SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diazepam Injection BP.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 5 mg of Diazepam.

Excipients with known effect:
Each ml contains 550 mg of propylene glycol – see sections 4.3 and 4.4.
Each ml contains 250 mg of ethanol – see sections 4.3 and 4.4.
Each ml contains a maximum of 23 micrograms of sodium – see section 4.4.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sterile injection.
Clear, colourless to greenish yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Diazepam is an anxiolytic, anti-convulsant and central muscle-relaxant. Diazepam is used to relieve anxiety and provide sedation in severe acute anxiety or agitation and for the management of agitation associated with delirium tremens.

Diazepam is used to relieve acute muscle spasm and tetanus.

Acute convulsions including status epilepticus, also convulsions due to poisoning and febrile convulsions. As an adjunct during endoscopy, in dentistry, surgery, radiology. Cardiac catheterisation, cardioversion, used pre-operatively to relieve anxiety, provide sedation, light anaesthesia and anterograde amnesia.

Paediatric patients
Diazepam Injection BP is used:

- to treat status epilepticus, convulsions due to poisoning, and febrile convulsions;
- to treat tetanus;
- as a pre-operative medication or premedication.

The suitability of treatment with Diazepam Injection BP in this population may need to be assessed on a case-by-case basis – see section 4.2.

General
Diazepam Injection BP contains propylene glycol and ethanol. This should be taken into consideration when use of a parenteral benzodiazepine is indicated, especially when used in high volumes (e.g. continuous infusion of high doses to treat tetanus or status epilepticus) and/or when used in patients at risk of developing propylene glycol toxicity (see section 4.4).

4.2 Posology and method of administration

Prior to starting treatment with diazepam, a discussion should be held with patients to put in place a strategy for ending treatment with diazepam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Posology

Adults

Severe acute anxiety or agitation:
10 mg by slow IV injection or IM injection which may be repeated after 4 hours.

Delirium Tremens:
10 – 20 mg by IV or IM injection.
Higher doses may be needed depending on the severity of symptoms.

Acute Muscle Spasm:
10 mg by slow IV injection or IM injection which may be repeated after 4 hours if required.

Tetanus:
Initially an IV dose of 100 – 300 micrograms/kg body weight every 1 - 4 hours. Continuous IV infusion of 3 – 10 mg / kg body weight per 24 hours can also be used. The chosen dose should be related to the severity of the case and in extremely severe cases higher doses have been used.

Status epilepticus, febrile convulsions, convulsions due to poisoning:
10 mg by IV injection, repeated if necessary 10 minutes later.
If indicated, this may be followed by slow intravenous infusion (maximum dose 3 mg / kg body weight over 24 hours).

Pre-operative medication or premedication:
10 – 20 mg to be administered immediately before the procedure. Higher doses may be necessary according to the clinical response.

Elderly or Debilitated Patients:
Doses should not exceed half those normally recommended.

Hepatic Impairment
In patients with chronic hepatic disease the dosage of Diazepam Injection BP may need to be reduced. Medical monitoring is required in patients with impaired hepatic function when Diazepam Injection BP is administered at doses of 0.45 mg / kg / day (equivalent to 50 mg / kg / day of propylene glycol) and above (see section 4.4).

Renal Impairment
In renal failure there is no clinically significant change to the half-life of diazepam and a dose adjustment is usually not necessary. Medical monitoring is required in patients with impaired renal function when Diazepam Injection BP is administered at doses of 0.45 mg / kg / day (equivalent to 50 mg / kg / day of propylene glycol) and above (see section 4.4)

Cardiorespiratory Impairment
A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Paediatric population

Diazepam Injection BP contains propylene glycol and ethanol (see section 4.4). The European Medicines Agency (EMA) has recommended daily exposure limits for the excipient propylene glycol in the following paediatric populations:

Population	**Recommended EMA propylene glycol exposure limit**
Neonates	1 mg / kg / day propylene glycol (equivalent to administration of Diazepam Injection BP at a dose of 9 micrograms / kg / day)
Infants and young children ≥ 1 month and < 5 years of age	50 mg / kg / day propylene glycol (equivalent to administration of Diazepam Injection BP at a dose of 0.45 mg / kg / day)
Children ≥ 5 years old	500 mg / kg / day propylene glycol (equivalent to administration of Diazepam Injection BP at a dose of 4.5 mg / kg / day)

Treatment with Diazepam Injection BP at the doses recommended for paediatric patients in the indications below may correspond to a propylene glycol dose which may exceed the associated EMA exposure limit. In such a situation any decision to use Diazepam Injection BP should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment (see section 4.4).

