Proposed Professional Information

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BETAPAM (TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg diazepam.

Contains sugar (lactose monohydrate): 145,7 mg per tablet

Contains TARTRAZINE

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Yellow, biconvex, scored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BETAPAM is used in the treatment of anxiety in neurotic patients, and for pre-operative medication. It may be effective in relieving the acute symptoms of the alcohol withdrawal syndrome.

BETAPAM is only indicated when the disorder is severe, disabling or when the individual is subject to extreme stress.

BETAPAM is indicated for the following conditions:

Anxiety: symptomatic relief of anxiety, tension and other somatic or psychological complaints associated with the anxiety syndrome. It can also be used as an adjunct to the treatment of anxiety or excitation associated with psychiatric disorders.

Muscle relaxation: as an adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation). It can also be used to combat spasticity arising from damage to spinal and supraspinal interneurons such as cerebral palsy and paraplegia, as well as athetosis and stiff-man syndrome.
Treatment should be as short as possible. The patient should be assessed regularly and the need for continued treatment should be re-evaluated especially when the patient is symptom-free. The overall duration of treatment of anxiety should not be more than 8 to 12 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.

4.2 Posology and method of administration

Duration of treatment

The duration of treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment evaluated, especially if the patient is symptom free. It should not exceed 2 - 3 months, including the tapering-off period. Extension beyond this period should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms, should they occur during withdrawal.
There is evidence that, in case of short-acting benzodiazepines, withdrawal phenomena can become manifest within the dosage interval especially when the dosage is high. When long-acting benzodiazepines such as diazepam are being used, it is important to warn against changing to short acting benzodiazepines as withdrawal symptoms may develop.

Standard adult dosage

For optimal effect, the dosage should be carefully individualised. Treatment should begin at the lowest effective dose appropriate to the particular condition and the maximum dose should not be

exceeded.

Average adult dosage for oral administration: Initial dose: 5 - 10 mg. Depending on symptom severity, the usual dose is 5 - 20 mg daily. The maximum single oral dose for adults should not exceed 10 mg.

Special dosage instructions

Chronic respiratory depression, Elderly and debilitated patients:

Elderly and debilitated patients who are at particular risk of over sedation, respiratory depression and ataxia should be given half of the usual adult dose. These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or frequency of administration to prevent overdose due to accumulation.

Impaired hepatic or renal function:

Patients with impaired hepatic function should be given a reduced dose.

The usual precautions in treating patients with impaired renal function should be observed.

Children's dosage: 0,1 - 0,3 mg/kg bodyweight daily.

BETAPAM should not be given to children without careful assessment of the indication; the duration of treatment must be kept to a minimum.

Safety and efficacy have not been demonstrated in children below 6 months of age.

4.3 Contraindications

BETAPAM is contraindicated in patients with:

- a known history of hypersensitivity to benzodiazepines;
- severe respiratory insufficiency;
- severe hepatic insufficiency;
- sleep apnoea syndrome;

- myasthenia gravis;

BETAPAM is not recommended for the primary treatment of psychotic illness.

BETAPAM should not be used alone to treat depression or anxiety associated with depression as suicide

may occur in such patients.

Dependence on other CNS depressants including alcohol, except in the acute withdrawal reactions. (See section 4.4).

4.4 Special warnings and precautions for use

Concomitant use of alcohol/CNS depressants

The concomitant use of **BETAPAM** with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of **BETAPAM** possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression. (See section 4.5).

Medical history of alcohol or drug abuse

BETAPAM should be used with extreme caution in patients with a history of alcohol or drug abuse, see Medicine abuse and dependence below.

BETAPAM should be avoided in patients with dependence on CNS depressants including alcohol. (see section 4.3).

An exception to the latter is the management of acute withdrawal reactions.

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression, (see section 4.3). Lower doses should also be used for elderly and debilitated patients.

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using **BETAPAM**. Should this occur, the use of **BETAPAM** should be discontinued. They are more likely to occur in children and in the elderly.

Amnesia

It should be borne in mind that **BETAPAM** may induce anterograde amnesia. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Tolerance

Some loss of response to the effects of **BETAPAM** may develop after repeated use for a prolonged period of time.

