PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

Pharma-Q Diazepam Injection 10 mg/2 ml solution for injection

COMPOSITION:

Each 2 ml ampoule contains 10 mg of diazepam with 5 % *m/v* benzoate buffer, 1,5 % *v/v* benzyl alcohol and 19,2 % *v/v* ethanol.

Excipients: Hydrochloric acid, propylene glycol, sodium hydroxide, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A. 2.6 Tranquillizers.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

The effect of diazepam, a benzodiazepine, results from its action on the central nervous system i.e. sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and anticonvulsant activity.

Pharmacokinetic properties:

Elimination follows a biphasic pattern, with a rapid distribution phase, followed by a prolonged terminal elimination phase of 1 to 2 days. The half-life of its principal metabolite, desmethyldiazepam, is 2 to 5 days. It is extensively metabolized in the liver and in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. It is extensively bound to plasma proteins (98 - 99 %). Diazepam is excreted in the urine, mainly as metabolites.

In addition to crossing the blood-brain barrier, diazepam and its metabolites also cross the placental barrier and is excreted in breast milk.

INDICATIONS:

Pharma-Q Diazepam Injection 10 mg/2 ml is used for:

- As an anxiolytic in anxiety and tension states.
- As a sedative.
- As pre-medication to surgical and other procedures.
- In the control of muscle spasm as in tetanus.
- In the management of alcohol withdrawal syndrome.
- For the control of status epilepticus.
- To facilitate labour (see **PREGNANCY AND LACTATION**).

Pharma-Q Diazepam Injection 10 mg/2 ml is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

CONTRAINDICATIONS:

Pharma-Q Diazepam Injection 10 mg/2 ml is contraindicated in:

- Patients with known hypersensitivity to diazepam or benzodiazepines.
- Patients who are infants as infants may be unable to metabolize diazepam.
- Patients who are pregnant as safety and efficacy has not been established (see **PREGNANCY AND LACTATION**).
- Patients who are breastfeeding (see **PREGNANCY AND LACTATION**)

WARNINGS and SPECIAL PRECAUTIONS:

Pharma-Q Diazepam Injection 10 mg/2 ml:

- Caution should be taken when administered to patients with impaired liver, kidney or respiratory function and patients with closed-angle glaucoma.
- Elderly and debilitated patients are especially sensitive to its side effects (over sedation, respiratory depression and ataxia).
- The effects may be enhanced by alcohol, barbiturates, narcotics and other depressants of the central nervous system.
- Should be avoided in psychotic patients unless there is a marked component of anxiety in their illness.
- Should be avoided in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency or sleep apnoea and should be administered with care in those with chronic pulmonary insufficiency.
- When given intravenously in the undiluted form, the injection should be administered at a rate not exceeding 5 mg/minute.
- There is potential for abuse and dependence, especially with prolonged use and high loses.
- Withdrawal symptoms may occur after long periods of ordinary therapeutic doses.

Special precautions:

Pharma-Q Diazepam Injection 10 mg/2 ml:

- Use with other agents that possess central nervous system depressant properties may enhance the sedation or respiratory and cardiovascular depression e.g. alcohol, antidepressants, anti-histamines, general anaesthetics, other hypnotics or sedatives, neuroleptics and opioid analgesics.
- Care should be taken in patients with personality disorders as diazepam-induced disinhibition may precipitate suicide or aggressive behaviour.
- Caution is required in patients with organic brain changes, particularly arteriosclerosis.
- In cases of bereavement, psychological adjustment may be inhibited by diazepam.

- Pain and thrombophlebitis may occur with some intravenous formulations of diazepam.
- Diazepam is not recommended for the primary treatment of psychotic illness. Diazepam should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients). Diazepam should be used with extreme caution in patients with history of alcohol or drug abuse.

Dependence:

There is potential for abuse and the development of physical and psychic dependence, especially with prolonged use and high doses. The risk of dependence is also greater in 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, muscle pain, 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.

Rebound effects:

A transient syndrome whereby the symptoms that led to treatment with diazepam recur in an enhanced form 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 (see **Duration of treatment-DOSAGE AND DIRECTIONS**).

