SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

DEMETRIN® 10 mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of prazepam.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each tablet contains 93,73 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

A white, slightly convex tablet with a bisecting score on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term relief of anxiety-tension states resulting from stressful circumstances, anxiety associated with anxiety neurosis and other psychoneuroses, and as an adjunct in other disease states in which anxiety is manifested.

DEMETRIN is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Posology

DEMETRIN is administered orally, usually in divided doses. The usual daily dose is 30 mg. The dose should be adjusted gradually within the range of 20 to 60 mg daily in accordance with the response of the patient. Drowsiness and fatigue may occur in some patients with moderate anxiety receiving higher doses on a daily basis.

In elderly or debilitated patients, it is advisable to initiate treatment at a daily dose of 10 to 15 mg (see section 4.4).

A single, daily dose at bedtime usually ranges between 20 to 40 mg.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Treatment period

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in the case of a patient being symptom free.

The overall duration of treatment should, generally, not be more than 6 - 8 weeks, including a tapering-off process. In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

Paediatric population

The safety and efficacy of DEMETRIN in children have not been investigated.

Method of administration

For oral use.

4.3 Contraindications

DEMETRIN is contraindicated in patients with:

- known hypersensitivity to prazepam, other benzodiazepines or to any excipients of DEMETRIN listed in section 6.1
- acute pulmonary insufficiency
- myasthenia gravis
- severe respiratory insufficiency
- severe hepatic insufficiency
- sleep apnoea syndrome
- Pregnancy and during breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2). The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in the case of a patient being symptom free. The overall duration of treatment should, generally, not be more than 6 – 8 weeks, including a tapering-off process. Extension beyond these periods should not take place without re-evaluation of the patient's status.

It may be useful to inform the patient, when treatment is started, that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms, should they occur while DEMETRIN is being discontinued.

Patients taking DEMETRIN for prolonged periods should have blood counts and liver function tests periodically.

Paradoxical reactions such as acute hyperexcitable states with rage may occur. If these occur, DEMETRIN should be discontinued. Such reactions are more frequent in children and in the elderly.

Caution should be exercised when DEMETRIN is given to porphyric patients.

Particular caution should be exercised:

- with the elderly and debilitated – who are at particular risk of over sedation, respiratory depression and ataxia. The initial oral dosage should be reduced in these patients.
- in patients with pulmonary disease and limited pulmonary reserve.
- in patients suffering from impairment of renal or hepatic function.
- in patients suffering from anxiety accompanied by an underlying depressive disorder.
- in patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together. Patients should be cautioned against the additive effect of alcohol. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.

- in patients with glaucoma or myasthenia gravis because of possible deleterious effects attributed to the benzodiazepines in such patients.

DEMETRIN is not recommended for the primary treatment of psychotic illness. DEMETRIN should not be used alone to treat depression or anxiety with depression; suicide may be precipitated in such patients.

Dependence

As there is a potential for abuse and development of physical and psychic dependence, especially with prolonged use and high doses, extreme caution should be observed in patients who are considered to have a psychological potential for drug dependence; these would include patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, tremor, abdominal and muscle pain, extreme anxiety, tension, restlessness, confusion, irritability, vomiting and sweating. In severe cases the following symptoms may occur; derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound effects

A transient syndrome, whereby the symptoms that led to treatment with DEMETRIN recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Tolerance

Tolerance to benzodiazepines may develop from continued therapy. Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for some weeks.

Lactose intolerance

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

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines, including DEMETRIN, produce additive CNS depressant effects, including respiratory depression, when co-administered with other CNS depressants such as opioids, phenothiazines, narcotics, barbiturates, monoamine oxidase inhibitors and other antidepressants (see section 4.4).

CYP3A4 inhibitors may reduce the metabolism of DEMETRIN and increase the potential for toxicity.

Combinations containing any of the following may also interact with DEMETRIN: Erythromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice.

Oral contraceptives can increase the effects of DEMETRIN because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased effects of DEMETRIN.

DEMETRIN should be combined cautiously with clozapine because this could cause additive CNS depressant effects. Severe confusion, hypotension and respiratory depression have occurred rarely in those patients receiving clozapine concurrently or following benzodiazepine therapy. In patients receiving concomitant clozapine, the starting doses of DEMETRIN should be approximately one-half of the usual dose until experience with the patient has been gained.

4.6 Fertility, pregnancy and lactation

Pregnancy

DEMETRIN is contraindicated during pregnancy and in women of childbearing potential not using contraception. When DEMETRIN is prescribed to a woman of child-bearing age, the woman should be advised to inform her medical practitioner if she wishes to become or is already pregnant, so that the medical practitioner can take the decision to discontinue treatment.

