SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DIAZEPAM 2mg/5ml ORAL SOLUTION SUGAR FREE

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml spoonful contains 2mg Diazepam.

Excipients with known effect
Each 5ml contains:
409mg of Propylene glycol PhEur
3.000ml (1.91g to 2.58g) Sorbitol, liquid (Non-crystallising) (E420) PhEur
2.500mg of Propyl parahydroxybenzoate (E216) PhEur
5.000mg of Methyl parahydroxybenzoate (E218) PhEur
0.500ml (0.63g) of Glycerol (E422) PhEur.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A pink syrup with an odour of raspberries.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diazepam has potent anxiolytic, anticonvulsant and central muscle-relaxing properties; these effects are probably mediated through special areas in the CNS. It also has uses in pre-operative medication and is used in the treatment of skeletal-muscle spasm, and the associated pain.

The main uses are:

Adults:
1) The short-term relief (2 to 4 weeks) only of anxiety which is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
The use of benzodiazepines to treat short-term anxiety is considered to be inappropriate.
2) The management of cerebral palsy spasticity in selected cases.
3) Muscle spasm; as an adjunct to the control of muscle spasm in tetanus.

4) As an adjunct to the management of certain types of epilepsy (e.g. myoclonus).
5) Symptomatic treatment of acute alcohol withdrawal.
6) As oral premedication.

Paediatric population:
1) Night terrors and somnambulism.
2) As an adjunct to the control of muscle spasms as in tetanus.
3) The management of spasticity in cerebral palsy in selected cases.
4) Oral premedication.

Diazepam should be used to treat insomnia only when it is severe, disabling or subjecting the individual to extreme stress.

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

As an anxiolytic, the lowest effective dose should be employed; dosage regimes should not exceed beyond 14 days, including tapering off. Patients who have received benzodiazepines for a long time may require an extended withdrawal period. Long-term chronic use is not recommended.

Adults:
Anxiety states, obsessive-compulsive neuroses, and other psychiatric disorders: 2-30mg daily in divided doses.
Insomnia associated with anxiety: 5mg to 15mg before retiring.
Management of cerebral palsy spasticity in selected cases: 2mg to 60mg daily in divided doses.
Muscle spasm of varied aetiology, fibrositis, cervical spondylosis: 2mg to 15mg daily in divided doses.
In the control of muscle spasms as in tetanus: 3mg to 10mg/kg body weight daily.
The selected dose should relate to the severity of the case and in extremely severe cases higher doses have been used. Intravenous diazepam is recommended initially (see separate prescribing information).
Adjunct to the management of some types of epilepsy: 2mg to 60mg daily in divided doses.
Symptomatic treatment of acute alcohol withdrawal: 5mg to 20mg, repeated if necessary in 2 to 4 hours.
Premedication: 5mg to 20mg.

Paediatric population:
Night terrors and somnambulism: 1mg to 5mg daily before retiring.
In the control of muscle spasms as in tetanus: 3mg to 10mg/kg body weight daily.
Management of spasticity in cerebral palsy in selected cases: 2mg to 40mg daily in divided doses.
Premedication: 2mg to 10mg.

Elderly and debilitated patients:
Doses should not exceed half the above recommended adult doses.

Hepatic impairment
Patients with impaired hepatic function should be given a reduced dose.

Renal impairment
Patients with impaired renal function should be given a reduced dose.

Duration
Treatment should be as brief as possible. The indication should be reassessed regularly especially in the absence of symptoms. The overall duration of treatment should not exceed 8 to 12 weeks for the majority of patients, including the period of reduction in dosage (see section 4.4). The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms. Treatment should always be tapered off gradually.

In some cases, it may be necessary to extend treatment beyond the recommended periods. This requires accurate and repeated assessments of the patient's condition.

Prevention and treatment of delirium tremens and other manifestations of alcohol withdrawal: short-term treatment in the range of 8 to 10 days.

Method of administration
For oral administration.

4.3 Contraindications

Diazepam is contra-indicated for patients with:

- Hypersensitivity to diazepam, benzodiazepines or any of the excipients listed in 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 (ventilatory failure may be exacerbated).
- Myasthenia gravis (condition may be exacerbated).
- Sleep apnoea (condition may be exacerbated).
- Severe hepatic insufficiency (elimination half-life of diazepam may be prolonged).
- Acute porphyria.
- Diazepam should not be used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients.
- Planning a pregnancy (see section 4.6).
- Pregnancy (unless there are compelling reasons – see section 4.6).

