SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diazepam Syri Pharma 0,4 mg/ml, suspensie voor oraal gebruik

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 0.4 mg of diazepam.

Excipients with known effect:
Each ml of oral suspension contains 1 mg methyl parahydroxybenzoate (E218), 0.22 mg propyl parahydroxybenzoate (E216), 0.302 mg sodium, 0.312 mg potassium, 1 mg ethanol (E1510), 220 mg sucrose, 0.0011 mg benzoic acid and 1.78 mg propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Suspension

A pink colour suspension

pH: 4.5-6.6

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
- Symptomatic treatment of anxiety. Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

- Symptomatic treatment of Alcohol Withdrawal syndrome.

Adults and children from 6 months of age
- Symptomatic treatment of skeletal muscle spasm (inflammation of muscles or joints, trauma), including spasticity caused by upper motor neuron disorders (such as cerebral palsy, paraplegia as well as athetosis and stiff-person syndrome).

4.2 Posology and method of administration

The dose of diazepam should be individualized according to the need of each individual and should be administered as in an effective dose which is as small as possible, especially in the paediatric population, elderly patients and debilitated individuals or in those with liver disease or low serum albumin level.

Diazepam will be given at times when they are most needed by the patient, usually in the afternoon or evening.

The patient should be monitored regularly at the beginning of treatment in order to reduce the dose or frequency of administration if deemed necessary and thus prevent overdosage due to accumulation.

The adult dose is:

Symptomatic treatment of anxiety: 2mg (5ml) to 10 mg (25ml), 2 to 3 times daily, depending on the severity of symptoms. Maximum dose is 30 mg per day.

Symptomatic treatment of Alcohol Withdrawal syndrome: 10 mg (25ml) 3 or 4 times during the first 24 hours, reducing to 5 mg (12.5ml) 3 or 4 times daily, as needed.

Symptomatic treatment of skeletal muscle spasm: 2mg (5ml) to 10 mg (25ml), 3 or 4 times daily.

Special Populations

Paediatric population: 0.1 - 0.3 mg /kg per day, in 2 to 4 divided doses. Benzodiazepines should not be used in children without careful evaluation of the indication. Because of the variety of responses of children to CNS-acting medications, treatment should be initiated at the lowest dose and increased as needed. Do not use in children under 6 months of age.

Elderly population (>65 years)

The pharmacological effects of benzodiazepines in elderly patients appear to be greater than in the rest of the adult population, even with similar plasma concentration, possibly due to age-related changes in drug-receptor interactions, post-receptor mechanisms and organ functions (see section 5.2).

In elderly patients or in the presence of debilitating diseases, it is recommended to administer the lowest possible dose, 2mg (5ml) to 2.5 mg (6.25ml), 1 or 2 times daily, increasing gradually, according to need and tolerance.

Patients with mild or moderate renal and/or hepatic impairment: 2mg (5ml) to 2.5 mg, (6.25ml) 1 or 2 times a day, increasing gradually, according to need and tolerance. These patients should be closely monitored at the start of treatment to minimise the dose and/or frequency of administration to prevent accumulation overdose (see section 5.2).

Patients with severe hepatic impairment: They should not be treated with diazepam (see section 4.3).

Duration of treatment

The duration of treatment should be as short as possible (see section 4.4). In general, treatment should not last longer than 4 weeks including tapering off process. Extension beyond this period should not take place without re-evaluation of the patient's status. The patient must be re-evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment. Long-term chronic use is not recommended. In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

Tapering off

Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced.

Method of administration

For oral administration.
Shake well before use for at least 10 seconds

[Product name] is provided with:

A 1ml oral syringe (with 0.01 ml intermediate graduations) for single doses up to 1 ml.
A 10 ml oral syringe (with 0.1 ml intermediate graduations) for single doses up to 10 ml.
A 30 ml measuring cup (with 2.5 ml intermediate graduations up to 25 ml) for single doses over 10 ml.

Paediatric doses may be given using the 1ml or 10 ml syringe
Adult doses may be given using the 10ml syringe or 25ml cup

After each use, the bottle should be closed with the screw cap and wash the syringe or cup with water.

Instructions for use are provided in the package leaflet.