Status epilepticus, convulsions due to poisoning, febrile convulsions:

By intravenous injection:

Paediatric population	**Dosing recommendation**
Neonates	300–400 micrograms / kg, then 300–400 micrograms / kg after 10 minutes if required. Each injection to be given over 3–5 minutes.
Children 1 month	300–400 micrograms / kg (maximum per dose 10 mg),

– 11 years	then a further 300–400 micrograms / kg injection after 10 minutes, if required. Each injection to be given over 3 – 5 minutes
Children 12 – 17 years	10 mg then a further 10 mg after 10 minutes, if required. Each injection to be given over 3 – 5 minutes.

Tetanus:

By intravenous injection:

- 100– 300 micrograms / kg every 1–4 hours.

By intravenous infusion:

- 3–10 mg / kg body weight, adjusted according to response, to be given over 24 hours.

Pre-operative medication or premedication:

0.2 mg / kg body weight. The injection should be given slowly (0.5 ml per minute).

Method of administration

Diazepam Injection BP may be given IV injection, IM injection, or by IV infusion. The absorption from IM injection of diazepam may be variable, particularly for the gluteal muscles, and therefore the IM route of administration should only be used if IV administration is not possible.

Dilution
When administered via intravenous *infusion*, Diazepam Injection BP should be diluted in either Glucose 5% or Sodium Chloride 0.9% to a concentration of no more than 80 micrograms diazepam / ml – see also section 6.2. Diazepam Injection BP should not be diluted when administered via intravenous or intramuscular *injection*.

Intravenous use
IMPORTANT: In order to reduce the likelihood of adverse effects during intravenous administration the injection should be given slowly (1.0 ml solution per minute). It is advisable to keep the patient supine for at least an hour after administration. Except in emergencies, a second person should always be present during intravenous use and facilities for resuscitation should always be available.

Intravenous injection may be associated with local reactions and thrombophlebitis and venous thrombosis may occur. In order to minimise the likelihood of these effects, intravenous injections of diazepam should be given into a large vein of the antecubital fossa.

Duration of treatment
The duration of treatment should be as short as possible and should not exceed 4 weeks, including the period of tapering off, in order to minimise the potential adverse effects of diazepam itself (e.g. the potential for dependence and associated withdrawal effects, the potential for interactions with other CNS depressants). The potential for the development of adverse effects associated with product excipients

such as propylene glycol and ethanol needs to be considered as well (see section 4.4).
Diazepam Injection BP is intended for short-term use to address an acute clinical need when parenteral diazepam is indicated. A transition from parenteral to oral therapy, if required, should be made as soon as the clinical situation allows.

Medical monitoring
In general, it is recommended that patients should remain under medical supervision until at least one hour has elapsed from the time of injection / infusion. Patients should always be accompanied home by a responsible adult, with a warning not to drive or operate machinery for 24 hours.

Depending on the dose of Diazepam Injection BP administered, further medical monitoring may be required in populations at risk of developing propylene glycol toxicity – see recommendations for use in patients with renal or hepatic impairment and for use in paediatric patients (Posology, above). See also section 4.4.

4.3 Contraindications

- Known hypersensitivity to diazepam, other benzodiazepines, propylene glycol or any of the other product excipients (see section 6.1).
- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)
- Acute pulmonary insufficiency, respiratory depression, acute or chronic severe respiratory insufficiency (ventilator failure may be exacerbated).
- Sleep apnoea syndrome (condition may be exacerbated).
- Marked neuromuscular respiratory weakness including unstable myasthenia gravis (condition may be exacerbated).
- Severe hepatic impairment (elimination half-life of diazepam may be prolonged).
- Acute porphyria
- Planning a pregnancy (see section 4.6)
- Pregnancy (unless there are compelling reasons – see section 4.6)

Diazepam Injection should not be used alone in the treatment of depression or anxiety associated with depression due to the risk of precipitation of suicide in this patient group.

4.4 Special warnings and precautions for use

Intramuscular administration
The IM use of diazepam injection can lead to a rise in serum creatinine phosphokinase activity, with a maximum level occurring between 12 and 24 hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

Propylene glycol
Diazepam Injection BP contains both propylene glycol (550 mg per ml) and ethanol (250 mg per ml) – see also *Ethanol content*, below. Various adverse events have been reported with high doses or prolonged use of propylene glycol, such as

hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction,. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following haemodialysis.
Propylene glycol safety thresholds by population:

- *Neonates*
  In neonates, a safety threshold of 1mg / kg / day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 9 microgram / kg / day dose of Diazepam Injection BP) Exceeding this threshold may induce serious adverse effects in this population when co-administered with any substrate for alcohol dehydrogenase (such as ethanol).

