SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

BIOTECH TRAZODONE 50 capsules

BIOTECH TRAZODONE 100 capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BIOTECH TRAZODONE 50: Each capsule contains 50 mg trazodone hydrochloride

BIOTECH TRAZODONE 100: Each capsule contains 100 mg trazodone hydrochloride

Contains sugar (lactose monohydrate):

BIOTECH TRAZODONE 50: 77, 66 mg per capsule.

BIOTECH TRAZODONE 100: 155,32 mg per capsule.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules

BIOTECH TRAZODONE 50: Hard gelatine size ‘3’ capsule with green body, violet cap containing white powder.

BIOTECH TRAZODONE 100: Hard gelatine size ‘2’ capsule with yellow body, violet cap containing white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOTECH TRAZODONE is indicated in the treatment of:

- Depression
- Mixed anxiety and depression

4.2 Posology and method of administration

Posology

The dosage of BIOTECH TRAZODONE must be individualised for each patient by titration and will depend on the diagnosis and severity of the condition as well as the individual patient's response. The daily dosage is usually administered as three divided doses.

Adults:

For the treatment of depression:

The optimal dosage range is between 300 – 400 mg/day in three divided doses. A starting dose of 150 mg/day is suggested for the first week, gradually increasing it to 300 mg/day or higher depending on the clinical response. (Dosages of 600 mg/day have been reported as used in hospital patients).

For the treatment of mixed anxiety and depression:

A starting dose of 100 – 150 mg/day is recommended. When depression is the predominant symptom, an increased dose of 300 – 400 mg/day may be required to achieve a satisfactory response.

Withdrawal of BIOTECH TRAZODONE should be gradual. Abrupt discontinuation of the treatment should

be avoided. (see section 4.4)

Special populations

Elderly population:

Elderly patients are more likely to experience the sedative and hypotensive effects of BIOTECH TRAZODONE and a lower initial dose is recommended with adjustments made as needed and tolerated. (see section 4.4)

Method of administration

For oral use.

BIOTECH TRAZODONE should be taken with food.

4.3 Contraindications

- Hypersensitivity to trazodone or to any of the excipients of BIOTECH TRAZODONE listed in section 6.1.
- Myocardial infarction during the acute recovery phase.
- Pregnancy and lactation (see section 4.6).
- Alcohol intoxication and intoxication with hypnotics.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18

BIOTECH TRAZODONE is not recommended for use 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 children and adolescents treated with antidepressants such as BIOTECH TRAZODONE. Safety data on children and adolescents regarding growth, maturation and cognitive and behavioural development are not available.

Cardiovascular disorders

BIOTECH TRAZODONE should be used with caution in patients with cardiovascular disorders, such as ischaemic heart disease, dysrhythmias, angina pectoris, conduction disorders or AV blocks of different degree and recent myocardial infarction.

Caution is advised when prescribing BIOTECH TRAZODONE with medicines known to prolong QT interval and should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval (see section 4.5).

Concomitant administration of antihypertensive therapy with BIOTECH TRAZODONE may require a reduction in the dose of the antihypertensive medicine, because of reports of hypotension, including orthostatic hypotension and syncope when using BIOTECH TRAZODONE (see section 4.5).

Epilepsy

BIOTECH TRAZODONE should be used with caution in epilepsy. In general, antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold (see section 4.5). Abrupt increases or decreases of BIOTECH TRAZODONE dosage should be avoided.

Renal and hepatic impairment

BIOTECH TRAZODONE should be used with caution in patients with renal- or hepatic impairment, particularly if severe.

Severe hepatic disorders with potential fatal outcome have been reported with BIOTECH 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 BIOTECH TRAZODONE therapy be considered.

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

Suicide/suicidal thoughts or clinical worsening

Suicidal thoughts, self-harm and suicide (suicide-related events) are inherent risks in a depressed patient and patients should be closely monitored during early antidepressant therapy with BIOTECH TRAZODONE until significant improvement is observed. The risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which BIOTECH 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. Adult patients less than 25 years old with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants such as BIOTECH TRAZODONE.

