Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diazemuls Emulsion for Injection 5 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains diazepam 10 mg/ 2 ml.

Excipients with known effect:
Each ampoule contains soya-bean oil 300 mg / 2 ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection
Sterile, white, opaque, oil-in-water emulsion for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Severe anxiety or agitation including delirium tremens.

2. In the control of acute muscle spasm including that associated with tetanus.

3. In the management of convulsions and of status epilepticus.

4. As pre-operative medication in minor surgery.

4.2 Posology and method of administration

Diazemuls may be administered by slow intravenous injection (1ml per min.), by intramuscular injection, or by infusion.
Diazemuls should be drawn up into the syringe immediately prior to injection. The minimum infusion rate should be 4 ml/h.

1. Severe anxiety or agitation:
The usual adult dose is 10 mg repeated 4 hourly, but should be titrated to patient response.

2. Acute Muscle Spasm:
0.1-0.3 mg/kg i.v. repeated every 1-4 hours as required, or a continuous infusion of 3-10 mg/kg every 24 hours.

3. Convulsions:
Adults: 10-20 mg i.v. or i.m.
Children: 0.2-0.3 mg/kg i.v. or i.m. (or 1 mg per year of life).
Status epilepticus: An initial dose of 0.15-0.25 mg /kg i.v. repeated in 30 to 60 minutes as required and followed if necessary by an intravenous infusion of up to 3 mg/kg over 24 hours.

4. Premedication:
0.1-0.2 mg/kg i.v. titrated to patient response.
In the elderly or debilitated patient, doses, should initially be reduced to half those stated above.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

The patient should be checked regularly at the start of the treatment in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

4.3 Contraindications

Diazemuls is contraindicated for patients with:

- Hypersensitivity to benzodiazepinesor to one or more of the excipients (see section 6.1)

- Myasthenia gravis

- Sleep apnoea syndrome

- Severe hepatic insufficiency

- Severe respiratory insufficiency

Diazepam emulsion for injection contains soya oil, which may contain soya protein. Diazepam emulsion for injection can provoke allergic reactions, presumably only in patients who are particularly sensitive to peanuts or soya.

4.4 Special warnings and precautions for use

Concomitant use of alcohol/CNS depressants
The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5)

Risk from concomitant use of opioids:
Concomitant use of diazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as diazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe diazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Medical history of alcohol or drug abuse
Diazepam should be used with extreme caution in patients with a history of alcohol or drug abuse.

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
Treatment with diazepam can result in mental or physical dependency. The risk increases with dose and duration of treatment: it is also greater in patients with a history of alcohol or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescription should be avoided and treatment should be withdrawn gradually.

Withdrawal
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: derealization, 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 a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.
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Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Sudden discontinuation of treatment with diazepam in patients with epilepsy or other patients who have had a history of seizures can result in convulsions or epileptic status. Convulsions can also be seen following sudden discontinuation in individuals with alcohol or drug abuse. Discontinuation should be gradual in order to minimize the risk of withdrawal symptoms.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2) 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 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, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.
There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to benzodiazepines with a short duration of action, as withdrawal symptoms may develop.

Amnesia
Anterograde amnesia may occur even if benzodiazepines are used within the normal dose range, though this is seen in particular at high dose levels. 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 an uninterrupted sleep of 7-8 hours (see also section 4.8). Amnestic effects may be associated with inappropriate behaviour.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions (such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects) have been reported from the use of benzodiazepines. Such reactions are possibly seen more often in the treatment of children and elderly patients and should result in the discontinuation of treatment.

Specific patient groups
Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.

Elderly and debilitated patients should be given a reduced dose (see section 4.2). Due to the myorelaxant effect of benzodiazepines there is a risk of falls and consequently of hip fractures in the elderly.

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Very slow intravenous injection is recommended due to the risk of respiratory inhibition.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. In patients with chronic hepatic disease dosage may need to be reduced.

The usual precautions in treating patients with impaired renal function should be observed. In renal failure, the half-life of diazepam is not clinically significantly changed, and dose adjustment is usually not necessary.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdosing.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic interactions
If diazepam 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 diazepam, 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.

Concomitant use not recommended

Alcohol
Alcohol should not be consumed while undergoing treatment with diazepam due to additive CNS inhibition and enhanced sedation (see section 4.4).

Phenobarbital
Mechanism: Additive CNS inhibition.
Effect: Increased risk of sedation and respiratory depression.

Clozapine
Mechanism: Pharmacodynamic synergism.
Effect: Severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest. Therefore, concomitant use is not recommended and should be avoided.

Special caution with concomitant use

Theophylline
Mechanism: A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain.
Effect: Counteraction of the pharmacodynamics effects of diazepam, e.g. reduction of sedation and psychomotor effects.

Muscle relaxants (suxamethonium, tubocurarin)
Mechanism: Possible pharmacodynamics antagonism.
Effect: Modified intensity of neuromuscular blockage.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as diazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Pharmacokinetic interactions
Diazepam is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam. The oxidative metabolism of diazepam 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 diazepam while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Concomitant use not recommended

Inducers

Rifamycins (rifampicin)
Mechanism: Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam.
Effect: Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Carbamazepine
Mechanism: Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam.
Effect: Reduced effect of diazepam.

