias (including agranulocytosis, thrombocytopenia and anaemia)
Frequency unknown:	eosinophilia, leukopenia

Immune system disorders

Frequency unknown:	allergic reactions

Endocrine disorders

Frequency unknown:	Syndrome of Inappropriate Antidiuretic Hormone Secretion

Metabolism and nutrition disorders

Frequency unknown:	hyponatraemia[1], weight loss, anorexia, increased appetite

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

Psychiatric disorders

Frequent:	confusional state
Frequency unknown:	suicidal ideation or suicidal behaviours[2], insomnia, disorientation, mania, anxiety, nervousness, agitation (less frequently exacerbating to delirium), delusion, aggressive reaction, hallucinations, nightmares, libido decreased, withdrawal syndrome

[2] See section 4.4.

Nervous system disorders

Frequent:	headache, dizziness, drowsiness[3], tremor, excitement
Frequency unknown:	serotonin syndrome[4], convulsion[4], neuroleptic malignant syndrome, vertigo, decreased alertness, restlessness, irritability, memory disturbance, expressive aphasia, dystonia, taste altered, paraesthesia, myoclonus

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

[4] Especially when associated with other psychotropic medicines.

Eye disorders

Less frequent:	blurred vision

Cardiac disorders

Less frequent:	bradycardia, tachycardia

Frequency unknown:	cardiac dysrythmias[5] (including torsades de pointes, palpitations, premature ventricular contractions, ventricular couplets, short episodes (3 – 4 beats) of ventricular tachycardia), ECG abnormalities (QT prolongation)[6]

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

[6] See section 4.4.

Vascular disorders

Less frequent:	orthostatic hypotension
Frequency unknown:	hypertension, syncope

Respiratory, thoracic and mediastinal disorders

Frequency unknown:	nasal congestion, dyspnoea

Gastrointestinal disorders

Frequent:	nausea, vomiting, dry mouth
Less frequent:	constipation, diarrhoea
Frequency unknown:	dyspepsia, increased salivation, stomach pain, gastroenteritis, paralytic ileus

Hepatobiliary disorders

Frequency unknown: hepatic function abnormalities (including jaundice and hepatocellular damage)[7], severe hepatic disorders (such as hepatitis/fulminant hepatitis), hepatic failure with potential fatal outcome, cholestasis intrahepatic

[7] Should such effects occur, TREZOT should be discontinued immediately. (See section 4.4).

Skin and subcutaneous tissue disorders

Less frequent: skin rashes

Frequency unknown: hyperhidrosis, pruritus

Musculoskeletal and connective tissue disorders

Frequency unknown: pain in limb, back pain, myalgia, arthralgia

Renal and urinary disorders

Frequency unknown: micturition disorder

Reproductive system and breast disorders

Less frequent: priapism[8]

[8] See section 4.4.

General disorders and administration site conditions

Less frequent: weakness

Frequency unknown: oedema, influenza-like symptoms, chest pain, fatigue, fever

Investigations

Frequency unknown: elevated liver enzymes

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

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 torsades de pointes. Symptoms may appear 24 hours or more after overdose.

Overdoses of TREZOT in combination with other antidepressants may cause serotonin syndrome.

Management

There is no specific antidote to TREZOT. Activated charcoal should be considered in adults who have ingested more than 1 g TREZOT, or in children who have ingested more than 150 mg TREZOT within 1 hour of presentation.

Observe for at least 6 hours after ingestion. Monitor blood pressure (BP), pulse and Glasgow Coma Scale (GCS). Monitor oxygen 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 or lorazepam. 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, such as dopamine or dobutamine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX05.

Trazodone 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 trazodone is not known precisely, its antidepressant activity may concern noradrenergic potentiation by mechanisms other than uptake blockade. A central antiserotonin effect may account for the anxiety reducing properties of trazodone.

5.2 Pharmacokinetic properties

Absorption

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.

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

No information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Lactose monohydrate

Magnesium stearate

TREZOT 50 capsule shell:

Gelatine

Quinolone yellow (E104)

Sunset yellow (E110)

Titanium dioxide (E171)

TREZOT 100 capsule shell:

Gelatine

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Sodium lauryl sulphate

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

TREZOT is packed in clear PVC/PVDC and aluminium foil blister strips, packed in an outer

carton.

Pack size: 100 capsules.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park,

Building B, Ground Floor

22 Karee Street,

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

47/1.2/1035

47/1.2/1035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 June 2021

10. DATE OF REVISION OF THE TEXT