4.4 Special warnings and precautions for use

Warnings
Benzodiazepines are not recommended for the main treatment of psychosis.

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).

Concurrent alcohol use/CNS depressant agents
The concomitant use of diazepam and alcohol (ethanol) (alcoholic beverage or alcohol-containing medication) and/or central nervous system depressants should be avoided.
This combination may increase the clinical effects of diazepam, which can lead to severe sedation, clinically significant respiratory and/or cardiovascular depression (see section 4.5).

Seizures
In patients presenting with drowsiness or hypotonia after diazepam, an infection affecting the nervous system should be excluded before attributing symptoms to diazepam.

Starting an anti-epileptic medication can be followed by an increase in seizures or the onset of a new type of seizure in the patient. This is independent of the natural fluctuations to be expected in certain types of epilepsy. Possible causes for seizures after diazepam include: epileptic syndrome of the patient, a concurrent modification of the anti-epileptic treatment, a pharmacokinetic interaction with another medicine, toxicity or overdose. Otherwise, it may be that there is no explanation other than a paradoxical reaction.

Pharmacological tolerance
Some loss of efficacy of diazepam may develop after repeated use for a few weeks.

Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardiorespiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients.

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 with the dose and duration of treatment, and 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. Routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

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.

As sudden discontinuation of benzodiazepines may result in convulsions, particular care should be taken in patients with epilepsy, other patients who have had a history of seizures or in alcohol or drug dependants. Discontinuation should be gradual in order to minimise the risk of withdrawal symptoms.

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.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with diazepam may recur in an enhanced form 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 (see section 4.2).

Amnesia
Diazepam may induce anterograde amnesia. 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 uninterrupted sleep of 7-8 hours. Amnestic effects may be associated with inappropriate behaviour.

Anterograde amnesia may occur even if benzodiazepines are used within the normal dose range, though this is seen in particular at high dose levels.

Behavioural disorders and paradoxical reactions
In some subjects, benzodiazepines and related products can cause a syndrome that involves varying degrees of impairment of consciousness and behavioural and memory disorders: worsening insomnia, nightmares, restlessness, nervousness, aggression, anger, delusions, hallucinations, confused-oniric state, psychotic symptoms, impulsive disinhibition, euphoria, irritability and anterograde amnesia. Should these reactions occur, treatment should be discontinued.

This syndrome can be accompanied by conditions that are potentially dangerous to the patient or others, such as: Unusual behaviour for the patient, self- or hetero-aggressive behaviour, especially if the environment attempts to interfere with the patient's activity, automatic driving with post-event amnesia. Paradoxical reactions are more likely to occur in children and the elderly.

Extreme caution should be used in prescribing diazepam to patients with personality disorders.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Hepatic disorders
Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. Diazepam should be used with caution in patients with chronic hepatic disease and dosage may need to be reduced.

Risk of accumulation
Benzodiazepines and related drugs (like all drugs) persist in the body for a period of about 5 half-lives (see section 5.2). In the elderly or those with kidney or liver failure, half-life can be increased considerably. When taken repeatedly, the drug and its metabolites reach steady-state much later and at a much higher level. It is only once steady-state has been reached that efficacy and safety can be fully evaluated. A dosage adjustment may be necessary (see section 4.2).

Elderly subject
Benzodiazepines and related products should be used with caution in the elderly, due to the risk of sedation and/or muscle-relaxant effects that may promote falls, with often serious consequences in this population. The lowest possible dose should be used in the elderly person (half the recommended dose in adults, for example).

In patients with a major depressive episode
Benzodiazepines should not be used alone in the treatment of depression or anxiety associated with depression as suicide may be precipitated in such patients.

Withdrawal steps must be clear to the patient.

In addition to the need for gradual decrease in doses, patients should be warned of the possibility of a rebound phenomenon, in order to minimize the anxiety that could result from the symptoms associated with rebound. The patient should be warned of the possible symptoms of this phase.

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

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. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.

Respiratory failure
In respiratory failure, the depressant effect of benzodiazepines should be taken into account (especially since anxiety and agitation may be signs of decompensation of respiratory function that justifies moving to the intensive care unit).

Diazepam should be used with caution in patients with porphyria, coma and organic brain changes, particularly arteriosclerosis.

Hypoalbuminaemia (may predispose the patient to higher incidence of sedative side effects).