Patients and in particular those at high risk should be closely monitored 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 BIOTECH TRAZODONE should be prescribed at each occasion.

Administration of BIOTECH TRAZODONE 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 BIOTECH TRAZODONE a depressive phase can change from a manic–depressive psychosis into a manic phase. In that case BIOTECH TRAZODONE must be stopped.

Serotonin syndrome

Concomitant administration of BIOTECH TRAZODONE and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

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, and may also occur with BIOTECH TRAZODONE. Malignant neuroleptic syndromes with fatal outcome have been reported in cases of co-administration with neuroleptics, for which this syndrome is a known possible side effect (see section 4.5 and section 4.8).

If concomitant treatment with other serotonergic medicines 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.

General

It is recommended that careful dosing and regular monitoring is adopted in patients with the following conditions:

- Hyperthyroidism
- Micturition disorders, such as prostate hypertrophy
- Acute narrow angle glaucoma, raised intraocular pressure.

Agranulocytosis may clinically reveal itself with influenza-like symptoms, sore throat and fever. In these cases it is recommended to check haematology.

The safe use of BIOTECH TRAZODONE in patients with porphyria has not been established.

BIOTECH TRAZODONE should be administered with care in patients receiving barbiturates, muscle relaxants and volatile anaesthetics since it can potentiate the CNS depressant effects of these substances (see section 4.5).

The concurrent administration with other psychotropic medicines should only be done with due recognition of

the possibility of potentiation of the effect (see section 4.5).

Potent CYP3A4 inhibitors may lead to increases in trazodone (as in BIOTECH TRAZODONE) serum levels (see section 4.5).

BIOTECH TRAZODONE may cause priapism that may be treated with an intracavernosum injection of an alpha-adrenergic medicine such as adrenaline or metaraminol. However, there are reports of BIOTECH TRAZODONE induced priapism which have required surgical intervention or led to permanent sexual dysfunction. Patients developing this suspected adverse reaction should cease BIOTECH TRAZODONE immediately (see section 4.8).

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. The patient/carer should be informed of the potential for these reactions and monitored closely for such effects following initiation of therapy, prior to and following upward dose titration.

BIOTECH TRAZODONE therapy should be withdrawn gradually (see section 4.2), to minimise the occurrence of withdrawal symptoms, characterised by nausea, headache, and malaise.

Elderly

The elderly are more prone to experience somnolence, orthostatic hypotension and other anticholinergic effects with the use of BIOTECH TRAZODONE (see section 4.2).

Excipients

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

4.5 Interaction with other medicines and other forms of interaction

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

BIOTECH TRAZODONE may enhance the CNS depressant effects such as drowsiness, dry mouth, tachycardia, blurred vision and constipation of:

- Muscle relaxants
- Antidyskinetics e.g., levodopa
- Volatile anaesthetics
- Phenothiazines
- Sedatives
- Antidepressants
- Alcohol
- Antihistamines
- Barbiturates
- Pimozide
- Anxiolytics

Dosage reductions are recommended in such instances (see section 4.4).

Trazodone intensifies the sedative effects of alcohol. Alcohol should be avoided during BIOTECH

TRAZODONE therapy.

BIOTECH TRAZODONE may increase plasma concentrations of:

- Digoxin and resultant digoxin toxicity
- Phenytoin and possibly other hydantoin anticonvulsants
- Carbamazepine

Monitoring of serum levels should be considered in these patients.

Severe orthostatic hypotension has been observed in case of concomitant use of phenothiazines, e.g., chlorpromazine, fluphenazine, levomepromazine, perphenazine. BIOTECH TRAZODONE can accelerate the metabolism of levodopa.

In general, antidepressants such as BIOTECH TRAZODONE may antagonise the activity of antiepileptics by lowering the convulsive threshold (see section 4.4).

Concurrent administration with monoamine oxidase inhibitors (MAOIs) or within two weeks of stopping treatment with BIOTECH TRAZODONE is not recommended. The concurrent administration of BIOTECH TRAZODONE with tricyclic or related antidepressants and lithium may enhance neurotoxic side effects (see section 4.3). Serotonin syndrome and cardiovascular side effects are possible.