Effects on the ability to drive and use machines:

Pharma-Q Diazepam Injection 10 mg/2 ml causes drowsiness and impaired concentration.

Affected patients should not drive or operate machinery, because loss of concentration could lead to serious accidents.

INTERACTIONS:

Pharma-Q Diazepam Injection 10 mg/2 ml:

May interact with other medicines. Enhanced sedation or respiratory depression may occur if given with medicines that cause central nervous system (CNS) depression or with medicines that interfere with the metabolism of **Pharma-Q Diazepam Injection 10 mg/2 ml** since it is extensively metabolized by hepatic microsomal enzymes.

Pharma-Q Diazepam Injection 10 mg/2 ml may interact with the following medicines. Its effects may be enhanced or reduced by these medicines:

- **Narcotic analgesics and other sedatives and muscle relaxants:** Additive sedative effect (e.g. fentanyl).
- **Antibiotics:** Enhanced effect. Antibiotics inhibit hepatic enzymes. Increases concentrations of diazepam (e.g. erythromycin, clarithromycin).
- **HIV medicines:** Enhanced effect. HIV medicines inhibit hepatic enzymes. Increases concentrations of diazepam (e.g. ritonavir).
- **Antifungals:** Enhanced effect. Antifungals inhibit hepatic enzymes. Increases concentrations of diazepam (e.g. itraconazole, ketoconazole).
- **Anti-epileptics:** Reduced effect. Anti-epileptics induce hepatic enzymes (e.g. carbamezapine, phenobarbitone, phenytoin).
- **Antidepressants:** Additive effects (e.g. fluoxetine, fluvoxamine).
- **Antihistamines and other cold and flu preparations:** Additive effects (e.g. diphenhydramine).

- **Antihypertensives and medicines used for the heart:** Increased effects (e.g. propranolol, diltiazem, verapamil).
- **Anti-Parkinson's medicine:** Reduces the effect of levodopa.
- **Gastro-intestinal agents:** Increased effects (e.g. cimetidine, omeprazole).
- **General anaesthetics:** Synergistic effects (e.g. halothane).
- **Alcohol:** Additive effects.

PREGNANCY AND LACTATION:

Pharma-Q Diazepam Injection 10 mg/2 ml:

Pregnancy:

- Contraindicated in pregnancy (see **CONTRAINDICATIONS**).
- Use of diazepam in the first trimester of pregnancy has been associated with various congenital malformations in infants, but no clear relationship has been established.

Lactation:

- Contraindicated while breastfeeding, since diazepam and its metabolites crosses into breast milk (see **CONTRAINDICATIONS**)
- Infants may be unable to metabolize diazepam (see **CONTRAINDICATIONS**).

Pharma-Q Diazepam Injection 10 mg/2 ml:

Use during labour (see **INDICATIONS**)**:**

Use in the third trimester and during labour may be associated in some infants with neonatal withdrawal syndrome or the floppy infant syndrome.

Care should be taken when administered during labour because of the possible effects of central respiratory depression, hypothermia, hypotonia, poor sucking and an increase in foetal

heart rate.

Infants may also be at risk of slow development in the initial years but that may be corrected by 4 years of age.

DOSAGE AND DIRECTIONS FOR USE:

Pharma-Q Diazepam Injection10 mg/2 ml:

- Treatment should be started with the lowest recommended dose.
- The maximum dose should not be exceeded.
- It should be given by deep intramuscular or slow intravenous injection.
- Absorption following intramuscular injection is erratic and provides lower blood concentrations than those following oral administration.
- Intravenous injection should be carried out slowly into a large vein of the antecubital fossa at a recommended rate of not more than 1 ml of a 0,5 % solution (5 mg) per minute to reduce the risk of thrombophlebitis.
- It should only be combined with 5 - 10 % dextrose or 0,9 % sodium chloride.
- It is advisable to keep the patient in the supine position for at least an hour after administration.
- Facilities for respiratory assistance must be available.