Children

Since the safety and effectiveness in paediatric patients below the age of 6 months have not been established, **BETAPAM** should be used in this age group with extreme caution and only when other therapeutic alternatives are not available.

Medicine abuse and dependence

Dependence

There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence is greater in patients with a medical history of alcohol and/or drug abuse. **BETAPAM** should be used with extreme caution in these patients.

Withdrawal

Once physical dependence had developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, convulsions, extreme anxiety, tension, restlessness, confusion and irritability. 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. Withdrawal symptoms may occur after long periods of ordinary therapeutic doses.

BETAPAM may increase the frequency and severity of attacks of grand mal epilepsy, during treatment or abrupt withdrawal.

Rebound anxiety

A transient syndrome, whereby the symptoms that led to treatment with **BETAPAM**, 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 and rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be gradually decreased.

Duration of treatment

The duration of treatment should be as short as possible. (see section 4.2). The overall duration of treatment, generally, should not be more than 8 to 12 weeks, including the tapering-off process.

Caution should be observed in patients suffering from anxiety accompanied by an underlying depressive disorder.

The action of other central nervous system depression substances such as narcotics, barbiturates and monoamine oxidase inhibitors may be enhanced. (see section 4.3).

Withdrawal should be gradual in patients receiving high doses for prolonged periods of time.

Patients should be cautioned regarding the additive effect of alcohol.

BETAPAM should be given with caution to the elderly, and to patients with hepatic or renal dysfunction, obstructive airways disease and arteriosclerosis.

BETAPAM should be given with caution to infants, who may not be able to metabolise diazepam. (see section 4.6).

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

BETAPAM contains Tartrazine which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of Tartrazine sensitivity in the general population is currently thought to be low it is frequently seen in patients who also have aspirin sensitivity.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic Interactions

Enhanced effects of sedation, respiration, and haemodynamics may occur when **BETAPAM** is coadministered

with other centrally acting depressants such as antipsychotics, anxiolytics or sedatives, antidepressants, hypnotics, anticonvulsants, narcotic analgesics, anaesthetics and sedative antihistamines, or alcohol.

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases cardiorespiratory depression with increased risk of apnoea.

Alcohol should be avoided in patients receiving **BETAPAM**. (See section 4.4 and 4.9).

Pharmacokinetic Interactions

The oxidative metabolism of diazepam, leading to the formation of N-desmethyldiazepam, of 3 hydroxydiazepam (tenazepam) and of oxazepam, is mediated by CYP2C19 and CYP3A cytochrome P450 isoenzymes.

As shown by in vitro study, the hydroxylation reaction is carried out mainly by CYP3A isoform whereas the N-desmethylation is mediated by both CYP3A and CYP2C19.

Results from in vivo studies in human volunteers have confirmed the in vitro observations.

In consequence substrates, which are modulators of CYP3A and or of CYP2C19, may potentially alter the pharmacokinetics of diazepam. Medicines like cimetidine, ketoconazole, fluvoxamine, fluoxetine and omeprazole which are CYP3A or CYP2C19 inhibitors may lead to increased and prolonged sedation. There have also been reports that the metabolic elimination of phenytoin is affected by diazepam.

Cisapride may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of diazepam for use in pregnancy has not been established. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. Continuous administration of benzodiazepines during pregnancy may give rise to the so-called floppy-infant syndrome, manifested by hypotension, reduced respiratory function and hypothermia in the newborn child. Withdrawal symptoms in newborn infants have been reported with **BETAPAM**. Special care must be taken when **BETAPAM** is used during labour and delivery, as high single doses may produce irregularities in the foetal heart rate and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the medicine is not yet fully developed (especially in premature infants).

Lactation:

Since diazepam passes into breast milk, **BETAPAM** should not be administered to breast feeding mothers.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

System Organ Class	Frequency	Adverse Reaction
Psychiatric disorders	Less frequent	Drowsiness, confusion, numbed emotions, depression, reduced alertness, increase or decrease in libido. Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. If these occur, **BETAPAM** should be discontinued. There is potential for abuse. Withdrawal symptoms (including convulsions) have occurred following abrupt cessation, especially in patients who have received large doses for prolonged periods.

