Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diazepam Macure 5 mg/ml emulsion for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of emulsion for injection contains 5 mg diazepam
Each ampoule of 2 ml contains 10 mg diazepam

Excipient with known effect:
Each ml contains 100 mg of soya oil, refined

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Emulsion for injection (inj.)

A milky white oil-in-water emulsion with a pH between 5.5 and 8.5 and an osmolality of 380 to 420 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Diazepam Macure is indicated for the treatment of:

- anxiety
- seizures
- alcohol withdrawal symptoms
- premedication before surgical or diagnostic procedures
- anaesthesia initiation and conscious anaesthesia
- spasms related to tetanus

Paediatric patients
Diazepam Macure is indicated for the treatment of:

- seizures
- premedication before surgical or diagnostic procedures
- spasms related to tetanus

4.2 Posology and method of administration

Dosing should be in accordance with local clinical guidelines. Dosage depends on the individual reaction, age and weight of the patient as well as the type and severity of the disease. The principle here is to keep the dose as low as possible and the duration of treatment as short as possible. For non-repeatable doses, the stated dose range represents the maximum recommended dose.

Posology

Adults:
Anxiety:

2 to 10 mg slowly i.v. (or if i.v. not possible deep i.m.), repeated if necessary

Convulsions and epileptic seizures:
10-20 mg slowly i.v. or deep i.m., possibly repeated.

Premedication before surgical or diagnostic procedures:
10-20 mg slowly i.v. or deep i.m.

Anaesthesia initiation and conscious anaesthesia:
10-20 mg slowly i.v. or deep i.m.

Alcohol withdrawal therapy:
The dose depends on age, weight, sex, somatic condition, degree of intoxication and emergency situation.
General dosage guideline: Initial dose of 5 to 20 mg, repeat after 2-4 hours if necessary or 10 mg diazepam 3 to 4 times on the first day, then reduce to 5 mg 3 to 4 times daily.

Spasms related to tetanus:
The usual initial dose is 5 to 10 mg slowly i.v., repeated if necessary. Much higher doses are often required.

Paediatric patients:
Convulsions and epileptic seizures:
0.2-0.3 mg/kg slowly i.v. or deep i.m., can be repeated once

Premedication before surgical or diagnostic procedures:
0.1-0.2 mg/kg slowly i.v. titrated to patient´s response

Spasms related to tetanus:
The usual initial dose is 5 to 10 mg slowly i.v., repeated if necessary. Much higher doses are often required.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.4). The patient should be reassessed after a maximum of 4 weeks and again regularly thereafter to assess the need for continued treatment, especially if the patient is symptom-free. Treatment should generally not last longer than 2-4 weeks, including the taper phase.
In some cases, it may be necessary to extend the treatment beyond the maximum recommended treatment time. If this is the case, this should not be done without reassessment with particular expertise of the patient's condition.

Withdrawal
Treatment should always be tapered gradually. Patients who have been receiving benzodiazepines for a longer period of time may require a longer taper phase (see section 4.4).

Special populations:
People in the following patient groups should be monitored regularly at the beginning of treatment. Monitoring during treatment is important to minimise dose and/or frequency of administration to avoid overdose due to accumulation, such as in children and adolescents, elderly patients and patients with hepatic impairment.

Elderly:
Distribution, elimination and clearance are altered in the elderly, resulting in prolonged half-life. Therefore, the dose should be reduced to 50 % of the normal recommended adult dose and then slowly adjusted according to the patient´s response. These patients should be monitored regularly at the start of treatment to minimise dose and/or frequency of administration to avoid accumulation overdose.

Renal impairment:
No dose adjustment is usually necessary. However, caution should be exercised when treating with diazepam in patients with renal impairment.

Hepatic impairment:
The dose should be reduced in people with cirrhosis and hepatic impairment. Patients with severe hepatic impairment should not be treated with diazepam due to the risk of hepatic encephalopathy (see section 4.3).

