Unival®

Diazepam 5 mg Tablets

swipha

Composition
Each tablet contains Diazepam 5 mg.

Description
Pale yellow tablets with SWIPHA 5 imprinted on one side and a break score on the other side of the tablet.

Clinical Pharmacology

Pharmacodynamic Properties
Unival® is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties.
Benzodiazepines, such as **Unival®**, bind to receptors in various regions of the brain and spinal cord. This binding increases the inhibitory effects of gamma-aminobutyric acid (GABA). GABAs functions include CNS involvement in sleep induction. Also involved in the control of hypnosis, memory, anxiety, epilepsy and neuronal excitability.

Pharmacokinetic Properties

Absorption
Unival® is readily and completely absorbed from the GI tract. Peak plasma concentrations occurring within about 30-90 minutes of oral administration, a steady plasma concentration is reached after 5-6 days and is directly related to dose.

Distribution
Unival® crosses the blood-brain barrier and is highly lipid soluble, this causes the initial effects to decrease rapidly as it is redistributed into fat deposits and tissues. **Unival®** is very extensively bound to plasma proteins (98-99%). **Unival®** and its metabolites also enters breast milk and crosses the placenta freely, this may lead to accumulation in the infant or foetus.

Biotransformation
Unival® is extensively metabolised in the liver and, in addition to desmethyl diazepam, its active metabolites include oxazepam and temazepam. **Unival®** has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2-5 days of its principle active metabolite, desmethyl diazepam (nordiazepam), the relative proportion of which increases in the body on long-term administration. The plasma half-life of **Unival®** is prolonged in neonates, in the elderly, and in patients with kidney or liver disease.

Elimination
It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Indications

Adults
- The short-term relief (2-4 weeks) only, of anxiety which is severe, disabling, or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
- Cerebral palsy.
- Muscle spasm.
- As an adjunct to certain types of epilepsy (eg myoclonus).
- Symptomatic treatment of acute alcohol withdrawal.
- As oral premedication for the nervous dental patient.
- For premedication before surgery.

Children
- Control of tension and irritability in cerebral spasticity in selected cases.
- As an adjunct to the control of muscle spasm in tetanus.
- Oral premedication.

Dosage and Administration

Adults:
Anxiety states, obsessive-compulsive neuroses, and other psychiatric disorders: 5-30 mg daily in divided doses.
Insomnia associated with anxiety: 5-15 mg before retiring to bed.
Cerebral palsy: 5-60 mg daily in divided doses.
Upper motor neuronic spasticity: 5-60 mg daily in divided doses.
Muscle spasm of varied etiology, fibrositis, cervical spondylosis:
5-15 mg daily in divided doses.
Adjunct to the management of some types of epilepsy: 2-60 mg daily in divided doses.
Alcohol withdrawal: 5-20 mg, repeated if necessary, in 2 to 4 hours.
Oral pre-medication in dental patients: 5 mg the night before, 5 mg on waking and 5mg two hours before the appointment.
Oral Pre-medication before surgery: 5 mg-20 mg.

Children:
Spastic children with minimal brain damage: 5-40 mg daily in divided doses.
Oral Premedication before surgery: 2 mg-10 mg

Elderly and Debilitated Patients:
Doses should be half the above recommended doses.

Renal and Hepatic Impairment
The use of **Unival®** in hepatic impairment may precipitate coma, therefore the dose should be reduced or an alternative drug considered. In severe renal impairment the dose should be reduced.

Contraindications
Unival® is contra-indicated for patients with:
- Hypersensitivity to the active substance, benzodiazepines or to any of the excipients
- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)
- Acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency (ventilatory failure may be exacerbated)
- Myasthenia gravis (condition may be exacerbated)
- Sleep apnoea (condition may be exacerbated)
- Severe hepatic insufficiency (elimination half-life of Unival® may be prolonged)
- Acute porphyria
- **Unival®** should not be used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients
- Planning a pregnancy
- Pregnancy (unless there are compelling reasons)

Special Warnings and Precautions for Use
- The concomitant use of **Unival®** with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of **Unival®** possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression

Duration of Treatment
- The duration of treatment should be as short as possible depending on the indication. The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms. In general, treatment must not last any longer than 8-12 weeks, including the tapering off 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 starts, that it will be of limited duration and to explain precisely how the dosage will be progressively decreased.

Dependence and Withdrawal
- Withdrawal symptoms occur with benzodiazepines following normal therapeutic doses given for short periods of time.
- Use of **Unival®** may lead to the development of physical and psychic dependence. The risk of dependence increases with the dose and duration of treatment, and in patients with a history of alcoholism and drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

- 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 the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.
- Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with **Unival**® may recur in an enhanced form on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances 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.
- As sudden discontinuation of benzodiazepines may result in convulsions, particular care should be taken in patients with epilepsy, other patients who have had a history of seizures or in alcohol or drug dependants.

Tolerance
- Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardio-respiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients.
- Some loss of efficacy to the hypnotic effects of **Unival**® may develop after repeated use for a few weeks.
- Alcohol should be avoided during treatment with **Unival**® (additive CNS depression).

Amnesia
- **Unival**® may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours. Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses.
- In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.
- **Unival**® should be used with caution in patients with a history of alcohol or drug abuse as these are patients predisposed to habituation and dependence.
- Hypo-albuminaemia may predispose patient to higher incidence of sedative side effects.
- Extreme caution should be used in prescribing **Unival**® to patients with personality disorders.

Pharmacokinetic Interactions
Unival® is mainly metabolised to the pharmacologically active metabolites N-desmethyl Diazepam, temazepam and oxazepam. The oxidative metabolism of **Unival**® is mediated by CYP3A4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid. Inhibitors of CYP3A4 and/or CYP2C19 can give rise to increased concentrations of **Unival**® while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of **Unival**®.

Pharmacodynamic Interactions
If **Unival**® is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of **Unival**®, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.
Anti-epileptic drugs, Narcotic analgesics, Opioids, Compounds that affect hepatic enzymes (particularly cytochrome P450)

Antihypertensives, Vasodilators & Diuretics:
Dopaminergics, Antacids, Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir), Increased zidovudine clearance by **Unival**®.
Oral contraceptives, Theophylline, Caffeine, Grapefruit juice, Clozapine, Carbamazepine, Phenytoin
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole), Fluvoxamine, Corticosteroids, Cimetidine
Omeprazole, Esomeprazole, Isoniazid, Fluoxetine, Disulfiram, Cisapride, Levodopa, Ketamine.

Pregnancy and Lactation

Pregnancy
The safety of **Unival**® in human pregnancy has not been established. It should not be used in the first and third trimesters. There may be a small increase in the risk of congenital malformation, particularly oral cleft with the use of benzodiazepines in the first trimester but a causal relationship has not been established.

Lactation
Benzodiazepines are found in the breast milk. There is a risk of accumulation in the breastfeeding child. Benzodiazepines should therefore, not be given to breast feeding mothers.

Symptoms of Overdosage and Management

Symptoms
The symptoms of **Unival**® overdose is usually manifested by central nervous system depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma (rarely) and death (very rarely). However, as with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

Management
In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken. Following overdose oral benzodiazepines, vomiting should be induced (within 1 hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiac function in intensive care. Flumazenil may be useful as an antagonist (caution should be observed in the use of flumazenil in cases of mixed drug overdose and in epileptics treated with benzodiazepines).

Storage Condition:

Store below 30°C

Presentation:

Packed in blisters of 1 x 10 and 10 x 10 Tablets

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

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Manufactured by:
Swiss Pharma Nigeria Ltd.,
5, Dopemu Road, Agege, Lagos, Nigeria.

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