		Physical and psychic dependence, (see section 4.4).
Nervous system disorders	Less frequent	Fatigue, headache, ataxia, dizziness, hypersalivation, slurred speech, dysarthria, tremor, numbed emotions, anterograde amnesia – (see section 4.4), reduced alertness, dry mouth, vertigo. **BETAPAM** may increase the frequency and severity of attacks of grand mal epilepsy, during treatment or abrupt withdrawal.
Eye disorders	Less frequent	Diplopia, blurred vision
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Cardiac failure including cardiac arrest, variations in pulse rate
Vascular disorders	Less frequent	Hypotension, variations in pulse rate, circulatory depression
Respiratory, thoracic and mediastinal disorders	Less frequent	Circulatory depression
Gastrointestinal disorders	Less frequent	Constipation, nausea
Hepato-biliary disorders	Less frequent	Elevated transaminases and alkaline phosphatase, jaundice

Skin and subcutaneous tissue disorders	Less frequent	Skin reactions
Renal and urinary disorders	Less frequent	Incontinence, urinary retention
General disorders and administration site conditions	Frequent	Fatigue, drowsiness and muscle weakness; they are usually dose-related. Drowsiness is more common in elderly and debilitated patients and in those receiving high doses.
Investigations	Less frequent	Elevated transaminases and alkaline phosphatase.
Injury and poisoning	Less frequent	There have been reports of falls and fractures in benzodiazepine users, including **BETAPAM.** The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

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 Reaction Reporting form",** found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/index/8

4.9 Overdose

Symptoms

Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension.

BETAPAM commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of **BETAPAM** may be life-threatening if the medicine is taken alone, and may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. **BETAPAM**'s respiratory depressant effects are more serious in patients with respiratory disease. **BETAPAM** increases the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

Further absorption should be prevented using an appropriate method e.g. treatment within 1 - 2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off.

Flumazenil is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6 Tranquilisers

Pharmacotherapeutic group: ATC code: N05B A01

Diazepam is a long-acting benzodiazepine hypnotic with anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnesic properties.

The major sites of action of diazepam on the spinal reflexes are supraspinal. However, this action is in part mediated by the brain stem reticular system. It depresses the duration of electrical after discharge in the limbic system, including the septal region, amygdala and hippocampus. These actions result from potentiation of the neural inhibition that is mediated by Gamma-aminobutyric acid (GABA).

5.2 Pharmacokinetic properties

Absorption

Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations appearing 30 to 90 minutes after oral ingestion.

Distribution

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98 %). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk. The volume of distribution at steady state is 0,8 - 1,0 ℓ/kg. The half-life of distribution is up to 3 hours.

Metabolism

Diazepam is mainly metabolised to the pharmacologically active metabolites such as N-desmethyldiazepam, temazepam and oxazepam.

The oxidative metabolism of diazepam is mediated by CYP3A and CYP2C19 isoenzymes.

Oxazepam and temazepam are further conjugated to glucuronic acid.

Elimination

The decline in the plasma concentration-time profiles after oral and i.v. administration of diazepam is biphasic; an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase (half-life up to about 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly into the urine, predominantly in their conjugated forms. The clearance of diazepam is 20 – 30 mℓ/min.

Pharmacokinetics in special populations

The elimination half-life may be prolonged in the newborn, in the elderly and in patients with liver disease. In renal impairment the half-life of diazepam is unchanged.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Certolake Tartrazine (C.I. 19140)
- Lactose monohydrate
- Magnesium stearate
- Microcrystalline cellulose
- Starch Maize

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months – Amber PVC containers of 30,100, 500, and 1000 tablets, polypropylene containers of 100 and 500 tablets and H.D.P.E. bucket of 5000 tablets.

15 Months – Patient ready packs of different pack sizes.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Amber PVC containers of 30,100, 500, and 1000 tablets.

Polypropylene containers of 100 and 500 tablets.

H.D.P.E. Bucket of 5000 tablets.

Patient ready packs of different pack sizes.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 Lautre Road,

Stormill, Ext.1,

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

L/2.6/185 (S.A)

NS3	90/2.6/00367 (Namibia)
Botswana List No.: B9314845	

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 1979

10. DATE OF REVISON OF THE TEXT

19 January 2022