Overweight:
Various studies have shown that kinetics are altered in overweight people compared to normal weight. In a study in which subjects received 2 mg diazepam overnight for 30 days, accumulation was delayed and the half-life of accumulated diazepam prolonged in obese compared to normal weight subjects (7.8 days versus 3.1 days). Similarly, the half-life of the accumulated amount of the active metabolite desmethyl-diazepam was significantly prolonged. The plasma elimination half-life of diazepam was extended to 82 hours in obese subjects. The altered pharmacokinetics of long-term treatment of obese patients is probably due to the increased volume of distribution.
These data indicate that overweight people require significantly longer treatment times than normal weight before the maximum effect of the medicine occurs with long-term treatment. Similarly, therapeutic efficacy and adverse reactions, including withdrawal symptoms, may occur for prolonged periods after discontinuation of long-term treatment in obese people.

Method of administration
Diazepam Macure may be administered by slow intravenous injection (1 ml per min.) or by deep intramuscular injection. Diazepam Macure should be drawn up into the syringe immediately prior to injection.

4.3 Contraindications

Diazepam Macure is contraindicated for patients with:

- Hypersensitivity to benzodiazepines, peanuts, soya oil or to any of the excipients listed in section 6.1.
- Myasthenia gravis
- Sleep apnea syndrome
- Severe hepatic insufficiency.
- Acute respiratory depression.

4.4 Special warnings and precautions for use

Concomitant use of alcohol/CNS inhibitory medicinal products
Concomitant use of diazepam with alcohol and/or CNS inhibitory medicinal products should be avoided. Concomitant use has the potential to increase the clinical effects of diazepam including possibly severe sedation, clinically relevant respiratory and/or cardiovascular inhibition (see section 4.5)

Concomitant use of clozapine
Concomitant use of diazepam and clozapine should be avoided. Concomitant use can result in severe hypotension, respiratory depression, loss of consciousness and potentially fatal respiratory and/or cardiac arrest (see section 4.5).

Risk of concomitant use of opioids
Concomitant use of diazepam and opioids can result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medications, such as benzodiazepines or similar medicinal products such as diazepam with opioids, should only be made to patients for whom alternative treatment options are not possible. If it is decided to use 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 recommendations in section 4.2).
Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this context, it is strongly recommended to inform patients and their carers, if any, to be aware of these symptoms (see section 4.5).

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 reduction in the hypnotic effect may develop after repeated use for a few weeks.

Dependence
Treatment with diazepam may lead to psychological or physical dependence. The risk increases with the use of high doses and with prolonged treatment. The risk is also greater in patients with a history of alcohol or drug abuse or in people with pronounced personality disorders. Regular monitoring of such patients is necessary, routine prescribing should be avoided, and treatment should be tapered gradually.

Withdrawal

Once physical dependence has developed, abrupt discontinuation of treatment will be accompanied by withdrawal symptoms. Discontinuation should be gradual in order to minimise the risk of withdrawal symptoms. These can be headaches, muscle pain, pronounced anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling and stabbing in the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia and anxiety: A transient syndrome in which the symptoms that led to treatment with a benzodiazepine reappear in amplified form may occur upon discontinuation of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. As the risk of discontinuation phenomenon/rebound phenomenon is greater after abrupt discontinuation of treatment, a gradual taper of the dose is recommended.

Abrupt discontinuation of diazepam therapy in patients with a history of epilepsy or other patients with seizures may result in convulsions or status epilepticus, Convulsions may also be seen after abrupt discontinuation in individuals with alcohol or drug abuse.

Duration of treatment

It may be useful to inform the patient at the start of treatment that treatment will be of limited duration and to explain precisely how the dose will be gradually reduced. In addition, it is important that the patient is aware of the possibility of a rebound phenomenon, thus minimizing the anxiety of such symptoms should they occur during the withdrawal phase.