Fluoxetine: Cases have been reported of elevated trazodone plasma levels and adverse effects when BIOTECH TRAZODONE had been combined with fluoxetine, a CYP1A2/2D6 inhibitor.

Serotonin syndrome: BIOTECH TRAZODONE should be used cautiously when co- administered with:

Buprenorphine/opioids, as the risk of serotonin syndrome, a potentially life- threatening condition, is increased (see section 4.4).

The concurrent use of BIOTECH TRAZODONE with amiodarone or medicines known to prolong the QT interval may increase the risk of ventricular dysrhythmias, including torsade de pointes. Caution should be used when these medicines are co-administered with BIOTECH TRAZODONE.

Antihypertensives with CNS depressant effects such as clonidine may potentiate CNS depression when concurrently used with BIOTECH TRAZODONE and the dose of other antihypertensives may need to be reduced because BIOTECH TRAZODONE may increase the likelihood of hypotension.

The dose of warfarin may need to be increased when used with BIOTECH TRAZODONE.

BIOTECH TRAZODONE is metabolised by the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this isoenzyme may limit the elimination of trazodone. Therefore, the dosage of BIOTECH TRAZODONE may need to be reduced when given with medicine known to be potent inhibitors of CYP3A4 such as the azole antifungals itraconazole and ketoconazole, erythromycin, and HIV-protease inhibitors such as ritonavir, indinavir and nefazodone. Exposure to ritonavir during initiation or resumption of treatment in patients receiving BIOTECH TRAZODONE will increase the potential for excessive sedation, cardiovascular, and gastrointestinal effects. The co-administration of BIOTECH TRAZODONE and potent CYP3A4 inhibitors should be avoided where possible.

Inducers of CYP3A4 such as carbamazepine may reduce the plasma concentration of trazodone as in BIOTECH TRAZODONE. Patients should be closely monitored to see if there is a need for an increased dose of BIOTECH

TRAZODONE when taken with carbamazepine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established (see section 4.3).

Breastfeeding

Safety during lactation has not been established (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

BIOTECH TRAZODONE can cause drowsiness, dizziness, light-headedness and hypotension. Patients affected should not be driving a motor vehicle or operate machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA System Organ Class	Frequency and adverse reaction
Blood and the lymphatic system disorders	*Frequency not known:* Blood dyscrasias (including agranulocytosis, thrombocytopenia, anaemia, eosinophilia, and leukopenia)
Immune system disorders	*Frequency not known:* Allergic reaction
Endocrine disorders	*Frequency not known:* Syndrome of Inapproriate Antidiuretic Hormone

	Secretion
Metabolism and nutrition disorders	*Frequency not known:* Hyponatraemia[1], anorexia, increased appetite, weight loss
Psychiatric disorders	*Frequency not known:* Suicidal ideation or suicidal behaviours[2], confusional state, insomnia, disorientation, mania, anxiety, nervousness, agitation may exacerbate to delirium), delusion, aggressive reaction, hallucinations, nightmares, libido decreased, withdrawal syndrome
Nervous system disorders	*Frequent:* Headache, dizziness, drowsiness[3]
	Less frequent: Tremors, confusional states, weakness, unusual excitement
	Frequency not known: Decreased alertness, neuroleptic malignant syndrome, memory disturbance, vertigo, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered, restlessness, irritability, insomnia, serotonin syndrome and convulsions (especially during concurrent use with other psychotropic medicine) (see section 4.3).
Eye disorders	*Less frequent:* Blurred vision
Cardiac disorders	*Less frequent:* Tachycardia, hypotension
	Frequency not known: Cardiac dysrhythmias (including Torsade de Pointes, palpitations, premature ventricular contractions, ventricular couplets, ventricular tachycardia), bradycardia, ECG abnormalities (QT prolongation)[2]
Vascular disorders	*Frequency not known:* Orthostatic hypotension, hypertension, syncope
Respiratory, thoracic and	*Frequency not known:* Nasal congestion, dyspnoea

