**1.3 Product Information**

**1.3.1 Summary of Product Characteristics (SmPC)**

**1. NAME OF THE MEDICINAL PRODUCT:**

JARZEPAM

**1.1 (INVENTED) NAME OF THE MEDICINAL PRODUCT**

**International Non-Proprietary Name:**

Diazepam Injection BP 10 mg/2ml

**1.2 STRENGTH**

10 mg/2ml

**1.3 PHARMACEUTICAL FORM**

Solution for Injection

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

**2.1 QUALITATIVE DECLARATION**

Each 2ml contains:

Diazepam BP……10 mg

Benzyl Alcohol BP….....2 %

(As preservative)

Water for Injections BP….q.s.

**2.2 QUANTITATIVE DECLARATION**

Each 2ml contains:

Diazepam BP……10 mg

Benzyl Alcohol BP….....2 %

(As preservative)

Water for Injections BP….q.s.

## 3. PHARMACEUTICAL FORM

Solution for Injection

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Diazepam is an anxiolytic, anticonvulsant and central muscle-relaxant. Diazepam is used to relieve anxiety and provide sedation in severe acute anxiety or agitation and for the management of agitation associated with delirium tremens.

Diazepam is used to relieve acute muscle spasm and tetanus. Acute convulsions including status epilepticus, also convulsions due to poisoning and febrile convulsions. As an adjunct during endoscopy, in dentistry, surgery, radiology. Cardiac catheterisation, cardioversion, used pre-operatively to relieve anxiety, provide sedation, light anaesthesia and anterograde amnesia.

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Diazepam Injection BP may be given IV, IM or by IV infusion.

Adults:

Severe acute anxiety or agitation:

10 mg IV or IM injection which may be repeated after an interval of not less than 4 hours.

Delirium Tremens:

10 – 20 mg IV or IM. Higher doses may be needed depending on severity of symptoms.

Acute Muscle Spasm:

10 mg IV or IM injection. Which may be repeated after an interval of not less than 4 hours.

Tetanus:

Initially an IV dose of 0.1 - 0.3 mg/kg body weight, repeated at intervals of 1 - 4 hours. Continuous IV infusion of 3 – 10 mg/kg body weight per 24 hours can also be used. The chosen dose should be related to the severity of the case and in extremely severe cases higher doses have been used.

Status epilepticus, convulsions due to poisoning:

10 – 20 mg IV or IM, repeated if necessary 30 - 60 minutes later.

If indicated, this may be followed by slow intravenous infusion (maximum dose 3 mg/kg body weight over 24 hours).

Pre-operative medication or premedication:

0.2 mg/kg body weight. The usual adult dose is 10 – 20 mg but higher doses may be necessary according to the clinical response.

Elderly or Debilitated Patients:

Doses should not exceed half those normally recommended.

Children:

Status epilepticus, convulsions due to poisoning, febrile convulsions: 0.2 - 0.3 mg/kg body weight IV (or IM) or 1 mg per year of life.

Tetanus:

As for adults.

Pre-operative medication or premedication:

0.2 mg/kg body weight. The injection should be given slowly (0.5 ml per minute).Diazepam injection should be given into a large vein of the antecubital fossa, the patient in a supine position throughout the procedure to reduce the possibility of hypotension or apnoea occurring.

**4.3 CONTRAINDICATIONS**

- Known hypersensitivity to diazepam, other benzodiazepines or propylene glycol.
- Acute pulmonary insufficiency or respiratory depression.
- Sleep apnoea syndrome.
- Marked neuromuscular respiratory weakness including unstable myasthenia gravis.
- Severe hepatic impairment.

Diazepam Injection should not be used for the primary treatment of chronic psychosis. It should not be used alone in the treatment of depression or anxiety associated with depression due to the risk of precipitation of suicide in this patient group.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Except in emergencies, a second person should always be present during the intravenous use of diazepam and facilities for resuscitation should always be available. Patients should ideally remain under medical supervision until at least one hour has elapsed from the time of injection.

They should always be accompanied home by a responsible adult, with a warning not to drive or operate machinery for 24 hours.

The IM use of diazepam injection can lead to a rise in serum creatinine phosphokinase activity, with a maximum level occurring between 12 and 24 hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

The absorption from IM injection of diazepam may be variable, particularly for the gluteal muscles. This route of administration should only be used if IV administration is not possible.

Diazepam Injection BP contains propylene glycol. There have been rare reports of propylene glycol toxicity (e.g. increased anion gap, metabolic acidosis, hyperosmolality, renal impairment) with the potential for organ system failure and circulatory shock, in patients treated with continuous infusions of diazepam. Central nervous system toxicity, including seizures, as well as unresponsiveness, tachypnoea, tachycardia and diaphoresis have also been associated with propylene glycol toxicity. Symptoms may be more likely to develop in patients with renal or hepatic impairment and in paediatric patients.

The elderly, and patients with impaired renal and/or hepatic function may be particularly susceptible to the adverse effects of diazepam listed. Dose reduction may be required.

Extreme care must be taken when administering diazepam injection to very ill patients and to those with limited pulmonary reserve, because of the possibility of respiratory depression or apnoea.

