SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diazepam-Lipuro 5 mg/ml emulsion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of the emulsion contains 5 mg of diazepam
One ampoule (2 ml) contains 10 mg of diazepam

Excipients with known effects:

One ml of emulsion for injection contains
Soya-bean oil refined 100 mg
Sodium 0.03 mg

For the full list of excipients, see section **6.1.**

3. PHARMACEUTICAL FORM

Emulsion for injection
Milky-white oil-in-water emulsion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Preparation (premedication) for operations and diagnostic procedures, (e.g. endoscopy) and postoperative medication
- Immediate treatment of acute tension, excitement, anxiety, restlessness.
- *Status epilepticus*
- Tetanus
- States of increased muscle tension

4.2 Posology and method of administration

Posology
The doses should be adjusted according to the patient's response, age, and body weight and according to type and severity of the disease. As a matter of principle the doses applied should be kept as low and the duration of treatment as short as possible.
Parenteral administration of diazepam may be indicated if oral treatment is ineffective due to impaired absorption from the gastro-intestinal tract.
In general, 5 – 10 mg diazepam (corresponding to 1 – 2 ml of Diazepam-Lipuro) can be given i.v. or i.m. 1 – 4 times daily.

- **Premedication for operations and diagnostic procedures and postoperative medication***:*

  Preparation for surgery

Adults and adolescents older than 14 years

In the evening before operation:

10 – 20 mg of diazepam (corresponding to 2-4 ml of Diazepam-Lipuro) i.m.

On the day of operation:

- 10 mg of diazepam (corresponding to 2 ml of Diazepam-Lipuro) i. m. 1 hour before induction of anaesthesia

or:

- 5 – 10 mg of diazepam (corresponding to 1 – 2 ml of Diazepam-Lipuro) i.v. 10 minutes before start of anaesthesia

Children up to 14 years:

On the day of operation:

- 2.5 – 10 mg of diazepam (corresponding to 0.5 – 2 ml of Diazepam-Lipuro) i.m. 1 hour before induction of anaesthesia

Induction of anaesthesia

In adults, anaesthesia is induced with 0.2 – 0.35 mg diazepam/kg body weight into the vein (i.v.); in high-risk patients, the dose is divided into smaller portions; in children, with 0.1 – 0.2 mg diazepam/kg body weight (i.v.).

The best method of adjusting the dose to each patient individually is to perform an initial injection of 5 mg diazepam (corresponding to 1 ml Diazepam-Lipuro) and subsequently to give repeated doses of 2.5 mg diazepam (corresponding to 0.5 ml Diazepam-Lipuro). The reaction of the patient must be observed after each additional injection of 2.5 mg during the 30 seconds following the injection until it is established that the eyelids are closed. However, the administered dose must not be higher than 0.35 mg/kg body weight.

After surgery

Adults and adolescents older than 14 years are given 5 – 10 mg diazepam (corresponding to 1 – 2 ml Diazepam-Lipuro) intramuscularly. The dose is to be reduced for children.

Note:

For premedication dosage in children, which is based on age and weight, dosing according to weight is recommended (0.1 – 0.2 mg/kg BW) (according to Pichlmayr):

Age (in months/years)	**Body weight in kg**	**Diazepam dose in mg***	**Corresponding diazepam dose in ml***
up to 3 months	3 – 5.5	–	-
4 – 6 months	6 – 7	0.5 mg	0.1 ml
6 – 8 months	8 – 9	1.0 mg	0.2 ml
12 months	10	2.0 mg	0.4 ml
24 months	12	5 mg	1 ml
2 – 3 years	12 – 14	5 mg	1 ml
3 – 5 years	14 – 18	5 mg	1 ml
5 – 8 years	18 – 25	7.5 mg	1.5 ml
8 – 10 years	25 – 30	7.5 mg	1.5 ml
10 – 12 years	30 – 35	10 mg	2 ml
12 – 15 years	35 – 40	10 mg	2 ml

* 5 mg = 1 ml

- **Treatment of acute tension, excitement, anxiety or restlessness:**

  Adults
  2 – 10 mg of diazepam, corresponding to 0.4 – 2 ml of Diazepam-Lipuro, (or 0.1 – 0.2 mg per kg body weight) i.v. This dose may be repeated according to requirements after 3 – 4 (or 8) hours until symptoms disappear.

