SCHEDULING STATUS S5

PROPRIETARY NAME (AND DOSAGE FORM)

Demetrin 10 mg (Tablet)

COMPOSITION

Each tablet contains 10 mg of Prazepam.

Demetrin tablets contain the following inactive ingredients: maize starch, lactose monohydrate, magnesium stearate, microcrystalline cellulose and silica, colloidal anhydrous.

PHARMACOLOGICAL CLASSIFICATION

A 2.6 Tranquillisers

PHARMACOLOGICAL ACTION

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 hyperpolarized 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.

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.

CONTRA-INDICATIONS

Demetrin is contra-indicated in patients with a known hypersensitivity to prazepam or other benzodiazepines; or who have acute narrow-angle glaucoma, or acute pulmonary insufficiency.

WARNINGS

Duration of treatment:

The duration of treatment should be as short as possible (See *Dosage and directions for use*). 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.

Particular caution should be exercised:-

(1) With the elderly and debilitated – who are at particular risk of oversedation, respiratory depression and ataxia. The initial oral dosage should be reduced in these patients.

(2) In patients with pulmonary disease and limited pulmonary reserve.

(3) In patients suffering from impairment of renal or hepatic function.

(4) In patients suffering from anxiety accompanied by an underlying depressive disorder.

(5) 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.

(6) 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.

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.

INTERACTIONS

Phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants – will potentiate the action of Demetrin.

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, ritinovir 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 they 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.

PREGNANCY AND LACTATION

Demetrin is not recommended during pregnancy until such time as its safety in pregnancy has been established. Given 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. It should not be administered to lactating mothers.

DOSAGE AND DIRECTIONS FOR USE

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 *Warnings*) A single, daily dose at bedtime usually ranges between 20 & 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.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

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

The table below contains side-effects categorized as follows utilizing the incidence rates: Very common ≥ 1/10 (≥ 10 %); Common ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %), Rare ≥ 1/10 000 and < 1/1000 (≥ 0,01 % and < 0,1 %); Very rare < 1/10 000 (< 0,01 %).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Psychiatric Disorders	*Common*	Confusion, depression, vivid dreams
Nervous System Disorders	*Very Common*	Drowsiness
	Common	Dizziness, lightheadedness, ataxia, headache, tremor, slurred speech, stimulation
	Uncommon	Syncope
Eye Disorders	*Common*	Blurred vision
Cardiac Disorders	*Common*	Palpitation
Gastrointestinal Disorders	*Common*	Dry mouth, various gastrointestinal complaints
Skin and Subcutaneous Tissue Disorders	*Common*	Diaphoresis, transient skin rashes
	Uncommon	Pruritus
Musculoskeletal and Connective Tissue Disorders	*Common*	Joint pains
	Uncommon	Swelling of feet
Renal and Urinary Disorders	*Uncommon*	Various genitourinary complaints
General Disorders and Administration Site	*Common*	Fatigue, weakness

Conditions		
Investigations	*Very Rare*	Transient and reversible aberrations of liver function tests, slight decreases in blood pressure, increases in body weight

Paradoxical reactions such as acute hyperexcitable states with rage may occur. If these occur, the medication should be discontinued.

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension. Vomiting should be induced. The stomach should be emptied by gastric lavage. 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 drug. 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.

IDENTIFICATION

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

PRESENTATION

Securitainers of 100 and 500 tablets.

Clear PVC/Aluminium foil blisters of 100 tablets.

STORAGE INSTRUCTIONS

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

G/2.6/188

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