PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAME (AND DOSAGE FORM):

Tranject Ampoules

COMPOSITION:

Diazepam 10 mg per 2 ml. Preserved with 1,5 % *v/v* Benzyl alcohol

Contains 5,8 % *v/v* Alcohol

Sugar Free

PHARMACOLOGICAL CLASSIFICATION:

A2.6 Tranquillisers

PHARMACOLOGICAL ACTION:

Diazepam is a benzodiazepine derivative with anxiolytic, sedative, anti-convulsant and muscle relaxant properties. Following an intravenous injection, these effects are due to actions on selected parts of the central nervous system, particularly, the brain stem reticular system.

Diazepam binds extensively to plasma proteins and part of its biotransformation occurs via active metabolites, such as oxazepam. Therefore, the duration of action exhibits little relationship to the half-life elimination time of diazepam. The conjugated metabolites are almost entirely eliminated in the urine in a biphasic manner.

INDICATIONS:

Diazepam is indicated in various psycho-reactive (psychoneurotic) disorders, such as anxiety, behavioural disorders of neurotic origin and excitation. It is useful as an adjuvant in pre-medication before surgery or for the control of acute alcohol withdrawal syndrome. It may be indicated as an anti-convulsant in the control of status epilepticus or tetanus.

CONTRA-INDICATIONS:

Diazepam is contra-indicated in patients sensitive to similar-acting benzodiazepines. It should not be administered to infants, and caution should be exercised in patients with impaired hepatic and/or renal functions. Diazepam is not indicated for the treatment of psychotic patients.

Closed angle glaucoma.

Patients suffering from mental depression or with suicidal tendencies.

WARNINGS:

There may be a risk of dependence, similar to the alcohol and barbiturate-type, especially when administered over a prolonged period. When undiluted diazepam is given intravenously the rate of administration must not exceed 1 ml per minute (5 mg per minute).

Patients should be advised against driving a vehicle or managing equipment or any other task, where full concentration is required.

Patients should also be made aware of possible potentiation of the effects of other central nervous system depressants, such as alcohol, hypnotics or narcotics.

DOSAGE AND DIRECTIONS FOR USE:

In general, the dose of diazepam administered must be individualised.

As a guideline the usual adult doses for pre-operative medication is 5 to 10 mg intravenously or by deep intramuscular injection, while for psychoreactive disorders doses of 2 to 10 mg may be required, which may be repeated after three or fours hours if necessary.

Doses of 100 to 200 µg per kg (usually 10 to 20 mg intravenously for adults) are recommended as pre-medication or sedation in surgical or diagnostic procedures and in dentistry. It is advisable to titrate the dose according to the desired sedation response.

In severe states of anxiety and acute muscle spasms as an adjunct a dose of 5 to 10 mg administered intramuscularly or intravenously may be required which may be repeated after 4 hours.

For the treatment of acute alcohol withdrawal symptoms, an initial dose of 10 mg administered intravenously or intramuscularly, followed by 5 to 10 mg after three to four hours, if necessary.

Larger doses may be required in the control of delirium tremens.

In cases of tetanus, diazepam may be given in a dose of 100 to 300 µg per kg body weight intravenously. This dose may have to be repeated at intervals of 1 to 4 hours. A continuous drip containing 3 to 10 mg/kg/24 hours may be used alternatively.

Tranject Ampoules may be given parenterally, preferably by intravenous route, in the control of status epilepticus or severe recurrent or febrile convulsions. Doses of 150 to 250 µg per kg (10 to 20 mg) for adults and 200 to 300 µg per kg (or 1 mg per year of life) for children are recommended. These doses may be repeated if required, after 30 to 60 minutes

Recurrence of seizures may be controlled by a slow infusion of diazepam with a maximal dose of 3 mg/kg per 24 hours for adults

Elderly and debilitated patients should not be given more than one half of the recommended adult dose (usually 2 to 5 mg per dose). The dosage may be increased gradually, as needed and tolerated. A reduction of the dose may be advisable in patients with liver or kidney dysfunction

Larger veins, such as the anticubital, should be selected for the intravenous administration of diazepam and the solution must be injected at a slow rate not exceeding 1 ml per minute. The use of smaller lumen vessels and to rapid an injection rate may lead to thrombophlebitis.