Use with caution in patients with myasthenia gravis, porphyria, known history of drug or alcohol abuse, or organic brain changes, particularly arteriosclerosis. Diazepam injection should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. The dependence potential of diazepam increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse.

Withdrawal symptoms may occur with benzodiazepines following normal use of therapeutic doses for only short periods and may be associated with physiological and psychological Sequelae.

The potential for withdrawal symptoms should be considered when treating patients for more than a few days; abrupt discontinuation should be avoided and the dose reduced gradually.

Abuse of diazepam has been reported.

Diazepam may induce anterograde amnesia. This occurs most often several hours after administration. In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines. Paradoxical reactions and disinhibition have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued. Extreme caution should be used in prescribing diazepam for patients with personality disorders. Suicide may be precipitated in patients who are depressed, as may aggressive behaviour towards self and others.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Particular attention should be paid to the potential effects of drug interactions with diazepam in the elderly.

CNS depressants:

Enhanced sedation, or respiratory or cardiovascular depression may occur when diazepam is administered concomitantly with other CNS depressants including other anticonvulsants, anxiolytics/hypnotics, sedative antihistamines, alcohol, neuroleptics, antidepressants, analgesics and anaesthetics.

Anticonvulsants:

Diazepam may increase or decrease plasma concentrations of phenytoin. Patients should be monitored for signs of increased phenytoin toxicity. Phenytoin and carbamazepine may reduce plasma levels of diazepam. Increased sedation or respiratory depression may occur with concurrent use of barbiturates. Concomitant sodium valproate may increase plasma levels of diazepam, with associated sedation.

Antidepressants:

The plasma levels of some benzodiazepines are increased by fluvoxamine. Concurrent use of selective serotonin receptor antagonists or tricyclic antidepressants may reduce attention and psychomotor performance and affect the ability to perform complex tasks (e.g. driving).

Antipsychotics:

Plasma concentrations of zotepine may be increased. Severe hypotension, collapse, loss of consciousness, respiratory depression, and potentially fatal respiratory arrest have been reported in a few patients taking benzodiazepines and clozapine. Salivary hypersecretion has also occurred. Caution is advised when initiating clozapine therapy in patients taking diazepam. There is an increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines are given with intramuscular olanzapine.

Sodium oxybate

Concomitant use of sodium oxybate (gamma hydroxybutyrate, GHB) should be avoided as benzodiazepines enhance the effects of this substance.

Antibacterials:

The metabolism of diazepam is inhibited by isoniazid, and to a lesser extent, by erythromycin. The effect of diazepam may be increased and prolonged. Known inducers of hepatic enzymes such as rifampicin may increase the clearance of diazepam.

Antivirals:

Concomitant use of amprenavir and ritonavir should be avoided, as they have been shown to reduce the clearance of benzodiazepines and may prolong their actions, with risk of extreme sedation and respiratory depression.

Alcohol:

The sedative effects of diazepam may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Gastric acid suppressants:

The metabolism of diazepam may be inhibited by cimetidine, Omeprazole and esomeprazole, resulting in increased plasma concentrations.

Antihypertensive agents:

Enhanced hypotensive effects may occur when diazepam is given with antihypertensive agents. Increased sedation may occur with alpha-blockers or moxonidine.

Disulfiram:

The metabolism of diazepam is inhibited by disulfiram resulting in increased sedation.

Levodopa:

Benzodiazepines may antagonise the effects of levodopa.

Theophylline:

Theophylline may reduce the effects of benzodiazepines.

Skeletal muscle relaxants:

Increased sedation may occur with concurrent use of baclofen or tizanidine and diazepam.

## 4.6 PREGNANCY AND LACTATION

Pregnancy:

There is no evidence as to drug safety in human pregnancy, nor is there evidence from animal studies, that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters unless there are compelling reasons.

Results of retrospective studies suggest an increased risk of congenital malformation in infants or mothers who received diazepam during the first trimester of pregnancy.

Infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. An increase in foetal heart rate has occurred after diazepam use during labour. Hypoactivity, hypotonia, hypothermia, apnoea, feeding problems, hyperbilirubinaemia and kernicterus have been reported in neonates born to mothers who receive large doses of diazepam (generally greater than 30 mg) shortly before delivery.

Lactation:

Diazepam has been detected in breast milk. If possible diazepam should be avoided during breast feeding.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no information on the effect of Artesunate on the ability to drive or use machines. The patient's clinical status should be considered when assessing ability to drive or operate machinery.

## 4.8 UNDESIRABLE EFFECTS

Most frequently reported adverse reactions associated with benzodiazepines include daytime drowsiness, sedation, unsteadiness and ataxia; these are dose-related and may persist to the following day.