  Children over 1 month of age

  1 – 2 mg of diazepam (corresponding to 0.2 – 0.4 ml of Diazepam-Lipuro) i.v. or i.m., depending on the severity of the illness. The dose may be repeated after 3 – 4 hours if it is absolutely necessary and if there has been no co-medication effecting deeper sedation.

  Treatment of status epilepticus:
  Adults
  Initially, 5 – 10 mg of diazepam (corresponding to 1 – 2 ml of Diazepam-Lipuro) i.v. or i.m. if i.v. injection is not possible.

  If necessary, the injection may be repeated after 30 – 60 minutes or every 10 – 15 minutes to a maximum of 30 mg of diazepam (6 ml of Diazepam-Lipuro).

  If appropriate, diazepam may also be given as continuous infusion up to a dose of 3 mg of diazepam per kg body weight per 24 hours.

  Children

  - Children over 5 years (from 22 kg body weight):
    0.3 mg/kg body weight of diazepam corresponding to 0.06 ml/kg body weight of Diazepam-Lipuro, slowly i.v., up to a maximum of 10 mg (corresponding to 2 ml of Diazepam-Lipuro). Should seizures persist the same dose may be repeated once after 5 minutes. Should seizures persist the same dose may be repeated once after 5 minutes..

  - Children below 5 years (below 22 kg body weight):
    0.3 mg/kg body weight of diazepam (corresponding to 0.06 ml/kg body weight of Diazepam-Lipuro), slowly i.v. up to a maximum of 5 mg (corresponding to 1 ml Diazepam-Lipuro). Should seizures persist the same dose may be repeated once after 5 minutes.

  Diazepam administration can be repeated after 2 – 4 hours, if required.

- **Treatment of muscle tension:**

  Adults
  If oral or rectal administration is not possible, first an initial dose of 5 mg of diazepam (corresponding to 1 ml of Diazepam-Lipuro) i.m. once or twice per day will suffice.
  If necessary, 10 - 20 mg of diazepam (corresponding to 2 – 4 ml of Diazepam-Lipuro) may be administered i.m. once per day.

  Children

  2 - 10 mg of diazepam (corresponding to 0.4 - 2 ml of Diazepam-Lipuro) i.m., depending on weight and age.

The medicinal product should preferably be given in the evening. If required, therapy may be continued with oral medication.

- **Treatment of tetanus:**

  As a rule, children should receive 2 – 5 mg of diazepam (corresponding to 0.4 - 1 ml of Diazepam-Lipuro) and *adults* 10 mg of diazepam (corresponding to 2 ml of Diazepam-Lipuro) - i.v., i.m. or via gastric or rectal tube every 1 – 8 hours, depending on the severity of illness or a continuous infusion of 3 – 4 mg per kg body weight of diazepam over 24 hours is also possible.

Dosage instruction for special patient groups or special conditions:
Elderly and debilitated patients, and those with organic cerebral alterations, circulatory and respiratory disease, or reduced liver or renal function should be given lower doses:
Initially not more than half of the usual dose or 2.5 mg should be given i.m. or i.v. twice per day. If the dose is to be increased, it should be done stepwise according to the achieved effect. A single parenteral dose should not exceed 5 mg.

This also applies to patients receiving concomitantly other drugs acting on the C.N.S.

If the plasma protein concentration is markedly reduced, it is recommended to halve all doses(both initial and subsequent).

For neonates, infants, toddlers and children oral or rectal preparations of diazepam, i.e. solutions or suppositories, should be preferred.