Amnesia

Anterograde amnesia may occur even if benzodiazepines are used within the normal dose range, although it is particularly noticeable at high doses. The condition most frequently occurs several hours after consuming the product. Therefore, to reduce the risk, patients should ensure that they can get 7-8 hours of continuous sleep (see also section 4.8). Amnestic effects may be associated with inappropriate behaviour.

Psychic and "paradoxical" reactions

Paradoxical reactions (such as restlessness, agitation, irritability, aggressiveness, delusions, tantrums, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural effects) have been reported with benzodiazepine use. Such reactions may be seen more frequently with treatment in children and elderly patients and should lead to discontinuation of treatment.

Special patient groups

Paediatric population

Benzodiazepines should not be administered to children without careful assessment of their need. The duration of treatment should be kept to a minimum. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.

Elderly

Elderly and debilitated patients should receive a reduced dose (see section 4.2). Due to the muscle relaxant effect, there is a risk of falls and, as a consequence, hip fractures in the elderly.

Respiratory insufficiency

A lower dose is also recommended in patients with chronic respiratory failure due to the risk of respiratory depression. Very slow intravenous injection is recommended due to the risk of respiratory retardation.

Hepatic impairment

Benzodiazepines are not indicated for the treatment of patients with severe hepatic impairment as they may develop hepatic encephalopathy (see section 4.3). In patients with chronic liver disease, a dose reduction may be required.

Renal impairment

The usual precautions should be taken when treating patients with renal impairment. In renal failure, the half-life of diazepam is not significantly altered, and no dose adjustment is required.

Benzodiazepines are not recommended as primary treatment for psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide can be triggered in such patients). Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdose.

Excipients:
Sodium
This medicinal product contains less than 1 mmol (23 mg) of sodium per ml, that is to say essentially 'sodium-free'.

Soya oil
Diazepam Macure contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

If diazepam is used in combination with other centrally acting substances, particular attention should be paid to the pharmacology of the substances used, in particular for substances that may potentiate or be enhanced by the action of diazepam such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, antiepileptics, sedating antihistamines, antipsychotics, general anaesthetics and analgesics. Such concomitant use may increase the sedative effect and cause an inhibition of respiratory and cardiovascular functions. The simultaneous use of narcotic analgesics can provoke psychological dependence due to the increase in the euphoric effect.

Concomitant use not recommended
Alcohol
Alcohol should not be consumed during treatment with diazepam due to additive CNS inhibition and increased sedation (see section 4.4).

Phenobarbital
Mechanism: Additive CNS inhibition.
Impact: Increased risk of sedation and respiratory depression (see section 4.4).

Clozapine
Mechanism: Pharmacodynamic synergy.
Impact: Severe hypotension, respiratory depression, loss of consciousness and potentially fatal respiratory and/or cardiac arrest (see section 4.4).

Opioids
Concomitant use of sedative drugs such as benzodiazepines or similar drugs such as diazepam together with opioids increases the risk of sedation, respiratory depression, coma and death due to the additive CNS suppressive effect. Therefore, the dose and duration of concomitant use should be limited (see section 4.4).

Special caution with concomitant use
Theophylline
Mechanism: One proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain.
Impact: Antagonistic effects on the pharmacodynamic action of diazepam, e.g. reduction of sedating and psychomotor effects.

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 also conjugated to glucuronic acid. CYP3A4 and/or CYP2C19 inhibitors may cause an increase in diazepam concentrations, while enzyme-inducing medicinal products such as rifampicin, Hypericum perforatum and some antiepileptic medicinal products may result in significantly reduced plasma concentrations of diazepam.

Diazepam has been reported to be displaced from protein-binding sites by sodium valproate (increased serum levels: increased risk of drowsiness).