- *Infants and children younger than 5 years old*
  In infants and children younger than 5 years old, a safety threshold of 50 mg / kg / day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 0.45 mg / kg /day dose of Diazepam Injection BP). The co-administration of propylene glycol at or above this safety threshold with any substrate for alcohol dehydrogenase (such as ethanol) may induce adverse effects in this population.

- *Adults and children aged 5 years and older*
  In adults and children aged 5 years and older a safety threshold of 50 mg / kg / day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 4.5 mg / kg /day dose of Diazepam Injection BP).

- *Patients with hepatic or renal impairment*
  Various adverse events attributable to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure, and liver dysfunction. A safety threshold of 50 mg / kg / day propylene glycol (equivalent to 0.45 mg / kg / day Diazepam Injection BP) has therefore been set by the EMA in patients with compromised hepatic or renal function.

Any decision to use Diazepam Injection BP at doses which would exceed the corresponding EMA exposure limit for propylene glycol should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment. Medical monitoring is required should treatment be considered appropriate.

The additive effect of treatment with Diazepam Injection BP with other products containing propylene glycol and/or any substrate for alcohol dehydrogenase and/or any dietary intake of these excipients should be taken into account.

Ethanol content
Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity – see section 4.3 and *Propylene glycol toxicity*, above.

A single dose of 20 mg (i.e. two ampoules) of this medicine administered to an adult weighing 70 kg would result in exposure to 14 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 2.4 mg/100 ml.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

Diazepam Injection BP may also be given by continuous intravenous infusion. IV infusion of the maximum recommended dose of 10 mg / kg body weight / 24 hours to treat tetanus in an adult patient weighing 70 kg would result in 700 mg (i.e. 70 ampoules) of this medicine being given in a 24-hour period. This would theoretically result in exposure to 500 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 83 mg/100 ml. Given the slow administration as an infusion within the 24-hour period, the effects of alcohol may be reduced.

The additive effect of treatment with Diazepam Injection BP with other ethanol-containing products and/or any dietary intake of ethanol should be taken into account.

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).

Concomitant use of alcohol/ other 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).

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with diazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with diazepam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with diazepam should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care, and for use in epilepsy).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person’s preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2), depending on the indication, and should not exceed 4 weeks, including the period of tapering off. Extension beyond this period 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 a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

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. 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 minimise the risk of withdrawal symptoms.

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.

Bereavement/ loss
Psychological adjustment may be inhibited by benzodiazepines.

Psychiatric and 'paradoxical' reactions
Reactions such as restlessness, agitation, irritability, aggressiveness, excitement, confusion, delusions, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects can occur.

These reactions are more likely in children and the elderly, and extreme caution should be used in prescribing benzodiazepines to patients with personality disorders. Should they occur, treatment should be discontinued.

Specific Patient Groups
Patients with depression
Diazepam should not be used alone to treat depression or anxiety associated with depression as suicide may be precipitated in such patients.

Patients with a history of alcohol & drug abuse, and patients on disulfiram
Diazepam should be used with extreme caution in patients with a history of alcohol or drug abuse– see *Drug dependence, tolerance and potential for abuse, Drug withdrawal syndrome, Propylene glycol toxicity* and *Ethanol content* above.

Diazepam should not be used concomitantly with disulfiram due to its ethanol content. A reaction may occur as long as two weeks after cessation of disulfiram (see section 4.5).

Patients with phobias and/or chronic psychoses
Diazepam is not recommended (inadequate evidence of efficacy and safety)

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

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

Paediatric population
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. Owing to the propylene glycol and ethanol content of Diazepam Injection BP, treatment at doses recommended of diazepam for paediatric patients may correspond to a propylene glycol dose which may exceed the associated EMA exposure limit. In such a situation any decision to use Diazepam Injection BP should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment (see section 4.2 and *Propylene glycol toxicity* and *Ethanol content*, above).

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

Hepatic Impairment
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. Medical monitoring in patients with impaired hepatic function may be required (see section 4.2 and *Propylene glycol toxicity*, above).