Method of administration
In case of acute disorders the period of administration has to be limited to usually a single administration or to a few days.
After long-term treatment (more than a week), which should only be performed exceptionally and up to a maximum of 4 weeks, medication should be discontinued stepwise. Otherwise there is an increased risk that withdrawal symptoms appear (see section 4.4).

Diazepam-Lipuro should be injected slowly i.v. over 2 – 5 minutes (not more than 1 mg of diazepam per minute) into a large vein (to avoid too sudden onset of the effect), the patient being in recumbent position and kept under supervision (control of blood pressure and respiration).

Intra-arterial injection should be avoided as there is the risk of necrosis. Paravenous injection will cause strong pain.

Intramuscular injections should be given slowly, deep in a large muscle. (Exercise caution in the case of thrombolytic therapy!) On rare occasions intramuscular injections may cause irritation and pain at the injection site.

For instructions on dilution of the medicinal product before, see section 6.6.

For instructions on shelf life after dilution, see section 6.3.

4.3 Contraindications

- hypersensitivity to the active substance, other benzodiazepines, soya, peanut or to any of the excipients listed in section 6.1. Drug dependence (see section **4.4**)
- Severe form of *Myasthenia gravis*

4.4 Special warnings and precautions for use

Diazepam should be prescribed with particular caution in cases of:

- acute alcohol, sedative, analgesic and psychotropic drug intoxication (neuroleptic drugs, antidepressants, lithium)
- cerebellar or spinal ataxia
- severe liver disease, e.g. jaundice with cholestasis (see also section 4.2)
- sleep apnoea syndrome
- acute aggravation of severe chronic respiratory insufficiency (chronic bronchitis, asthma) (see also section 4.2)
- allergic skin diseases
- increased vascular permeability
- disorders of haematopoiesis
- impaired renal function (see also section 4.2)
- elderly and/or weakened patients (see also section 4.2)

To note:
Not all states of tension, excitement, or anxiety require treatment with medicinal products. Frequently these conditions represent symptoms of physical or mental disorders and can be influenced by other methods or specific treatment of the underlying disease.

Because of the pronounced muscle relaxation patients should be observed for an appropriate period of time after the injection.

At the beginning of therapy, the doctor should control the patient's response to the medication in order to recognise relative overdose as soon as possible. This applies in particular to children, elderly and debilitated patients, and those with organic cerebral alterations, circulatory and respiratory disease, or reduced liver or renal function.

During prolonged use of the emulsion, blood cell counts and liver function should be checked.

The patient should be instructed how to behave in normal life, taking account of the particulars of her/his personal situation (e.g. professional occupation).After an ambulant administration for diagnostic purposes the patient should only be discharged after 1 hour and only under supervision. Furthermore the patient has to be instructed, not to take alcohol (see also section 4.7).

Benzodiapezine are not recommended for primary therapy of psychosis.

Benzodiazepines should not be used as the sole treatment of depressions or states of anxiety associated with depression. In some cases, the depressive symptom complex can intensify if a suitable treatment of the underlying disease with antidepressants (risk of suicide) is not undertaken.

Amnesia

Benzodiazepines can cause anterograde amnesia. See also section 4.8.

This risk increases with higher dosage and can be decreased through a sufficiently long, uninterrupted period of sleep (7 - 8 hours).

Psychical and "paradoxical" reactions

During treatment with benzodiazepines, psychical and so-called “paradoxical” reactions can occur, especially in elderly patients or children (see section 4.8). In such cases, the treatment with this product should be discontinued.

Development of tolerance

After repeated intake of benzodiazepines over a few weeks, there may be loss of efficacy (tolerance).

Development of dependency
Diazepam-Lipuro possesses a primary dependence potential.
The use of benzodiazepines can cause the development of psychical and physical dependency. This applies not only to misuse of especially high doses, but also to the therapeutic dose range. The risk for dependency increases with the dose and duration of treatment. This risk is higher for patients with a medical history of alcohol, medication or drug dependence.