Dosages:

- **In severe anxiety or acute muscle spasm:**

  Pharma-Q Diazepam Injection 10 mg/2 ml may be given intramuscularly or intravenously and repeated after 4 hours.

  Higher doses may be required for treatment of delirium tremens.

- **Patients with tetanus** may be given 100 to 300 µg per kg body mass intravenously and

repeated every 1 to 4 hours. Similar doses may be given by nasoduodenal tube.

- Treatment should be as short as possible.
- The patient should be re-assessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally 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.

❖ **In status epilepticus:**

Adults:

150 to 250 µg per kg is given by intramuscular or intravenous injection and repeated if required after 30 to 60 minutes.

Children:

A suggested parenteral regimen for children with status epilepticus or severe recurrent seizures or febrile convulsions is 200 to 300 µg per kg body mass or 1 mg per year of age; if necessary these doses may be repeated 30 minutes or 1 hour later. Maintenance therapy may then follow.

❖ **Dose in minor surgical procedures and dentistry:**

100 to 200 µg per kg by injection adjusted to the patient's requirements.

❖ **Sedative dose for children:**

Up to 200 µg per kg body mass.

❖ **Elderly and debilitated patients:**

Should be given not more than one half the usual adult dose.

❖ **Liver or kidney dysfunction:**

Dosage reduction may be required in patients with liver or kidney dysfunction.

❖ **For facilitation of labour:**

20 mg intramuscularly at 2 - 3 fingers dilation.

❖ **For anaesthesia:**

10 to 20 mg intravenously.

Duration of treatment

- The duration of treatment should be as short as possible but should not exceed 8 to 12 weeks in case of anxiety, including tapering of process.
- Extension beyond these periods 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 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 (see **Special precautions**), hereby minimizing anxiety over such symptoms, should they occur while the product is being discontinued.

SIDE EFFECTS:

Pharma-Q Diazepam Injection 10 mg/2 ml may have side effects:

Nervous system disorders:

Frequency unknown: Dizziness, vertigo, light-headedness, headache, contusion, mental depression, slurred speech or dysarthria, ataxia, tremor, amnesia and paradoxical excitation which may lead to hostility, aggression and disinhibition.

Eye disorders:

Frequency unknown: Blurred vision.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Respiratory depression may occur with high dosage and parenteral administration

Gastro-intestinal disorders:

Frequency unknown: Gastro-intestinal disturbances and changes in salivation

Hepato-biliary disorders:

Frequency unknown: Jaundice.

Renal and urinary disorders:

Frequency unknown: Urinary retention or incontinence.

Reproductive system and breast disorders:

Frequency unknown: Changes in libido.

General and administrative site disorders:

Frequency unknown: Blood disorders and hypotension may occur with high dosage and parenteral administration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See **SIDE-EFFECTS** and **WARNINGS and SPECIAL PRECAUTIONS**.

Overdosage of **Pharma-Q Diazepam Injection 10 mg/2 ml**:

- Coma, central nervous system depression, respiratory depression and cardiovascular depression may occur.
- Cardiovascular, respiratory and renal functions must be maintained.
- Treatment is intensive and symptomatic and supportive measures should be employed, such as administration of intravenous infusions to maintain electrolytic balance.
- Adequate air passage control must be observed and oxygen can be administered.
- Gastric aspiration and lavage should be performed, followed with 50 g of activated charcoal administered intragastrically.
- Hypotension, if it occurs must be controlled with sympathomimetics.

IDENTIFICATION:

A clear, colourless to pale yellow solution in amber ampoules.

PRESENTATION:

Amber glass ampoules of 10 mg diazepam per 2 ml packed in boxes of 10 or 100.

STORAGE INSTRUCTIONS:

Protect from light.

Keep at or below 25 °C.

This product may be refrigerated, but do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

32/2.6/0197

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

PHARMA-Q HOLDINGS (PTY) LTD

50 COMMANDO ROAD

INDUSTRIA WEST 2003

JOHANNESBURG

SOUTH AFRICA

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Original date of registration: 21 October 2003

Revised package insert approval: 6 March 2015