Excipients
Diazepam oral solution contains 409mg Propylene glycol per 5ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. See also section 4.6.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis

Diazepam Oral solution contains Sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Diazepam oral solution contains 2.500mg of Propyl parahydroxybenzoate (E216) per 5ml solution and 5.000mg of Methyl parahydroxybenzoate (E218) per 5ml solution. May cause allergic reactions (possibly delayed).

Diazepam oral solution contains 0.63g of glycerol per 5ml solution. May cause headache, stomach upset and diarrhoea in doses higher than 31mg.

This medicine contains less than 1 mmol sodium (23 mg) per dosage that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 psychic dependency due to enhancement of euphorigenic effects.

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).

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, suxethonium and tubocurarin.

Compounds that affect hepatic enzymes (particularly cytochrome P450):
• Inhibitors (eg 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 ACEinhibitors, 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.

Antacids
Concurrent use may delay absorption of diazepam.

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.

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

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. 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 ezomeprazole 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
Numerous data from cohort studies did not show the occurrence of malformative effects during exposure to benzodiazepines during the first trimester of pregnancy. However, in some case-control epidemiological studies, an increase in the occurrence of cleft palates has been

observed with benzodiazepines. According to these data, the incidence of cleft labio-palatins in newborns is less than 2/1000 after exposure to benzodiazepines during pregnancy, while the expected rate in the general population is 1/1000.

Intake of high doses of benzodiazepines in the second and/or third trimesters of pregnancy has resulted in decreased fetal active movements and variability in fetal heart rate. Treatment with benzodiazepines in the later stages of pregnancy, even with low doses, may be responsible for signs of exposure in the newborn such as axial hypotonia, or impaired suction leading to poor weight gain. These signs are reversible, but can last 1 to 3 weeks depending on the benzodiazepine prescribed. In high doses, respiratory depression or apnea, and hypothermia may occur in the newborn. Neonatal withdrawal syndrome is possible, even in the absence of signs of exposure, characterized by hyperexcitability, agitation and tremors.

Given these data, as a precautionary measure, the use of diazepam is not recommended during pregnancy regardless of the term.

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

At the end of pregnancy, if it is really necessary to introduce diazepam treatment, avoid prescribing high doses and take into account, for the monitoring of the newborn, the effects previously described.

Breast-feeding
Benzodiazepines are found in the breast milk -Reports have demonstrated milk: plasma concentration ratios to vary between 0.2 and 2.7. There is therefore a risk of accumulation in the breastfeeding child. Benzodiazepines should not be given to breast feeding mothers.

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, impaired concentration, dizziness, blurred vision and impaired muscular function may adversely effect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose. Concurrent medication may increase these effects (see section 4.5).

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. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.
Increased salivary and bronchial secretion has been reported, in particular in children.

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

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

The frequencies of adverse events are ranked according to the following:
Very common (≥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
Immune system disorders	Very rare	Anaphylaxis.
Psychiatric disorders	Common	Confusion.
	Rare	Drug dependence (see section 4.4). Emotional poverty, decreased alertness and depression.[a]
Nervous system disorders	Very common	Drowsiness.
	Common	Ataxia, impaired motor ability, tremor.
	Uncommon	Anterograde amnesia.[b] Concentration difficulties, balance disorders, dizziness, headache, slurred speech.
	Rare	Unconsciousness, insomnia, dysarthria.
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus.
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest.
Vascular disorders	Rare	Hypotension, syncope.
Respiratory, thoracic and	Uncommon	Respiratory depression.

mediastinal disorders	Rare	Respiratory arrest, increased bronchial secretion.
	Not Known	Apnoea
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	Drug withdrawal symptoms (see 4.4).[c]
Investigations	Very rare	Elevation of transaminases.

[a] Pre-existing depression may be unmasked during benzodiazepine use.

[b] May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

[c] Drug withdrawal symptoms (see 4.4 Special warnings and precautions).
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.

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

4.9 Overdose

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

Symptoms
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.

Coma usually lasts only a few hours but in elderly people it may be more protracted and cyclical.

Treatment
Monitor the patient's vital signs and introduce support measures based on the patient's clinical condition. In particular, patients may need symptomatic treatment of central cardio-respiratory and neurological effects.

Consider activated charcoal (50g for an adult, 1g/kg for a child) in adults who have taken more than 100mg or children who have taken more than 1mg/kg within one hour, provided they are not too drowsy.

Gastric lavage is unnecessary if these drugs have been taken alone. Patients who are asymptomatic at four hours are unlikely to develop symptoms.