If such a physical dependency has developed, withdrawal symptoms develop if the treatment is abruptly discontinued (see below).

Potential for abuse / dependence
Diazepam has a primary potential to cause dependence. The risk of becoming dependent is already present after daily use over a few weeks. This applies not only to misuse of especially high doses, but also to the therapeutic dose range.

Psychical and physical dependence as well as tolerance may develop after daily administration of diazepam over several weeks. This applies not only when misused in particularly large doses, but also in the therapeutic dose range. Continuous use should only be prescribed for imperative indications. The therapeutic benefit should be weighed carefully against the risk of tolerance and dependence. This risk is higher for patients with a medical history of alcohol, medication or drug dependence or during concomitant intake of narcotic analgesics. If such a physical dependency has developed, withdrawal symptoms develop if the treatment is abruptly discontinued (see below).

Drug withdrawal syndrome
Especially following continued daily treatment it is possible that stopping diazepam may cause withdrawal symptoms. These may manifest as sleep disorders, increased dreams, headache, muscle pain, anxiety, tension, agitation, hyperhidrosis, chills, confusion, mood swings, and irritability. In severe cases confusion, depersonalisation, derealisation, photophobia, phonophobia, hyperaesthesia, numbness, paraesthesia in the extremities, hallucinations and epilepsy.

Temporary withdrawal symptoms (rebound phenomenon) can also develop with the abrupt discontinuation of a short treatment; here the symptoms that led to the treatment with diazepam reappear in intensified form. Concomitant reactions such as mood changes, anxiety and agitation are possible.

Because the risk for withdrawal symptoms after an abrupt discontinuation of the treatment is higher, it is recommended to end the treatment by gradually reducing the dose.

It is advisable to inform the patient at the beginning of the treatment of the limited duration of the treatment and to explicitly explain the gradual decrease in the dose. Furthermore, it is

important that the patient is aware of the possibility of a rebound phenomenon. Through this, the fear of such symptoms, if they occur while discontinuing the medicine, can be reduced.

Paediatric population
Neonates and infants up to the age of 6 months should not be given diazepam except for imperative indications during in-patient treatment.
Diazepam should not be administered to children and adolescents unless there is an imperative indication.

Special patient groups
Patients in hypovolaemic shock should be given diazepam injections only if the fluid deficit is corrected at the same time.
Comatose patients should be given diazepam injections only if they are very agitated or convulsing and if the unconsciousness has not been caused by poisoning.

Only exceptionally (e.g. acute withdrawal reactions) and over short periods, diazepam may be administered to patients with a history of dependence on medicinal products with a centrally depressing effect including alcohol.

Elderly patients
Special care has to be taken if the medicinal product was administered to elderly patients as the risk of falling, especially when getting up at night, is increased in this patient group.

Special warnings / precautions regarding excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. it is essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

- **Medicinal products acting on the central or peripheral nervous system**
  (e. g. psychotropic drugs or other central depressants, such as sedatives, hypnotics, narcotics, or antihistamines and some analgesics):
  If these are given together with diazepam, the central and respiratory depressant effects of both those medicinal products and diazepam may be intensified.
- **Narcotic analgesics**
  If narcotic analgesics were taken concomitantly with diazepam the resulting euphoric effects may be intensified. Therefore the predisposition of such patients to habituation and dependence may be accelerated.
- **Muscle relaxants**
  The effect of muscle relaxants may be intensified by diazepam. This applies in particular to elderly patients and when higher doses are applied (risk of falling).
- **Inhibitors, inducers or other subtstrates of cytochrome P450 isoenzyme CYP3A4 and/or CYP2C19**
  As diazepam is metabolized via cytochrome P450 isoenzymes CYP3A4 and CYP2C19 the effect (or toxicity) of diazepam may be increased if administered concurrently with inhibitors or substrates of CYP3A4 and/or CYP2C19 (e.g. Cimetidine, disulfiram or omeprazole). Parallel intake of CYP3A4 and/or CYP2C29 inducers (e.g. phenobarbital, phenytoin, HIV-protease-inhibitors) may lead to reduced levels of diazepam.
- **Theophylline**

Theophylline in low doses antagonises sedation brought about by diazepam.