Concomitant use not recommended
Rifamycins (rifampicin)

Mechanism: Rifampicin is a potent inducer of CYPA4 and significantly increases the hepatic metabolism and clearance of diazepam. In a study in healthy subjects receiving 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased approximately 4-fold. Concomitant administration of rifampicin results in significantly reduced concentrations of diazepam.
Impact: Reduced efficacy of diazepam. Concomitant use of rifampicin and diazepam should be avoided.

Carbamazepine
Mechanism: Carbamazepine is a known inducer of CYP3A4 and increases the hepatic metabolism of diazepam. This may result in plasma clearance up to 3 times greater and a shorter half-life of diazepam.
Impact: Reduced efficacy of diazepam.

Phenytoin
Mechanism – effect on diazepam: Phenytoin is a known inducer of CYP3A4 and increases diazepam's hepatic metabolism.
Mechanism – effect on phenytoin: Diazepam may unpredictably increase or decrease phenytoins metabolism or metabolism may remain unchanged.
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 the hepatic metabolism of diazepam.
Impact: Reduced efficacy of diazepam.

Antivirals (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)
Mechanism: Antivirals may inhibit diazepam's CYP3A4 metabolic pathway.
Impact: Increased risk of sedation and respiratory depression. Concomitant use should therefore be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)
Mechanism: Increased plasma concentrations of benzodiazepines due to inhibition of the CYP3A4 and/or CYP2C19-metabolic pathway.

Fluconazole: Co-administration of 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single oral dose of 5 mg diazepam 2.5-fold and extended the half-life from 31 hours to 73 hours.

Voriconazole: A study in healthy subjects showed that 400 mg voriconazole twice daily on day one day and 200 mg twice daily on day two increased AUC of a single oral dose of 5 mg diazepam 2.2-fold and extended half-life from 31 hours to 61 hours.
Impact: Increased risk of adverse reactions and toxicity of benzodiazepines. Concomitant treatment should be avoided or the dose of diazepam reduced.

Fluvoxamine
Mechanism: Fluvoxamine inhibits both CYP3A4 and CYP2C19, resulting in inhibition of oxidative metabolism of diazepam. Concomitant administration of fluvoxamine results in an increased half-life and an increase in diazepam plasma concentration (AUC) of approximately 190%. Impact: Drowsiness, impaired psychomotor skill and memory. Instead, benzodiazepines metabolised by non-oxidative route should be preferred.

Special caution with concomitant use
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.
Impact: Reduced efficacy of diazepam.

Cimetidine
Mechanism: Cimetidine inhibits the hepatic metabolism of diazepam, reduces its clearance and prolongs its half-life. In a study in which 300 mg cimetidine was administered four times daily for 2 weeks, a 57 % increase in combined plasma levels of diazepam and its active metabolite desmethyldiazepam was observed, but reaction time and other motor and intellectual tests remained unaffected.
Impact: Increased efficacy of diazepam and increased risk of somnolence. Reduction of diazepam dose may be required.

Esomeprazole and omeprazole

Mechanism: Esomeprazole and omeprazole inhibit diazepam's CYP2C19-metabolic pathway. Concomitant administration of esomeprazole results in an extended half-life and an approximately 80 % increase in diazepam plasma concentration (AUC). Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam by 10% and 35% in slow and rapid metabolisers, respectively.
Impact: Increased efficacy of diazepam. Reduction of diazepam dose may be required.

Isoniazid
Mechanism: Isoniazid inhibits diazepam's CYP2C19 and CYP3A4 metabolic pathways. Concomitant administration of 90 mg isoniazid twice daily for 3 days resulted in an extended elimination half-life of diazepam and in a 35 % increase in diazepam plasma concentrations (AUC).
Impact: Increased efficacy of diazepam.

Itraconazole
Mechanism: Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study in healthy subjects receiving itraconazole 200 mg daily for 4 days, the AUC of a single oral dose of 5 mg diazepam increased by approximately 15 %, but there was no clinically significant interaction as measured by psychomotor performance tests.
Impact: Possible increased efficacy of diazepam.