The measuring syringe or cup provided in the pack should be used to deliver the required dose. After each use, the bottle should be closed with the screw cap and wash the syringe or cup with water.

When prescribing Diazepam Oral Suspension especially for adults the volume of suspension to be administered should be considered and if judged too large, alternative formulations should be considered

4.3 Contraindications

Diazepam is contraindicated for patients with:

- Hypersensitivity to diazepam, benzodiazepines or any of the excipients listed in section 6.1
- Myasthenia gravis
- Severe respiratory failure
- Sleep apnoea syndrome
- Severe liver failure, as benzodiazepines can cause hepatic encephalopathy

4.4 Special warnings and precautions for use

Concomitant Use of Alcohol/CNS Depressants
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, including severe sedation that may result in coma or death, respiratory and/or clinically relevant cardiovascular depression (see section 4.5).

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 (see section 4.5)

History of alcoholism or drug addiction
Diazepam should be used with extreme caution in those patients with a history of alcoholism or drug addiction.

Diazepam should be avoided in patients with dependence on CNS depressants, including alcohol.

An exception to the latter is the treatment of acute withdrawal symptoms.

Hepatic impairment
Benzodiazepines may contribute to the precipitation of episodes of hepatic encephalopathy in severe hepatic impairment. Particular caution should be exercised when administering Diazepam to patients with mild to moderate hepatic impairment (see section 4.3).
Tolerance
Continued use of diazepam over a long period of time may result in a decreased response to the action of benzodiazepines.

Dependence
Treatment with benzodiazepines and benzodiazepines-type drugs may lead to the development of physical and psychological dependence (see section 4.8). The risk of dependence increases with the dose and duration of treatment and is also higher in patients with a history of drug addiction and/or alcoholism or in patients with marked personality disorders. Abuse has been reported in polydrug abusers. Diazepam should be used with extreme caution in patients with a history of drug and/or alcohol addiction. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Withdrawal
Once physical dependence has developed, abrupt termination of treatment may be accompanied by withdrawal symptoms, such as headaches, diarrhoea, muscle pain, severe anxiety, tension, restlessness, confusion, and irritability. In severe cases, the following symptoms have been described: loss of sense of reality, depersonalisation, hyperacusis, tingling and cramping in the limbs, intolerance to light, sound and physical contact, hallucinations or convulsions (see section 4.8).

When using benzodiazepines, withdrawal symptoms can develop when switching to a benzodiazepine with a considerably shorter elimination half-life.

Rebound insomnia and anxiety
A transient syndrome has been described after withdrawal of treatment, characterized by the reappearance of the symptoms – although more accentuated – that led to the initiation of treatment. It can be accompanied by other reactions such as mood swings, anxiety or sleep disturbances and restlessness. Since the probability of the occurrence of a withdrawal/rebound phenomenon is greater after abrupt termination of treatment, it is recommended to reduce the dose gradually until it is definitively discontinued.

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.

Duration of treatment
The duration of treatment should be as short as possible and must not last any longer than 4 weeks, including the tapering off process (see section 4.2).

Treatment should never be prolonged without a reassessment of the patient's situation.

It may be useful to inform the patient at the beginning of treatment that the treatment is of limited duration and to explain precisely how to decrease the dose progressively. It is also important that the patient is aware of the possibility of the appearance of a rebound phenomenon, which will reduce their anxiety about the symptoms that may appear when withdrawing the medication.

Since diazepam is a long-acting benzodiazepine, the patient should be informed of the inadvisability of switching to another short-acting benzodiazepine, because of the possibility of withdrawal phenomenon.

Amnesia
It should be noted that benzodiazepines may cause anterograde amnesia even at therapeutic doses, and that the risk is increased with increasing dose. 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 to 8 hours (see also section 4.8) Amnesic effects may be associated with behavioural disturbances.

Psychiatric and Paradoxical Reactions
Benzodiazepines can produce reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusions, fits of anger, nightmares, hallucinations, psychosis, inappropriate behaviour, and other adverse behavioural effects. If this occurs, treatment should be discontinued.
These reactions are more frequent in the paediatric population and elderly patients.