Blood and lymphatic system disorders:

Very rare reports of thrombocytopenia, leucopenia, agranulocytosis

Immune system disorders:

Hypersensitivity reactions, including anaphylaxis

Metabolism and nutrition disorders:

Metabolic disorders including metabolic acidosis, increased anion gap and hyper osmolality have been reported as a consequence of propylene glycol toxicity

Psychiatric disorders:

Confusion, depression and unmasking of depression, numbed emotions, disinhibition, euphoria, appetite changes, sleep disturbance, change in libido, dependence, suicidal ideation/attempt. Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, insomnia, nightmares, hallucinations, psychoses, sexual arousal, and inappropriate behavior are known to occur with benzodiazepines including diazepam.

These are more likely to occur in children and the elderly.

Nervous system disorders:

Daytime drowsiness, sedation, dizziness, ataxia, tremor, headache, reduced alertness, dysarthria/slurred speech, transient anterograde amnesia or memory impairment.

Eye disorders:

Visual disturbance.

Ear and labyrinth disorders:

Vertigo.

Vascular disorders:

Hypotension may occur. The incidence of hypotension may be reduced by not exceeding the recommended rate of administration. Patients should be managed in the supine position and kept there throughout the procedure.

Intravenous injections of diazepam may be associated with local reactions and thrombophlebitis and venous thrombosis may occur.

Respiratory thoracic and mediastinal disorders:

Apnoea, respiratory depression, particularly with high doses. Worsening of sleep apnoea, worsening of obstructive pulmonary disease.

Gastrointestinal disorders:

Gastrointestinal disturbances (nausea, salivation changes).

Hepatobiliary disorders:

Raised liver function test values, jaundice.

Skin and subcutaneous tissue disorders:

Rash, allergic dermatitis, urticaria.

Musculoskeletal disorders:

Muscle weakness.

Renal and urinary disorders:

Urinary retention, incontinence

General disorders:

Fatigue, injection site pain or irritation

**4.9 OVERDOSE**

Symptoms:

The symptoms of a mild overdose may include confusion, somnolence, lethargy, impairment of consciousness, diminished reflexes or paradoxical excitation. In more serious cases, and especially when other CNS depressant drugs or alcohol are ingested, symptoms may include ataxia, hypotension, hypotonia, respiratory depression, coma and,

very rarely, death. Rarely, propylene glycol toxicity has been reported following higher than recommended doses.

Treatment:

Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored and supportive measures taken to maintain cardiovascular and respiratory function. Hypotension may be controlled if necessary by IV administration of adrenaline (epinephrine). Benzodiazepines are poorly dialysable. The benzodiazepine antagonist, flumazenil, may be useful in hospitalized patients for the management of benzodiazepine overdose. The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, the abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties. It is used in the treatment of anxiety and tension states, as a sedative and pre-medicant, in the control of muscle spasm as in tetanus, and in the management of alcohol withdrawal symptoms. It is of value in patients undergoing orthopaedic procedures endoscopy and cardioversion.

### 5.2 PHARMACOKINETIC PROPERTIES

Absorption:

Diazepam is highly lipid soluble and crosses the blood brain barrier. These properties qualify it for intravenous use in short term anaesthetic procedures since it acts promptly on the brain, and its initial effects decrease rapidly as it is distributed into fat deposits and tissues. Following the administration of an adequate intravenous dose of diazepam, effective plasma concentrations are usually reached within 5 minutes (ca. 150-400

ng/ml). Absorption is erratic following intramuscular administration and lower peak plasma concentrations may be obtained than those following oral administration.

Distribution:
Diazepam is extensively protein bound (95-99%). The volume of distribution is between 0.95 and 2 l/kg depending on age. Diazepam and its main metabolite, N-desmethyldiazepam, cross the placenta and are secreted in breast milk.

Metabolism:
Diazepam is metabolised predominantly in the liver. Its metabolites, N-desmethyldiazepam (nordiazepam), temazepam and oxazepam, which appear in the urine as glucuronides, are also pharmacologically active substances. Only 20% of the metabolites are detected in the urine in the first 72 hours.
Diazepam has a biphasic half life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1-2 days. For the active metabolites N-desmethyldiazepam, temazepam and oxazepam, the half lives are 30-100 hours, 10-20 hours and 5-15 hours, respectively.

Excretion:
Excretion is mainly renal and also partly biliary. It is dependent on age as well as hepatic and renal function.
Metabolism and elimination in the neonate are markedly slower than in children and adults. In the elderly, elimination is prolonged by a factor of 2 to 4. In patients with impaired renal function, elimination is also prolonged. In patients with hepatic disorders (liver cirrhosis, hepatitis), elimination is prolonged by a factor of 2.

**5.3 Preclinical safety data**

No further information other than that which is included in the Summary.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Propylene Glycol BP

Sodium Acetate Anhydrous USP

Benzyl Alcohol BP

Glacial Acetic Acid BP

Water for Injections BP

### 6.2 INCOMPATIBILITIES

None stated.

### 6.3 SHELF LIFE

36 Months

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C, Do not refrigerate. Protect from light

### 6.5 NATURE AND CONTENTS OF CONTAINER

5 x 2ml amber glass ampoules packed in a monocarton with plastic tray. such 2 monocarton is packed in an outer carton along with an insert. (2 x 5 x 2 ml)

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use. Discard any unused contents.

## 7. MANUFACTURER

Swiss Parenterals Ltd.

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