- **Phenytoine**
  In rare instances, diazepam can inhibit the metabolisation of phenytoine and hence its effect may be augmented.
- **L-dopa**
  Diazepam can inhibit the action of L-dopa.

In patients undergoing **long-term treatment with other drugs**, such as **centrally acting antihypertensives, beta receptor blockers, cardiac glycosides** or **anticoagulants**, interactions are unpredictable as to nature and extent of drug interactions in individual cases. It is therefore necessary to give diazepam with particular caution, particularly at the beginning of the therapy. The attendant physician should ascertain whether the patient is receiving any long-term medication before administering diazepam.

Because diazepam is slowly excreted from the body, interactions may still occur when treatment with diazepam has finished.

Alcohol
The effect of Diazepam-Lipuro can be altered and intensified in an unpredictable manner by concomitant intake of alcohol. Therefore alcohol has to be avoided during a therapy with diazepam.

Interaction with tobacco / smoking
In **smokers** the excretion of diazepam is accelerated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If the product is prescribed to a woman of childbearing potential the woman should be advised to contact her physician in case she intends to become or suspects to be pregnant, in oder to consider the discontinuance of the product.

Pregnancy
There are no controlled clinical data from the use of diazepam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Diazepam should not be given during pregnancy, except for imperative indications on special prescription. It should not be administered at high doses and over an extended period.

There seems to be only a minor risk of malformations when diazepam is taken during early pregnancy in therapeutic doses, although some epidemiologic studies gave indications of an increased risk of cleft palate.
There are some case reports on malformations and mental retardation of children having been exposed prenatally to high doses of benzodiazepines after overdose or intoxication.

If for compelling medical reasons diazepam was administered during late pregnancy or parturition this might have effects on the infant: hypothermia, neonatal hypotonia, mild depression of respiration and difficulty in feeding (the so-called “floppy infant syndrome”).

Breast-feeding
Diazepam/metabolites are excreted in human milk. Reports have demonstrated a very high inter-individual variety of milk: plasma concentration ratios. As metabolism of diazepam is markedly slower in neonates than in children or adults, there is a risk of accumulation of

diazepam/metabolites in the breastfed child.. Therefore diazepam should not be given to breast feeding mothers.

Fertility
No data available regarding the use of Diazepam-Lipuro in humans. In male mice, after one to six weeks of exposure to diazepam, anomalies of the spermheads were seen (see also section 5.3.)

4.7 Effects on ability to drive and use machines

Reactivity may be altered so much, even with normal doses of diazepam and when used in accordance with the directions given, that traffic safety and the ability to operate moving machinery may be markedly impaired.

Intake of alcohol during medication with diazepam may lead to stronger impairment of motor function and normal behaviour than with diazepam alone, even 10 hours after the last dose. There are implications of substantial risks for work-related and traffic accidents. Consequently, patients should not drive cars, operate machinery, or perform any other activities with a risk of accidents during treatment with diazepam or within 24 hours following the last injection. After administration of diazepam for diagnostic procedures, patients should be discharged not earlier than 1 hour following completion of the procedure and should not go home unattended. The patient should be instructed to avoid drinking alcohol.

4.8 Undesirable effects

The most frequently observed undesirable effects of diazepam are related to its pharmacological effects. Both their intensity and frequency are dose-dependent and occur especially at the beginning of therapy. Side effects can mostly be avoided or reduced by careful and individual adaptation of the daily dose.

Most common side effect is drowsiness.