The patient should be kept in a supine position for at least an hour after administration.

Diazepam may be administered by continuous intravenous infusion. However, the solution must be freshly prepared and constantly monitored because of the risk of precipitation.

Furthermore, administration sets should contain a minimum amount of polyvinyl chloride tubing and the volume control chamber should be free of cellulose propionate, because of the substantial sorption capacities of these materials for diazepam with the subsequent uncontrollable loss of activity.

Absorption of diazepam from intramuscular site may be erratic depending on the site and may provide lower blood levels than those following oral administration. It is advisable to administer diazepam deep into a deltoid muscular site for a more rapid and constant absorption rate.

Tranject Ampoules should not be administered to neonates because it contains benzyl alcohol. Besides no dosage for diazepam has been established for neonates.

IMPORTANT: If administered as an infusion, diazepam may be mixed into 5 or 10% dextrose in water or with 0,9% sodium chloride solution.

The content of the ampoule must be mixed quickly into the desired volume of the infusion, which should be at least 250 ml. Addition of other medication to the infusion should be avoided, because of the danger of precipitation of the active medicines.

Care should be taken with the parenteral administration of diazepam to avoid intra-arterial administration or extravasation, in order to reduce the possibility of vascular thrombosis, phlebitis or other local irritations.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Generally, the most frequently observed side-effects with diazepam are drowsiness and excessive sedation, especially when given in large doses to elderly patients.

Less common are depression of mood, disorientation or confusion, lightheadiness, dizziness, tremor, lethargy, ataxia, constipation, nausea, diarrhoea and changes in libido.

Blood dyscrasias, skin rashes, jaundice, dysarthria, urinary retention, incontinence, blurred vision, vertigo, slurred speech and headaches have been reported.

Diazepam enhances the effects of other central nervous system depressants and patients should be cautioned regarding the possible additive effect of alcohol.

The adverse effects most commonly encountered with parenterally administered diazepam are centrally mediated cardiovascular and respiratory depression.

Amnesia may occur, persisting for variable periods and care should be exercised especially in elderly patients, in whom drowsiness, ataxia and over-sedation are also more common.

Large doses may produce syncope and care should be taken in patients with pulmonary disease or limited pulmonary reserve.

Care must also be taken when diazepam is administered during labour, because it crosses the placenta and may lead to a possible risk of central respiratory depression, hypothermia and hypotonia of the foetus, (floppy infant syndrome). Benzodiazepines should not be administered to lactating, breast-feeding mothers and should be used judiciously during pregnancy, where they should preferably be avoided.

Diazepam should be given with caution to patients with impaired hepatic and renal function, and to infants who may not be able to metabolise diazepam.

Caution should be exercised in patients with myasthenia gravis.

The intramuscular route of administration may lead to an elevation of serum creatinine phosphokinase and should not be considered in cases of a differential diagnosis of myocardial infection. This does not occur after an intravenous administration.

Diazepam should not be mixed in a syringe containing other aqueous medications, since precipitation may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The main phenomenon occurring after a overdose of diazepam intravenously administered include coma, reversible apnoea, hypotension, respiratory depression, and rarely cardiac arrest. Confusional states, somnolesence, respiratory depression and hypotonia may be early warning signs of an impending overdosage.

The treatment is symptomatic and supportive. The patient should be monitored closely. It is essential to maintain adequate air passage at all times and oxygen may be administered.

IDENTIFICATION:

Amber glass ampoules containing a clear colourless to pale yellow solution.

PRESENTATION:

Carton with 10 x 2 ampoules.

STORAGE CONDITIONS:

Store at or below 25 ^{o}C and protect from light

Keep out of reach of children

REGISTRATION NUMBER:

28/2.6/0578

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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