Renal Impairment
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. Medical monitoring in patients with impaired renal function may be required (see section 4.2 and *Propylene glycol toxicity*, above).

Cardiorespiratory Impairment
A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression (see section 4.2).

Diazepam injection should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Particular attention should be paid to the potential effects of drug interactions with diazepam in the elderly.

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).

Not recommended

Alcohol

Diazepam should not be used together with alcohol (CNS inhibition enhanced sedative effects: impaired ability to drive/ operate machinery).

Sodium oxybate
Avoid concomitant use (enhanced effects of sodium oxybate)

HIV-protease inhibitors
Avoid concomitant use (increased risk of prolonged sedation) – see below for zidovudine.

Take into account

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 psychological dependency due to enhancement of euphorigenic effects.

Anti-epileptic drugs
Pharmacokinetic studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change have been reported.

Phenobarbital taken concomitantly may result in an additive CNS effect. Increased risk of sedation and respiratory depression. Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

Special care should be taken in adjusting the dose in the initial stages of treatment.

Side effects may be more evident with hydantoins or barbiturates.

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

Narcotic analgesics
Enhancement of the euphoria may lead to increased psychological dependence.

Other drugs enhancing the sedative effect of diazepam
*C*isapride, lofexidine, nabilone, disulfiram and the muscle-relaxants – baclofen, Tizanidine, suxamethonium and tubocurarine.

Compounds that affect hepatic enzymes (particularly cytochrome P450):
- Inhibitors (e.g. cimetidine, isoniazid, erythromycin, omeprazole, esomeprazole) reduce clearance and may potentiate the action of benzodiazepines.

Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepines. The effects of benzodiazepines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Rifamycins (rifampicin)
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. Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Antihypertensives, vasodilators & diuretics
Enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin–II receptor antagonists, calcium channel blockers adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.
Enhanced sedative effect with alpha-blockers or moxonidine.

Dopaminergics
Possible antagonism of the effect of levodopa.

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

Zidovudine
Increased zidovudine clearance by diazepam

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

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

Caffeine
Concurrent use may result in reduced sedative and anxiolytic effects of diazepam.

Grapefruit juice
Inhibition of CYP3A4 may increase the plasma concentration of diazepam (possible increased sedation and amnesia). C_{max} is increased by 1.5 times and AUC by 3.2 times. Possible increased effect of diazepam.
This interaction may have little significance in healthy individuals, but it is not clear is if other factors such as old age or liver cirrhosis increase the risk of adverse effects with concurrent use.

Antipsychotics
Plasma concentrations of zotepine may be increased. Severe hypotension, collapse, loss of consciousness, respiratory depression, and potentially fatal respiratory arrest have been reported in a few patients taking benzodiazepines and clozapine. Salivary hypersecretion has also occurred. Caution is advised when initiating clozapine therapy in patients taking diazepam. There is an increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines are given with intramuscular olanzapine.

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.

Carbamazepine
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. Reduced effect of diazepam.

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

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)
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.
Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

Fluvoxamine
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. Drowsiness, reduced psychomotor performance and memory impairment may result. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

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

Cimetidine
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. Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole

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. Increased action of diazepam. Reduction of the diazepam dose may be necessary.

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

Isoniazid
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. Increased effect of diazepam.

Itraconazole
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. Possible increased effect of diazepam.

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

Disulfiram
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. Increased risk of CNS inhibition such as sedation.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no evidence regarding the safety of diazepam in human pregnancy, nor is there evidence from animal studies, that it is free from hazard.

Diazepam Injection BP contains propylene glycol (see sections 2 and 4.4). Although propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus. Diazepam Injection BP should not be used during pregnancy, especially during the first and last trimesters unless there are compelling reasons.

If diazepam is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of diazepam if she intends to become, or suspects that she is pregnant.

Results of retrospective studies suggest an increased risk of congenital malformation in infants or mothers who received diazepam during the first trimester of pregnancy.

Results of observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy.

Infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

An increase in foetal heart rate has occurred after diazepam use during labour. Hypoactivity, hypotonia, hypothermia, apnoea, feeding problems, hyperbilirubinaemia and kernicterus have been reported in neonates born to mothers who receive large doses of diazepam (generally greater than 30 mg) shortly before delivery.

Breast-feeding
Diazepam has been detected in breast milk. Diazepam Injection BP contains propylene glycol (see sections 2 and 4.4) which has also been found in breast milk. Administration of Diazepam Injection BP to lactating patients should be considered on a case-by-case basis.