Special Patient Groups

Paediatric population
The safety and efficacy of Diazepam in children younger than 6 months have not been established, so it should not be used in this age group. It can only be used with extreme caution if there are no other therapeutic alternatives.

The duration of treatment in children older than 6 months should be kept to a minimum.

Elderly population
Elderly patients should receive a lower dose (see section 4.2). Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in the elderly.

It is also recommended to use lower doses in patients with chronic respiratory failure because of the associated risk of respiratory depression.

Benzodiazepines are not recommended for the first-line treatment of psychotic illness.

Benzodiazepines should not be used alone for the treatment of depression or anxiety associated with depression (suicide risk).

Excipient warning:
Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216): May cause allergic reactions (possibly delayed).

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.
Ethanol (E1510): This medicinal product contains 1 mg of alcohol (ethanol) per ml. The amount in 5 ml dose of this medicinal product is equivalent to less than 1 ml beer or 1 ml wine. Adults and older children should not experience any effect but effects on younger children are less certain.

Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product. This medicinal product contains 220mg of sucrose per ml. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth.

Propylene glycol (E1520): This medicinal product contains 1.78 mg propylene glycol per ml.

Benzoic acid (E210): This medicinal product contains 0.0011 mg benzoic per ml.

4.5 Interaction with other medicinal products and other forms of interaction

Drug-drug pharmacokinetic interaction
The metabolism of diazepam and its major metabolite, DMDZ, depend on the isoenzymes CYP3A4 and CYP2C19 cytochrome P450. Modulators of these enzymes can produce changes in the arrangement and effects of diazepam. Strong interactions with compounds that simultaneously affect diazepam's oxidative metabolic pathways are observed; If only one metabolic pathway of diazepam is affected, even with strong inhibitors, only moderate effects may occur. CYP3A4 and CYP2C19 inhibitors decrease metabolic activity and may lead to higher concentrations of diazepam and the demethylated metabolite and consequently lead to longer/more intense sedation and anxiolytic effects. These changes may be increased in patients with increased sensitivity to the effects of diazepam, for example, due to age, reduced liver function, or treatment with other oxidation-causing medications. CYP3A4 andCYP2C19 inducers can lead to lower than expected concentrations and thus a lack of desired efficacy.

Effects of Other Drugs on the Pharmacokinetics of Diazepam

Enzyme inhibitors

Grapefruit juice contains strong CYP3A4 inhibitors. When grapefruit juice was administered instead of water, exposure to diazepam was strongly increased (3.2 times AUC; 1.5 times C_{max}) and the time at which peak concentration was reached was delayed.

Antifungal azole derivatives inhibit CYP3A4 and CYP2C19 pathways and lead to increased exposure to diazepam (AUC ratio diazepam-fluconazole 2.5; diazepam-voriconazole 2.2) and a prolonged elimination half-life of diazepam (with fluconazole from 31 h to 73 h; with voriconazole from 31 h to 61 h). The influence of antifungals on diazepam levels was only observed after 4 h of administration and thereafter. Itraconazole has a more moderating effect with no clinically significant interaction with diazepam as determined by psychomotor developmental tests.

The serotonin reuptake inhibitor, fluvoxamine, is also an inhibitor of both degradation pathways of diazepam and not only increases exposure to diazepam by 180% and prolongs its elimination half-life from 51 h to 118 h, but also increases exposure and time to steady state of the demethylated metabolite. This may cause drowsiness, reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Fluoxetine showed a more moderate effect on the AUC of diazepam (approximately a 50% increase) and did not affect psychomotor response because the combined concentrations of diazepam and demethylated diazepam were similar with and without fluoxetine.
Combined hormonal contraceptives appear to reduce clearance (by 67%) and prolong the elimination half-life (by 47%) of diazepam. Diazepam-induced psychomotor disturbance in women on contraceptives may be greater during the 7-day menstrual break when hormonal combinations are removed than when contraceptives are taken. There is limited evidence that benzodiazepines may increase the incidence of breakthrough bleeding in women on hormonal contraceptives. No contraceptive failures have been observed.