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

Disulfiram
Mechanism: Reduced metabolism of diazepam resulting in prolonged half-life and increased plasma concentrations of diazepam. The elimination of diazepam's N-desmethyl metabolites is delayed, which may lead to pronounced sedative effects.
Impact: Increased risk of CNS inhibition such as sedation.

Oral contraceptives
Mechanism – effect on diazepam: Inhibition of oxidative metabolism of diazepam with potential increased effect.
Mechanism – effect on oral contraceptives: Breakthrough bleeding has been reported, but no contraceptive failure

Grapefruit juice
Mechanism: Grapefruit juice is thought to inhibit CYP3A4 and increase plasma concentrations of diazepam. Cmax increases 1.5 times and AUC 3.2 times.
Impact: Possible increased efficacy of diazepam.

Others

Levodopa
Mechanism: Unknown.
Impact: Concomitant use of diazepam resulted in a reduced efficacy of levodopa in a few reports.

Ketamine
Mechanism: As a result of similar oxidative processes, diazepam competitively inhibits the metabolism of ketamine. Premedication with diazepam results in prolonged half-life of ketamine resulting in increased efficacy.
Impact: Increased sedation.

4.6 Fertility, pregnancy and lactation

Women of childbearing age

Any woman who wishes to become pregnant or expects to become pregnant should be encouraged to contact her doctor regarding discontinuation of treatment.

Pregnancy

There are limited data from the use of diazepam in pregnant women.

The risk for birth defects in humans after administration of therapeutic doses of benzodiazepines during early pregnancy is low, however, some epidemiological studies suggest an increased risk for cleft palate, which is also observed in animal studies.
There have been some cases of birth defects and mental retardation of children who were prenatally exposed to overdoses or poisoning with benzodiazepines. Furthermore, CNS defects and functional deficiencies have been observed in animal offspring.

Animal studies have shown reproductive toxicity (see section 5.3).

Diazepam should only be used in pregnant women on compelling indication with the lowest possible dose for the shortest possible duration. If diazepam is administered in the last trimester of pregnancy or in high doses up to the time of birth, effects in the newborn such as hypothermia, hypotonia ("Floppy Infant Syndrome"), irregular heartbeat, poor sucking ability and moderate respiratory depression due to its pharmacological action are to be expected.
In addition, infants of mothers who have taken benzodiazepines regularly in the latter part of pregnancy may develop physical dependence and be at risk of withdrawal symptoms after birth.

Breastfeeding

Diazepam is excreted in breast milk. Diazepam should not be used during lactation.

Fertility

Animal studies have shown a decrease in birth rates and a reduced number of surviving offspring in rats at high doses. No human data are available.

4.7 Effects on ability to drive and use machines

Diazepam has significant influence on the ability to drive and use machines.
This is typically due to impaired motor skills, tremor, somnolence and fatigue (see section 4.8).
Exposure may occur immediately after initiation of treatment and may last for several days after discontinuation due to the long half-life of diazepam.

4.8 Undesirable effects

Drowsiness, emotional numbness, decreased alertness, confusion, fatigue, dizziness, muscle weakness, ataxia, or double vision occur mainly at the start of treatment but usually resolve with repeated administration. In the elderly, confusion may occur at high doses. There is a risk of falls and associated fractures in elderly patients using benzodiazepines.
Increased salivary and bronchial secretion has been reported, especially in children.

Amnesia
Anterograde amnesia can occur at high therapeutic doses and the risk increases with higher doses. 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 psychological dependence: interruption of treatment may lead to discontinuation or rebound phenomena (see section 4.4). Misuse of benzodiazepines has been reported.

Respiratory depression
Respiratory depression may develop after diazepam use. Patients in particular risk are those with a history of respiratory depression and sleep apnoea syndrome (see section 4.3).