Listing of undesirable effects

Definition of frequency terms used in this section:

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)

Metabolism and nutrition disorders

Rare: Increased appetite

Psychiatric disorders

Common: Stronger sedation than desired over the day, confusion, and anterograde amnesia
Rare:
Depressed mood, depression, aggravation of pre-existing depressive disease.
If this occurs, the diazepam dose must be reduced for subsequent administrations.
Decrease of libido

Not known: Drug dependence see 'Information on particular undesirable effects below'

Nervous system disorders

Common: Fatigue, (including somnolence, sedation, hypoaesthesia, lengthened reaction times), vertigo, ataxia headache.
A "hangover" effect after evening administration of diazepam, i.e. residual sedation, can affect reactivity on the following day.

Not known: After high doses dysarthria, more frequent after prolonged administration.

Eye disorders

Not known: vision blurred, (diplopia, nystagmus),
more frequent after prolonged administration and/or high doses.

Cardiac disorders

Rare: bradycardia, arrhythmia, cardiac failure*, cardiac arrest*.

Vascular disorders

Rare: hypotension

Respiratory, thoracic and mediastinal disorders

Rare: Laryngospasm; depression of respiration*
The respiratory depressant effect can be more pronounced in the presence of airway obstruction or pre-existing cerebral damage. It can generally be avoided by a careful adjustment of the dose for each individual, especially if other medicaments acting on the central nervous system are taken concomitantly (see also sections 4.4 and 4.5).

Gastrointestinal disorders

Rare: Nausea, vomiting, epigastric discomfort, constipation, diarrhoea, dry mouth

Not known: increased salivation

Hepatobiliary disorders

Rare: Jaundice

Skin and subcutaneous tissue disorders

Rare: Allergic skin reactions (pruritus, urticaria, flush)

Musculoskeletal and connective tissue disorders

Common: muscle weakness

Renal and urinary disorders

Rare: Urinary retention
Not known: Incontinence

Reproductive system and breast disorders

Rare: in women: dysmenorrhoea.

General disorders and administration site conditions

Rare: I.m. injections: irritation and pain at the injection site.

Not known: Risk of falling, paradoxical drug reaction, drug tolerance, drug withdrawal syndrome see 'Information on particular undesirable effects below'.

Investigations

Not known: increased transaminases and alkalic phosphatase

*****During rapid i.v. administration, the cardiovascular and respiratory functions may be affected which could lead to a drop in blood pressure, cardiac arrest and respiratory arrest.
For children and elderly patients with unstable cardiovascular systems in particular, supportive measures for cardiovascular and respiratory functions should be available. Injection into a vein that is too small could cause irritation of the vein wall (also thrombophlebitis).

Information on particular undesirable effects

Paradoxical reactions

Patients may experience "paradoxical" reactions such as acute excitement instead of sedation, anxiety, insomnia, outbursts of temper, increased incidence of muscle cramps, or suicidal tendencies. If such reactions occur, treatment with diazepam should be stopped.

Withdrawal symptoms

Especially following continued daily treatment it is possible that stopping diazepam may produce sleep disturbances and increased dreaming after 2 – 4 days. Anxiety, tension, excitement or internal restlessness may reappear at a higher degree. Symptoms of withdrawal may include trembling and sweating, and proceed to dangerous somatic and psychic reactions such as convulsions and symptomatic psychoses (e. g. withdrawal delirium).

Dependence, tolerance

Tolerance towards Diazepam-Lipuro may develop during longer lasting or repeated use of this drug.

Dependence, see section **4.4**.

<to be complete nationally: only for EU-countries>
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 the national reporting system listed in Appendix V*.

4.9 Overdose

Symptoms of intoxication are more severe after concomitant use of alcohol or drugs with a centrally depressant effect.

Symptoms of overdose
Minor overdose may cause confusion, sleepiness, disturbances of gait and movement (ataxia), dysarthria, drop of blood pressure, and muscle weakness.

Severe intoxication may especially lead to centrally induced depression of cardiac, circulatory and respiratory functions, becoming manifest as cyanosis, and unconsciousness, up to respiratory and cardiac arrest. In such cases patient monitoring in an intensive care unit is absolutely necessary.

During the fading-out phase states of extreme agitation may occur.