The proton pump inhibitor, omeprazole, CYP3A4 inhibitor and CYP2C19, administered at doses of 20 mg daily increases the AUC of diazepam by 40% and half-life by 36%, at the dose of 40 mg daily, omeprazole increased the AUC of diazepam by 122% and half-life by 130%. Elimination of demethylated diazepam was also reduced. The effect of omeprazole was only observed in large metabolisers, but not in poor metabolisers of CYP2C19. Esomeprazole (but not lansoprazole or pantoprazole) has the potential to inhibit diazepam metabolism to a similar degree to omeprazole.

The histamine H2 receptor antagonist, cimetidine, which is an inhibitor of multiple CYP isoenzymes, includingCYP3A4 and CYP2C19, reduces the clearance of diazepam and demethylated diazepam from 40% to 50%. The effect is no different after one day of treatment or after chronic treatment with cimetidine and results in increased exposure and prolonged elimination half-life of diazepam and its major metabolite after a single dose and at increased steady-state concentrations after multiple doses of diazepam. Increased sedation has been observed with co-administration of cimetidine. Reduction of the diazepam dose may be necessary. No further pharmacokinetic interactions have been observed with the H2 antagonists ranitidine or famotidine.

Disulfiram inhibits diazepam metabolism (median clearance decrease to 41%, increase in half-life 37%), and probably increased metabolism of diazepam's active metabolites. Sedative effects may occur.

Antituberculosis therapy may change the disposition of diazepam. In the presence of isoniazid, mean diazepam exposure (AUC) and its half-life increased (by 33%-35% on average), with the greatest changes observed in subjects with slow acetylation phenotype.

The calcium channel blocker diltiazem, a substrate for the same isoenzymes as diazepam and a CYP3A4 inhibitor, increased AUC (approximately 25%) and prolonged the half-life (by 43% in extensive metabolizers of CYP2C19) of diazepam with small differences between subjects with different CYP2C19 phenotypes. In the presence of diltiazem, it also tended to increase exposure to desmethyl-diazepam.

The primary metabolite of idelalisib is a strong CYP3A4 inhibitor and increases plasma concentrations of diazepam and a dose reduction may have to be considered.

The psychostimulants modafinil and armodafinil induce CYP3A4 and inhibit CYP2C19: they can prolong the elimination of diazepam and cause excessive sedation.

Enzyme inducers
Rifampicin is a potent inducer of CYP3A4 and also has a significant accelerating effect on the CYP2C19 pathway. When doses of 600 mg daily were administered for 7 days, diazepam clearance was increased by 4.3-fold and AUC decreased by approximately 77%. A significant reduction in exposure to all diazepam metabolites was observed. Doubling the daily dose of rifampicin did not further increase its effect. The concomitant use of rifampicin and diazepam should be avoided.

Carbamazepine is a known inducer of CYP3A4 so it accelerates the elimination of diazepam 3-fold (increases clearance, reduces half-life), increasing desmethyl-diazepam concentrations.
Food & Antacids
Food and antacids may slow down, but will not decrease, the absorption of diazepam; this may lead to attenuated effects after a single dose, but does not influence steady-state concentrations during multiple-dose treatment.

Prokinetic drugs increase the absorption rate of diazepam.

Compounds that inhibit certain liver enzymes (particularly cytochrome P450) may potentiate the activity of benzodiazepines. To a lesser degree, this also applies to those benzodiazepines that are metabolized exclusively by conjugation.

Metoclopramide administered intravenously (but not orally) increases the absorption rate of diazepam and increases the maximum concentration achieved after oral administration.

Narcotics (morphine, pethidine) slow the rate of absorption and decrease peak concentrations of orally administered diazepam.

Effects of Diazepam on the Pharmacokinetics of Other Drugs
Diazepam has not been shown to induce or inhibit metabolizing enzymes. However, some drug interactions precipitated by diazepam do occur.

Phenytoin
Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.

The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way. Concomitant use may lead to a reduced effect of diazepam and increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

Drug-drug pharmacodynamic interaction

Alcohol consumption should be avoided in patients receiving Diazepam (see section 4.4).

For information on overdoses and precautions with other central nervous system depressants, including alcohol, see section 4.9.