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

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (See also section 4.5). Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

Details regarding a driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration.

Elderly patients may experience confusion 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, particularly in children.

The frequencies of adverse events are ranked according to the following:

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	Undesirable effects
Blood and lymphatic system disorders	Rare	Blood dyscrasias
	Very rare	Leukopenia, Thrombocytopenia, Agranulocytosis
Immune system disorders	Very rare	Hypersensitivity reactions, including anaphylaxis.
Metabolism and nutrition disorders	Not known	Metabolic disorders including metabolic acidosis, increased anion gap and hyperosmolality have been reported as a consequence of propylene glycol toxicity (see section 4.4).
Psychiatric disorders	Common	Confusion.

	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse behavioural effects.[a] Emotional poverty, decreased alertness and depression.[b]
	Not known	Drug dependence (see section 4.4)
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.
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest.
Vascular disorders	Rare	Hypotension, syncope. The incidence of hypotension may be reduced by not exceeding the recommended rate of administration. Patients should be managed in the supine position and kept there throughout the procedure.
	Not known	Intravenous injections of diazepam may be associated with local reactions and thrombophlebitis and venous thrombosis may occur.
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression.
	Rare	Respiratory arrest, increased bronchial secretion.
	Not Known	Apnoea, worsening of obstructive pulmonary disease
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, Drug withdrawal symptoms (see section 4.4). Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed. In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.
	Not known	Anaphylaxis, injection site pain or irritation (see also Vascular disorders)
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 dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

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 MHRA website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Features

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of the signs and to seek immediate medical help if they occur.

The symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, profound sleep, hypotension, bradycardia, nystagmus) or paradoxical excitation. In most cases only observation of vital functions is required.

Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Rarely, propylene glycol toxicity has been reported following higher than recommended doses (see section 4.4).

Management
Maintain a clear airway and adequate ventilation.

Monitor level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.

Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.

Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.
If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered.

Supportive measures are indicated depending on the patient's clinical state.

Benzodiazepines are poorly dialysable.

Flumazenil, a benzodiazepine antagonist, is not advised as a routine diagnostic test in patients with reduced conscious level. It may sometimes be used as an alternative to ventilation in children who are naive to benzodiazepines, or in patients with COPD to avoid the need for ventilation. It is not necessary or appropriate in cases of poisoning to fully reverse the benzodiazepine effect. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a benzodiazepine and a tricyclic antidepressant or any other drug that causes seizures. This is because the benzodiazepine may suppress seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.

The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, the abrupt suppression of the

protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patients postcardiac arrest is also contraindicated.

It should be used with caution in patients with a history of seizures, head injury, or chronic benzodiazepine use.

Occasionally a respirator may be required but generally few problems are encountered, although behavioural changes are likely in children.

If excitation occurs, barbiturates should not be used.

Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytic drug, Benzodiazepine derivatives, ATC code: N05BA01

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties. It is used in the treatment of anxiety and tension states, as a sedative and pre-medicant, in the control of muscle spasm as in tetanus, and in the management of alcohol withdrawal symptoms. It is of value in patients undergoing orthopaedic procedures endoscopy and cardioversion.

5.2 Pharmacokinetic properties

Diazepam is metabolised to two active metabolites, one of which, desmethyldiazepam, has an extended half-life. Diazepam is therefore a long-acting benzodiazepine and repeated doses may lead to accumulation.

Diazepam is metabolised in the liver and excreted via the kidney. Impaired hepatic or renal function may prolong the duration of action of diazepam. It is recommended that elderly and debilitated patients receive initially one half the normal recommended dose.

During prolonged administration, for example in the treatment of tetanus, the dosage should generally be reduced after 6-7 days, to reduce the likelihood of accumulation and prolonged CNS depression.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Propylene Glycol
Sodium Hydroxide
Water for Injections

6.2 Incompatibilities

Diazepam injection should not be mixed with other drugs or IV fluids and should not normally be diluted except when given slowly in large intravenous infusions of normal saline or glucose.

Not more than 40 mg of Diazepam Injection BP should be added to a 500 ml infusion solution (i.e. a maximum concentration of 80 micrograms diazepam /ml). The solution should be freshly made up and used within six hours.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.
Keep ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type I clear glass ampoule, 2ml.
Packed in cardboard cartons to contain 10 arnpoules x 2m1.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Nexus, Gloucester Business Park
Gloucester, GL3 4AG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 November 1983/ October 2004

10 DATE OF REVISION OF THE TEXT

30/01/2026