mediastinal disorders	
Gastrointestinal disorders	*Frequent:* Nausea, vomiting, dry mouth and an unpleasant taste
	Less frequent: Constipation, diarrhoea
	Frequency not known: Dyspepsia, stomach pain, gastroenteritis, increased salivation, paralytic ileus
Hepato-biliary disorders	*Frequency not known*: Hepatic function abnormalities (including jaundice and hepatocellular damage)[5], cholestasis intrahepatic, severe hepatic disorders such as hepatitis/fulminant hepatitis, hepatic failure with potential fatal outcome
Skin and subcutaneous tissue disorders	*Less frequent:* Skin rash
	Frequency not known: Pruritus, hyperhidrosis
Musculoskeletal, connective tissue and bone disorders	*Frequency not known*: Arthralgia, weakness, muscle tremors, pain in limb, back pain, myalgia
Renal and urinary disorders	*Frequency not known*: Micturition disorder
Reproductive system and breast disorders	*Less frequent:* Priapism [2]
General disorders and administration site conditions	*Frequency not known*: Weakness, oedema, influenza-like symptoms, fatigue, chest pain, fever
Investigations	*Frequency not known*: Elevated liver enzymes

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

[2] See section 4.4

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

[5] Adverse effects on hepatic function, sometimes severe, have been reported. Should such effects occur, BIOTECH 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 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

Signs and symptoms of an overdosage may include drowsiness, loss of muscle coordination, nausea and vomiting, priapism. In more serious cases coma, tachycardia, hypotension, hyponatraemia, convulsions, respiratory arrest, have been reported. ECG changes may include bradycardia, QT prolongation and torsade de pointes. Symptoms may appear 24 hours or more after overdose.

No specific antidote is known. Activated charcoal should be considered in adults who have ingested more than 1 g BIOTECH TRAZODONE, or in children who have ingested more than 150 mg BIOTECH TRAZODONE within 1 hour of presentation.

Observe for at least 6 hours after ingestion. Monitor blood pressure, 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 (0,1 to 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 is symptomatic and supportive in the case of hypotension and excessive sedation. If severe hypotension persists consider use of inotropes, e.g., dopamine or dobutamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: other antidepressants, ATC code: N06A x05.

Trazodone is a triazolpyridine antidepressant also known as an atypical antidepressant. It weakly inhibits the reuptake of serotonin at presynaptic neurones and has an antagonistic action at 5-ht2a/2c receptors. It does not appear to have significant antimuscarinic properties but has a marked sedative effect.

5.2 Pharmacokinetic properties

Absorption:

Trazodone is readily absorbed from the gastrointestinal tract. Absorption is affected by food.

Distribution:

Protein binding is high at about 89 to 95 %.

Biotransformation:

Trazodone is extensively metabolised in the liver to its active metabolite m-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4.

Elimination:

Trazodone is mainly excreted in the urine, almost entirely in the form of its metabolites, either in free or in

conjugated form, some is excreted via biliary elimination in the faeces.

The terminal elimination half-life of trazodone is 5 to 9 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silica anhydrous

Lactose monohydrate

Magnesium stearate

BIOTECH TRAZODONE 50:

Capsule body:	*Capsule cap:*
Gelatine	Erythrosin
Indigo carmine	Gelatine
Yellow iron oxide	Patent blue V
	Titanium dioxide

BIOTECH TRAZODONE 100:

Capsule body:	*Capsule cap:*
Gelatine	Erythrosin
Titanium dioxide	Gelatine
Yellow iron oxide	Patent blue V
	Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place at or below 25 °C and protect from light.

Keep the capsules in the blister in the outer carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVdC and silver aluminium foil blister strips each containing 10, 12 or 14 capsules per strip. The strips are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

BIOTECH LABORATORIES (PTY) LTD.

Block K West,

Central Park

400 16th Road

Halfway House

Midrand

Gauteng, 1685

8 REGISTRATION NUMBER(S)

BIOTECH TRAZODONE 50: 43/1.2/0698

BIOTECH TRAZODONE 100: 43/1.2/0699

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of Registration: 10 April 2014

10 DATE OF REVISION OF THE TEXT

29 August 2024.