Paradoxical reactions
Paradoxical reactions to benzodiazepines administration are characterized by increased talkativeness, emotional release, excitement, excessive movement, and even hostility and rage. Some of the predisposing factors include young and advanced age, genetic predisposition, alcoholism, and psychiatric and/or personality disorders. Children and elderly patients may be more predisposed than other patients to paradoxical reactions with benzodiazepines.

The frequencies of adverse reactions are listed as follows:
Very common (≥1/10)

Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).

System organ class	Frequency	Side effects
Blood and lymphatic system disorders	Very rare	Leukopenia.
Immune system disorders	Very rare	Anaphylaxis.
Psychiatric disorders	Common	Confusion.
	Rare	Psychological and paradoxical reactions such as agitation, restlessness, irritability, aggressiveness, delusion, tantrums, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour, and other undesirable behavioural effects.[1] Emotional numbness, decreased alertness and depression.[2]
Nervous system disorders	Very common	Lethargy.
	Common	Ataxia, impaired motor skills, tremor.
	Uncommon	Anterograde amnesia.[3] Difficulty concentrating, balance disturbances, dizziness, headache, slurred speech.
	Rare	Unconsciousness, insomnia, dysarthria.
Eye disorders	Not known	Reversible visual disturbances: 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 disturbances (nausea, vomiting, constipation, diarrhea), increased salivation.
	Rare	Dry mouth, increased appetite.
Hepatobiliary disorders	Rare	Icterus, changes of liver parameters (increase in ALT, AST, alkaline phosphatase).
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (pruritus, erythema, rash).
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia.
Renal and urinary disorders	Rare	Urinary retention, incontinence.
Reproductive system and breast disorders	Rare	Gynecomastia, impotence, increased or reduced libido.
General disorders and administration site conditions	Common	Tiredness, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremors, gastrointestinal disturbances, irritability, aggressiveness, disturbed sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium and epileptic seizures).[4]
Investigations	Very rare	Increase in transaminases.

[1] Known to occur with benzodiazepines or benzodiazepine-like substances. These reactions can be very serious. They are most likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur (see section 4.4).
[2] Pre-existing depression can be induced during benzodiazepine use.
[3] May occur at therapeutic doses. The risk increases at higher doses. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).
[4] The likelihood and severity of withdrawal symptoms depend on the duration of treatment, dose level and degree of dependence.
In general, a negligible to moderate lowering of blood pressure is observed in both patients with normal cardiac function and patients with ischaemic cardiac function by intravenous injection. Hypovolemic patients are most sensitive. At doses similar to heavy sedation (>0.2 mg/kg), PO2 decreases briefly 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
Website: www.hpra.ie

4.9 Overdose

In any case of overdose, it should be assessed whether more substances are involved, e.g. in suicide attempts. Symptoms of an overdose are more pronounced in the presence of alcohol or drugs that cause an inhibition of the central nervous system.

Symptoms:

Symptoms of a slight overdose include slurred speech, mental confusion and lethargy. In more severe cases, symptoms may include ataxia, dysarthria, hypotension and hypotonia. Severe overdose may lead to central circulation inhibition and respiratory depression (cyanosis, loss of consciousness leading to respiratory arrest, cardiac arrest) and coma. Hospitalization in the intensive care unit is required. During the convalescence period following an overdose, severe agitation has been reported.

Treatment:

Treatment is symptomatic and supportive. Particular attention should be paid to respiratory and cardiovascular functions in intensive care.

The use of flumazenil, a specific benzodiazepine antagonist, may be considered for complete or partial counteraction of the sedative effect of benzodiazepines. Flumazenil should only be administered under close monitoring. Due to flumazenil's short half-life, symptoms of benzodiazepine poisoning may reappear after a short time. Therefore, monitoring of the patient's clinical condition is of paramount importance. Treatment with flumazenil may be useful in certain patient groups, especially to avoid the need for artificial ventilation. This applies, for example, to patients with existing respiratory disease or threatening respiratory insufficiency, elderly patients and children.