Phenytoin
Mechanism – effect on diazepam: Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.
Mechanism – effect on phenytoin: The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way.
Effect on diazepam: Reduced effect of diazepam.
Effect on phenytoin: Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

Phenobarbital
Mechanism: Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.
Effect: Reduced effect of diazepam.

Inhibitors

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)
Mechanism: Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam.
Effect: Increased risk of sedation and respiratory depression. Therefore, the concomitant use should be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)
Mechanism: Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.
Fluconazole: Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.
Voriconazole: A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.
Effect: Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

Fluvoxamine
Mechanism: Fluvoxamine inhibits both CYP3A4 and CYP2C19 which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190% increased plasma concentrations (AUC) of diazepam.
Effect: Drowsiness, reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Special caution with concomitant use

Inducers

Corticosteroids
Mechanism: Chronic use of corticosteroids may cause increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation.
Effect: Reduced effects of diazepam.

Inhibitors

Cimetidine
Mechanism: Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of diazepam and its active metabolite, desmethyldiazepam, was found to be increased by 57%, but reaction times and other motor and intellectual tests remained unaffected.
Effects: Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole
Mechanism: Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam approximately between 30% - 120%. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam.
Effects: Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Esomeprazole
Mechanism: Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Co-administration with ezomeprazole results in an extended half-life and an increase in plasma concentrations (AUC) of diazepam by approximately 80%.
Effect: Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid
Mechanism: Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half-life of diazepam and in a 35% increased plasma concentration (AUC) of diazepam.
Effect: Increased effect of diazepam.

Itraconazole
Mechanism: Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of diazepam by about 15%, but there was no clinically significant interaction as determined by psychomotor performance tests.
Effect: Possible increased effect of diazepam.

Fluoxetine
Mechanism: Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam.
Effect: Increased effect of diazepam. Concomitant use should be monitored closely.

Disulfiram
Mechanism: Reduced metabolism of diazepam leading to prolonged half-life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of diazepam is slowed down which can give rise to marked sedative effects.
Effect: Increased risk of CNS inhibition such as sedation.

Oral contraceptives
Mechanism – effect on diazepam: Inhibition of oxidative metabolism of diazepam.
Mechanism – effect on oral contraceptives: Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown.
Effect on diazepam: Increased effects of diazepam.
Effect on oral contraceptives: Breakthrough bleeding, but no contraceptive failures have been reported.

Grapefruit juice
Mechanism: Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. C_{max} is increased by 1.5 times and AUC by 3.2 times.
Effect: Possible increased effect of diazepam.

Other

Cisapride
Mechanism: Accelerated absorption of diazepam.
Effect: Temporary increase of the sedative effects of orally administered diazepam.

Levodopa
Mechanism: Unknown.
Effect: Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Valproic acid
Mechanism: Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism.
Effect: Increased serum concentrations of diazepam.

Ketamine
Mechanism: Due to similar oxidative processes, diazepam competitively inhibits ketamin metabolism. Pre-medication with diazepam leads to prolonged half-life of ketamine with enhanced effect as a result.
Effect: Increased sedation.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:
Any woman wishing to become or suspecting that she is pregnant should be urged to contact her doctor concerning stopping the treatment.

Pregnancy
There are limited amount of data from the use of diazepam in pregnant women.
If, for compelling medical reasons, diazepam is administered during the last trimester of pregnancy, or at high dose levels around the time of birth, effects can be expected in the neonate, such as hypothermia, hypotonia ("Floppy Infant Syndrome"), irregularities in the heart rate, poor suckling and moderate respiratory depression, due to the substance's pharmacological effect.
In addition, infants born to mothers who have taken benzodiazepines regularly during the last stage of pregnancy may develop a physical dependence and be at risk of developing withdrawal symptoms following the birth.

Studies in animals have shown reproductive toxicity (see section 5.3). Data from animal experiments shows that the use ofdiazepam in the first trimester produces an increased risk of cleft lip and palate, CNS abnormalities and permanent functional disorder in the offspring.

Diazepam should only be used in pregnant women on compelling indication.

Breast-feeding:
Diazepam is excreted in breast-milk. Diazepam should not be used during breast-feeding.

Fertility
Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There are no human data.

4.7 Effects on ability to drive and use machines

Diazepam significantly affects the ability to drive and to operate machines.
This is usually due to impaired motor skills, tremor, somnolence, amnesia, impaired concentration and tiredness (see section 4.8).
The effect can be observed immediately after the start of treatment and it can last for several days following discontinuation due to the long half-life of diazepam.
If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or doubled vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.
Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Dependence
Chronic use (even at therapeutic doses) may lead to the development of physical and psychic dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Abuse of benzodiazepines has been reported.