Treatment of overdose

Besides monitoring of respiration, heart rate, blood pressure, and body temperature, in general fluid should be substituted by i.v. infusion. Further general supportive measures may be required.
Emergency equipment and medication to treat airway obstructions should be available.

Hypotension is treated with sympathomimetics.

Respiratory insufficiency, which may also be caused by muscle relaxants, may require assisted ventilation.

Morphine antagonists are contraindicated.

Haemodialysis or transperitoneal dialysis have not been described in the literature to date. It is reasonable to assume that because of the high protein binding and large volume of distribution, forced diuresis and dialysis are not very effective for intoxication involving diazepam alone.

For neutralisation of the central depressant effects of diazepam, flumazenil may be given. It is mainly used for the following indications:
- Termination of general anaesthesia induced and maintained by benzodiazepines in hospitalised patients;
- Termination of therapeutic sedation effected by benzodiazepines in hospitalised patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group

Anxiolytics, Benzodiazepine derivatives,
ATC code: N05B A01.

Clinical efficacy and safety

Diazepam is a psychotropic substance from the categorie of 1,4 benzodiazepine with a pronounced effect to calm down tension, excitement and anxious behaviour as well as sedative and hypnotic effects.
Moreover, diazepam reduces muscle tension and has anticonvulsive activity.

Mechanism of action
Diazepam couples to specific receptors in the central nervous system and in some peripheral organs. The benzodiazepine receptors are in close functional relationship to those belonging to the GABA-dependent transmitter system (GABA = gamma amino butyric acid). After binding to the benzodiazepine receptor diazepam intensifies the inhibitory effect brought about by the GABA mediated transmission.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of diazepam show great interindividual variability.

Absorption

After i.v. injection of the emulsion, peak plasma concentrations of diazepam are attained within 10 min., while after i.m. injection maximum plasma concentrations are achieved not earlier than after 125 min. After both i.v. and i.m. injection of 10 mg, serum concentrations of diazepam are between 250 – 600 µg/l. Because the plasma concentration of diazepam decreases rapidly after a single i.v. injection due to rapid distribution, it is necessary to repeat the injection already after 20 – 30 min.
Protein binding, distribution volume

The plasma protein binding rate of diazepam is 95 – 99 % there are lower values available by liver and renal disease

The distribution volume is 0.95 – 2 l/kg b.w., depending on age.

Metabolisation, elimination
Diazepam mainly is metabolised in the liver, yielding the pharmacologically active moieties N-desmethyldiazepam (nordazepam), temazepam and oxazepam that appear in urine in the form of their glucuronides.

Only 20 percent of the metabolites are excreted in urine within 72 hours after injection.

The plasma half-lives of the metabolites are as follows:

N-Desmethyldiazepam	30	–	100 h
Temazepam	10	–	20 h
Oxazepam	5	–	15 h

After repeated administration the proportion of N-desmethyldiazepam predominates, however, with great interindividual variability. This metabolite has a longer terminal biological half-life than diazepam itself.
During chronic medication with diazepam, elimination is further delayed by accumulation and therapeutically relevant serum concentrations of the metabolite appear.

Diazepam and its main metabolite are eliminated from the plasma only slowly. The initial half life is 1 hour and the terminal half life varies – depending on age and liver function – between 20 and 100 hours.

Excretion occurs mainly via the kidneys, in part also in bile. Excretion also depends on age as well as on liver and kidney function.

Pharmacokinetics in special patient groups

In **neonates** the metabolisation and elimination rates are markedly lower than in children and adults.

In **elderly people**, elimination is slowed down by a factor of 2 – 4.

Elimination is also slowed down in patients with **impaired kidney function**.

In patients with **liver diseases (cirrhosis of the liver, hepatitis)**,, elimination is slowed down by a factor of 2.

Passage into the cerebro spinal fluid
Diazepam is lipophilic and together with its main metabolite it passes rapidly into the cerebrospinal fluid.