When DEMETRIN is administered for medical reasons during the third trimester of pregnancy or during labour, DEMETRIN and its metabolites cross the placental barrier and may cause the floppy-infant syndrome (characterised by central respiratory depression, hypothermia, hypotonia and poor sucking) and withdrawal syndrome (tremors, irritability, hypertonicity, diarrhoea/vomiting and vigorous sucking) in the new-born.

Breastfeeding

DEMETRIN should not be administered to lactating mothers.

Fertility

Studies in animals have shown reproductive toxicity.

The use of DEMETRIN in high doses decreased male fertility in rats possibly due to a decrease in spermatogenesis. A decrease in fertility and female mating have also been observed in rats.

4.7 Effects on ability to drive and use machines

Patients should be advised, particularly at the initiation of therapy, not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery. In these situations, impaired decision making could lead to accidents.

4.8 Undesirable effects

The administration of DEMETRIN is restricted to adults only (18 and above).

Tabulated summary of adverse reactions

The table below contains side effects categorised as follows utilising the incidence rates: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000).

MedDRA System organ class	**Frequency**	**Undesirable effects**
Psychiatric disorders	Common	Confusion, depression, vivid dreams
	Very common	Drowsiness

Nervous system disorders	Common	Ataxia, dizziness, headache, hyperactivity, light-headedness, slurred speech, tremor
	Uncommon	Syncope
Eye disorders	Common	Blurred vision
Cardiac disorders	Common	Palpitation
Gastrointestinal disorders	Common	Dry mouth, gastrointestinal disorder
Skin and subcutaneous tissue disorders	Common	Diaphoresis, skin rash
	Uncommon	Pruritus
Musculoskeletal and connective tissue disorders	Common	Joint pains
Renal and urinary disorders	Uncommon	Urogenital disorder
General disorders and administration site conditions	Common	Fatigue, weakness
	Uncommon	Swelling of feet
Investigations	Very rare	Decreased blood pressure, abnormal liver function test, increased weight

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

Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension. Vomiting should be induced. General supportive care with close observation is indicated. Hypotension may be controlled with noradrenaline or another suitable vasopressors e.g. levarterenol bitartrate, or metaraminol bitartrate.

Flumazenil (as an adjunct to, not as a substitute for, overdosage treatment) is indicated for the complete or partial reversal of the sedative effects of the medicine. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. Consult the complete flumazenil package insert prior to use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6 Tranquillisers

Prazepam is a benzodiazepine derivative with anxiolytic and central muscle relaxant activity.

Benzodiazepines exert their effects through enhancement of the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex. GABA is an inhibitory neurotransmitter that exerts its effects at specific receptor subtypes designated GABA-A and GABA-B. GABA-A is the primary receptor subtype in the CNS and is thought to be involved in most of the inhibitory neurotransmission in the CNS.

Benzodiazepines enhance the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of GABA to the site opens the chloride channel resulting in a hyperpolarised cell membrane that prevents further excitation of the cell.

Benzodiazepines reportedly act as agonists at the benzodiazepine receptors, which have been shown to form a component of a functional supramolecular unit known as the benzodiazepine-GABA receptor-chloride ionophore complex.

5.2 Pharmacokinetic properties

Absorption and distribution

Prazepam is readily and completely absorbed from the gastro-intestinal tract independently from the gastric pH.

The bioavailability of desalkylprazepam due to prazepam is 51 ± 5 %. Prazepam pharmacokinetics is characterized by constant blood levels and absence of plasma peaks. After single doses of 20 mg prazepam tablets the highest blood level of the active metabolite is reached after 5 - 6 hours; then blood levels slowly decrease. The distribution volume is 14,4 ± 5,1 l/kg. Prazepam is extensively bound (97,5 %) to plasma proteins. Following repeated doses, blood concentrations increase in several days reaching the steady-state at day 9. After discontinuation of the drug, blood levels decrease gradually.

Biotransformation

Because of extensive first-pass metabolism in the liver, prazepam is not present - or present in very small amounts - in peripheral blood. The principal active metabolite found in peripheral blood is desalkylprazepam. The other major metabolites include 3-hydroxyprazepam and oxazepam; they are partially conjugated with glucuronic acid, ready for excretion in the urine, and have no clinical activity.

Elimination

The elimination half-life of the active metabolite is 60 hours and it is more prolonged in the elderly, in obese patients and in patients with liver disease and with hepatic cirrhosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool, dark (at or below 25 ºC) dry place.

6.5 Nature and contents of container

Clear PVC/Aluminium foil blisters of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

G/2.6/188

9. DATE OF FIRST AUTHORISATION

12 November 1975

10. DATE OF REVISION OF THE TEXT

14 September 2022

NAMIBIA:

Reg. No.: 90/2.6/00763