Flumazenil is intended in addition to, but not as a substitute for, the proper treatment of a benzodiazepine overdose. Attention should be paid to the induction of withdrawal symptoms and convulsions, especially in long-term benzodiazepine users and in mixed poisoning with substances that lower the seizure threshold (e.g. tricyclic antidepressants).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties
Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivatives.
ATC code: N 05 BA 01.

Mechanism of action:

Diazepam is an agonist that binds to specific benzodiazepine receptors in the brain, thereby enhancing the normal transmission of the signalling substance GABA. GABA inhibits the transmission of important signalling substances, thereby achieving neuronal inhibition. The muscle relaxing effect is mediated via spinal synaptic reflexes.

Pharmacodynamic effects:

Diazepam is an anxiolytic that works by alleviating anxiety symptoms, restlessness and tension. Furthermore, diazepam has a sedating and muscle-relaxing effect.

5.2 Pharmacokinetic properties

Distribution:

Maximum plasma concentration occurs 1/2-1 hour after intramuscular administration of diazepam. Following intravenous administration of 10 mg diazepam, a maximum plasma concentration of approximately 600 ng/ml is reached after a few minutes. The additional distribution results in a noticeable plasma concentration decrease of 2-4 hours duration. Protein binding: 96-98 %. Volume of distribution: 1.11 to 2.64 L/kg. Diazepam is lipid soluble with good tissue penetration and crosses the blood-brain barrier.

Elimination:
Metabolism:
Diazepam is mainly metabolised in the liver by hydroxylation and glucuronidation. The half-life of the metabolite N-desmethyldiazepam, which is biologically active, is 2-4 days. Half-life: Adults: 20-50 hours, older: 70-100 hours. Children: premature 40-110 hours, newborns full-term approx. 30 hours, up to 1 year approx. 10 hours, over 1 year approx. 20 hours.

Excretion:
Diazepam is excreted mainly in the urine as metabolites and approximately 10 % is excreted in faeces.

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 carcinogenicity in addition to effects already included in other sections of the SmPC.

Reduced fertility:
Reproductive studies in rats demonstrated a reduction in postnatal survival in offspring.

Teratogenicity:
Exposure to diazepam in the first trimester of pregnancy leads to an increased risk of cleft palate in mice offspring and CNS defects and permanent behavioural impairment in rat offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya oil, refined
Triglycerides, medium-chain
Glycerol
Egg phospholipids for injection
Sodium oleate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with medicinal products other than those listed in section 6.6.
Incompatibilities may occur with other intravenous solutions. Diazepam Macure should be used by infusion only with those solutions which have been demonstrated to be compatible. In addition, adsorption may occur to plastic infusion equipment.

6.3 Shelf life

2 years
After first opening: to be used immediately.

6.4 Special precautions for storage

Store below 30 °C
Keep the ampoule in the outer carton in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

Colourless glass ampoules of 2 ml in a pack size of 10 ampoules.

6.6 Special precautions for disposal and other handling

No special precautions for disposal.

If a continuous infusion is required Diazepam Macure can be added to a dextrose solution 5 % or 10 % to achieve a final diazepam concentration within the range 0.08-0.20 mg/ml (i.e. 4-10 ml Diazepam Macure per 250 ml dextrose solution). The minimum infusion rate should be 4 ml/h. A dextrose solution containing added Diazepam Macure should be used within 6 hours of admixture when stored in a glass bottle. Storage in plastic containers is not recommended. Diazepam Macure can be mixed in all proportions with Lipofundin MCT/LCT 10 % or 20 %.
Diazepam Macure should be used by infusion only with the solutions which have been shown to be compatible. As with other diazepam injections, diazepam sorption, including adsorption and absorption to plastic infusion equipment, in particular made of PVC or PU, may occur. This adsorption occurs to a lesser degree with Diazepam Macure than with aqueous diazepam injection preparations when mixed with dextrose solutions.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th June 2026

10 DATE OF REVISION OF THE TEXT