In case of severe CNS depression, consider the use of flumazenil a benzodiazepine antagonist. It should only be administered under close supervision. Since flumazenil has a short half-life (about an hour), patients will need to be monitored after its effects have disappeared. Flumazenil should be used with extreme caution in the presence of medications that reduce the epileptogenic threshold (e.g. tricyclic antidepressants). See the prescription information for flumazenil for more information on the proper use of this medication.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N05B A01
Pharmacotherapeutic group: Anxiolytics.

Diazepam belongs to the class of 1-4 benzodiazepines and has a pharmacodynamic activity qualitatively similar to that of other compounds in this class: muscle relaxant, anxiolytic, sedative, hypnotic, anticonvulsant and amnesiac.

These effects are related to a specific agonist action on a central receptor that is part of the "GABA-OMEGA macromolecular receptors" complex, also known as BZ1 and BZ2 and modulating the opening of the chlorine channel.

5.2 Pharmacokinetic properties

Absorption
The absorption of diazepam is rapid: the t_{max} is between 0.5 and 1.5 hours. Bioavailability is high and ranges from 80% to 100%.

Distribution
The distribution volume varies from 1 to 2 L/kg. The total plasma clearance of diazepam, calculated after intravenous administration, is 30 ml/min. It tends to decrease in multiple administrations. Protein binding is important, averaging 95-98%.

The plasma elimination half-life of diazepam is between 32 and 47 hours. The state of equilibrium of plasma concentrations is reached after a minimum of one week.

A concentration-effect relationship could not be established for this class of products, due to the intensity of their metabolism and the development of a tolerance.

Benzodiazepines pass through the blood-brain barrier as well as into the placenta and breast milk. For diazepam, the milk/plasma ratio is equal to 2.

Biotransformation and elimination
The liver plays a major role in the process of metabolizing benzodiazepines, which explains the negligible percentage (0.1%) unchanged product found in the urinary tract.

The main metabolite of diazepam is desmethyldiazepam, also active, whose half-life is longer than that of the mother molecule (between 30 and 150 hours). The hydroxylation of this molecule is mediated by the isoenzymes CYP3A and CYP2C13 and gives rise to two other active metabolites, oxazepam and temazepam. Inactivation is by glucuronoconjugation, resulting in water-soluble substances eliminated in the urine.

Pharmacokinetic interactions:
The oxidative metabolism of diazepam, leading to the formation of N-demethyldiazepam, 3 hydroxydiazepam (tenazepam) and oxazepam, is mediated by CYP2C19 and CYP3A isoenzymes of cytochrome P450.
As one in vitro study has shown, the hydroxylation reaction is performed primarily by the CYP3A isoform while N-demethylation is mediated by both CYP3A and CYP2C19.

The results of in vivo studies in human volunteers confirmed in vitro observations.

As a result, substrates that are modulators of CYP3A and CYP2C19, can potentially alter diazepam pharmacokinetics.

Populations at risk
Elderly subject: liver metabolism decreases as well as total clearance with increased half-life, free fraction, and concentrations at steady state. Doses should be reduced accordingly.

Liver failure: there is an increase in the free fraction (and therefore the volume of distribution) as well as the half-life.

Pregnant women: the distribution volume and half-life of diazepam are increased.

5.3 Preclinical safety data

The carcinogenic potential of diazepam was studied in mice and rats treated orally at a dose of 75 mg/kg/day for 80 and 104 weeks respectively. An increase in the incidence of hepatocellular tumours was observed in male mice. No significant increase in tumor incidence was observed in female mice or rats.

Diazepam has been shown to have teratogenic potential in mice at doses of 45 mg/kg/day (3.6 times the maximum recommended dose in humans of 1 mg/kg on a mg/m2 basis) and in hamsters at 280 mg/kg/day (38 times the maximum recommended dose in humans).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains:

Docusate sodium
Aluminium magnesium silicate
Propylene glycol
Raspberry flavour
Saccharin sodium
Erythrosine (E127)
Sorbic acid (E200)
Propyl parahydroxybenzoate (E216)
Methyl parahydroxybenzoate (E218)
Sorbitol, liquid (Non-crystallising) (E420)
Glycerol (E422)

6.2 Incompatibilities

None known

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton and keep the container tightly closed.

6.5 Nature and contents of container

The product containers are amber glass bottles with plastic screw caps contained in a carton.

Pack sizes: 50ml, 100ml, 150ml, 200ml, 300ml, 400ml, 500ml, 1000ml, 5000ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 00142/0103

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/1978 / 16/12/2003

10 DATE OF REVISION OF THE TEXT

09/02/2026