The frequencies of adverse events are ranked according to the following:
Very common (³1/10)
Common (³1/100 to <1/10)
Uncommon (³1/1,000 to <1/100)
Rare (³1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Very rare	Leukopenia
Immune system disorders	Very rare	Anaphylaxis
Psychiatric disorders	Common	Confusion
	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rage, hallucinations, psychoses, memory loss, nightmares, inappropriate behavior and other adverse behavioural effects [a] Emotional poverty, decreased alertness and depression [b]

Nervous system disorders	Very common	Drowsiness
	Common	Ataxia, impaired motor ability, tremor
	Uncommon	Anterograde amnesia [c] Concentration difficulties, balance disorders, dizziness, headache, slurred speech
	Rare	Unconsciousness, insomnia, dysarthria
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest
Vascular disorders	Rare	Hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression
	Rare	Respiratory arrest, increased bronchial secretion
Gastrointestinal disorders	Uncommon	Gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), increased salivary secretion
	Rare	Dry mouth, increased appetite
Hepatobiliary disorders	Rare	Jaundice, changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase)
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (itching, erythema, rash)
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia
Renal and urinary disorders	Rare	Urinary retention, incontinence
Reproductive system and breast disorders	Rare	Gynaecomastia, impotence, increased or reduced libido
General disorders and administration site conditions	Common	Fatigue, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium and epileptic attacks) [d] Pain at the injection site, thrombophlebitis
Investigations	Very rare	Elevation of transaminases

[a] Known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur (see section 4.4).

[b] Pre-existing depression may be unmasked during benzodiazepine use.
[c] May occur using therapeutic dosages, the risk increasing at higher dosage. Amnestic effects may be associated with inappropriate behavior (see section 4.4).
[d]The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

Generally, a slight to moderate reduction of blood pressure is observed in both patients with normal heart function and patients with ischemic heart failure by intravenous injection. Hypovolemic patients are most sensitive. At doses corresponding to heavy sedation (> 0.2 mg/kg) PO_2 decreases shortly after injection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

In every case of overdose it should be assessed whether multiple agents are involved, for example in an attempted suicide. Symptoms of overdose are more pronounced in the presence of alcohol or drugs causing a depression in central nervous system.

Symptoms:
Respiratory depression is the most serious problem with overdosing on benzodiazepines. Coma, hypothermia, hypotension and bradycardia are also seen in connection with overdosing. Ataxia, lethargy and slurred speech are commonly observed.

Treatment:
Treatment is symptomatic and supportive. Active charcoal and flumazenil can be considered. Flumazenil counteracts the CNS-inhibiting action of benzodiazepines. Emesis is contra-indicated due to the risk of CNS depression and coma. Flumazenil should only be administered under closely monitored conditions. Due to the short half-life of flumazenil, symptoms of benzodiazepine intoxication can recur after a short period of time. Therefore, monitoring of the patient's clinical state remains essential. For some patient groups treatment with flumazenil might be useful, especially with regard to preventing the need for artificial respiration. This applies for example to patients with pre-existing respiratory disorder or threatening respiratory insufficiency, elderly patients and children.
Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Anxiolytics, benzodiazepine derivates, ATC code: N05BA01.

A benzodiazepine with anxiolytic, sedative, muscle relaxant and anticonvulsant properties.

5.2 Pharmacokinetic properties

Diazepam is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30-90 minutes of oral administration; the rate of absorption is age-related and tends to be delayed in the elderly. Diazepam has biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 to 2 days; its action is further prolonged by the even longer half-life of 2 to 5 days of its active metabolite, desmethyldiazepam (Nordazepam), the relative proportion of which increases in the body on long-term administration. Diazepam is very extensively bound to plasma proteins.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Impairment of fertility
Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of diazepam prior to and during mating and throughout gestation and lactation.

Teratogenicity
Exposure to diazepam in the first trimester produces an increased risk of cleft palate (mice), CNS abnormalities and permanent functional disorder in the offspring (rats).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil
Diacetylated monoglycerides
Purified egg phospholipids
Glycerol
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Incompatibilities may occur with other intravenous solutions. Diazemuls should be used by infusion only with those solutions which have been demonstrated to be compatible. In addition, absorption may occur to plastic infusion equipment.

6.3 Shelf life

2 years.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.
Refer to section 6.6 for information on the physical and chemical stability of diluted product.

6.4 Special precautions for storage

Store below 25°C.
Do not freeze.
Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml, type I Ph. Eur., clear, glass ampoule.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

If a continuous infusion is required Diazemuls can be added to dextrose solution 5% or 10% to achieve a final diazepam concentration within the range 0.1-0.4 mg/ml (i.e. 2-8 ml Diazemuls per 100 ml dextrose solution). A dextrose solution containing added Diazemuls should be used within 6 hours of admixture when stored in a glass bottle. Storage in plastic containers is not recommended. Diazemuls can be mixed in all proportions with Intralipid 10% or 20%. Diazemuls should not be mixed in the container with saline solutions. It can be injected into the infusion tube during an ongoing infusion of isotonic saline or dextrose solution 5% or 10%. Diazemuls should be used by infusion only with the solutions which have been shown to be compatible. As with other diazepam injections, adsorption may occur to plastic infusion equipment. This adsorption occurs to a lesser degree with Diazemuls than with aqueous diazepam injection preparations when mixed with dextrose solutions.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/098/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 1989

Date of last renewal: 31 August 2009

10 DATE OF REVISION OF THE TEXT

April 2019
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