*Passage across the placental barrier and lactation*Diazepam and its main metabolite N-desmethyldiazepam pass across the placental membranes and are secreted into breast milk.

Diazepam accumulates in the fetal compartment and its concentration in fetal blood may reach three times the level in maternal blood.

In pre-term neonates, elimination is intensively delayed up to 10 days because of immature liver and renal function.

When diazepam has been given immediately before or during parturition, or the mother has received repeated high doses, in both pre-term and term neonates APGAR scores are significantly decreased, the incidence of hyperbilirubinaemia is significantly increased and marked oedema and low muscle tension have been observed until 4 days *postpartum.*
Biovavailability

The systemic bio-availability of diazepam, after i.v. injection, is 100 percent. It is markedly lower after i.m. injection and corresponds to the bio-availability after oral administration, i.e. 75 – 80 percent, depending on the galenical particulars of the dosage form.

5.3 Preclinical safety data

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

Carcinogenicity, genotoxicity
Several studies yielded weak indications that diazepam could be mutagenic, but only at concentrations far above the human therapeutic dose range.

There are no long-term animal studies on the carcinogenic potential of diazepam.

Reproduction toxicity

Diazepam and its main metabolite pass across the placenta.

Diazepam is accumulated in the fetal compartment and can reach the triple of maternal serum concentration .The risk of deformation seems to be small when taking therapeutic doses of benzodiazepine, although some epidemiology studies indicate an increased risk of cleft palate.

Cases of malformation and mental retardation of the prenatal exposed child after overdoses and poisoning have been reported (see also section 4.4 Special warnings and precautions for use).

Results of experimental animal studies:

In mice, cleft palate was observed after prenatal exposure to diazepam. In hamsters, besides cleft palate, also exencephalus and malformations of the extremities were found after very high doses of diazepam. In rats and primates, no teratogenic affect of diazepam was demonstrated.

Studies in animals gave indications of behavioural alterations of the offspring after long-term exposure of the dams to diazepam. In male mice, after one to six weeks' exposure to diazepam, anomalies of the spermheads were found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil refined,
medium-chain triglycerides,
glycerol,
egg lecithin,
sodium oleate,
water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6..

6.3 Shelf life

-unopened:
2 years

-after first opening the container
Partially used containers must not be stored for later use and any remaining content must be discarded. .

-after dilution
Dilutions must be administered immediately after preparation. See also section **6.6**.

Chemical and physical in-use- stability has been demonstrated for 24 hours at 25 °C.
From the microbiological point of view the product must be used immediately. If not used immediately, in-use- storage times and conditions prior to use are the responsibility of the user .

6.4 Special precautions for storage

<to be completed nationally>

Climate zones I and II
This medicinal product does not require any special storage conditions.

Climate zones III and IV
Do not store above 25 °C.

Do not freeze. If accidentally frozen, discard ampoule.

Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

<to be completed nationally>
Ampoules of colourless glass type I (Ph. Eur.);
contents: 2 ml
Pack sizes: 5 x 2 ml, 10 x 2 ml, 20 x 2 ml, 10 x 10 x 2 ml
Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

The ampoules are for single dose use only. Discard unused contents. Shake well before use.

Do not use the product if the emulsion shows phase separation or large oil drops or if it is discoloured or if the ampoule is leaking.

Diazepam-Lipuro does not contain antimicrobial preservatives. The emulsion should be drawn up into a syringe immediately after opening of the ampoule under sterile conditions because fat emulsions promote microbial growth.

For continuous intravenous infusion, Diazepam-Lipuro can be diluted in

- lipid emulsions for injection or infusion containing as a base soya-bean oil emulsions emulsified with egg yolk (e.g. Lipofundin MCT/LCT 10%-20%, Lipoplus 20 %), or
- in 50 mg/ml (5 %) to 400 mg/ml (40 %) glucose solutions for infusion.

Diazepam-Lipuro can also be injected directly via an indwelling venous catheter into the tubing of a temporarily halted infusion of physiological saline.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

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8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

July 2014