Potentiation of adverse effects on sedation and respiratory depression may also occur when diazepam is administered concomitantly with CNS depressants, including alcohol.
Severe hypotension, respiratory depression, or loss of consciousness have been reported in patients on combination therapy with clozapine and benzodiazepines, including diazepam, on several occasions.

Cumulative CNS depressant effects can be expected when phenothiazines and benzodiazepines are combined: sedation, respiratory depression, and air obstruction have been reported with the combined use of levopromazine and diazepam.

Cumulative effects of olanzapine and diazepam on sedation and hypotension have occurred in the absence of pharmacokinetic interaction. Concomitant parenteral use is not recommended.

Diazepam potentiates the subjective opioid effects of methadone. It increases methadone's effects on pupil diameter and sedation and also causes significantly greater impairment in reaction time compared to methadone alone. There is no pharmacokinetic interaction between the two drugs.

Reversible loss of control of Parkinson's disease has been observed in some patients treated with levodopa combined and diazepam. This could be caused by decreased striatal dopamine levels.
The xanthines, theophylline, and caffeine oppose the sedative and possibly anxiolytic effects of diazepam partially through blockade of adenosine receptors.

Pretreatment with diazepam changes the pharmacodynamics and pharmacokinetics of anesthetic ketamine. Ketamine N-demethylation was inhibited, leading to a prolonged half-life and prolonged ketamine-induced sleep time. In the presence of diazepam, a reduced concentration of ketamine is required to achieve adequate anesthesia.

In the case of narcotic analgesics, there can also be an increase in the feeling of euphoria, which can increase psychic dependence.

Muscle relaxants
The effects of muscle relaxants (suxamethonium, tubocurarine), analgesics and nitrous oxide may be enhanced due to possible pharmacodynamic antagonism which may result in altered intensity of neuromuscular blockade.

Opioids
The concomitant use of benzodiazepines and 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).

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

Phenobarbital
Phenobarbital can cause additive CNS inhibition resulting in increased risk of sedation and respiratory depression.

Pharmacokinetic interactions
Diazepam is primarily metabolized into 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. CYP3A4 and/or CYP2C19 inhibitors may cause increased concentrations of diazepam, while enzyme-inducing agents such as rifampicin, St. John's Wort, and certain anti-epileptics may lead to decreased plasma concentrations of diazepam.

Valproic acid
Valproate displaces diazepam from its plasma albumin binding site and inhibits the metabolism of diazepam which may result in increased serum concentrations of diazepam.

Cisapride
Cisapride may accelerated absorption of diazepam resulting in temporary increase in the sedative effect of orally administered diazepam.

Corticosteroids
Chronic use of corticosteroids may lead to increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4 or of enzymes responsible for glucuronidation resulting in reduced effect of diazepam

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
If the product is prescribed to a woman who may become pregnant during treatment, she will be advised to contact her doctor to withdraw treatment when planning a pregnancy or detecting that she is pregnant.

Pregnancy
The safety of Diazepam in pregnant women has not been established. An increased risk of birth defects associated with benzodiazepine use during the first trimester has been suggested.

The review of spontaneous reporting of adverse events does not show a higher incidence than would be expected from a similar untreated population. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Before administering Diazepam during pregnancy, especially during the first trimester, the potential risks to the fetus should be weighed against the expected therapeutic benefit to the mother.
If, as strictly required by medical conditions, the product is administered continuously during pregnancy, or at high doses during delivery, it is foreseeable that effects on the neonate such as hypothermia, hypotonia, hypotension and decreased respiratory function may occur (see section 5.2). Withdrawal symptoms in the newborn have been reported occasionally on this class of medications.

Children born to mothers who chronically take benzodiazepines during the last period of pregnancy may develop physical dependence, and withdrawal may be triggered in the postnatal period. Therefore, special precautions need to be taken before using Diazepam during delivery, as high single doses cause fetal heart rate irregularities and hypotonia, reduced sucking, hypothermia, and moderate respiratory depression in newborns. It is worth remembering that the enzyme system responsible for the breakdown of this drug is not fully developed in newborns (especially premature infants).

Breastfeeding
As Diazepam is excreted in breast milk, it should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Diazepam significantly affects the ability to drive and to operate machines.

This is usually due to impaired motor skills, tremor, somnolence, amnesia, impaired concentration and tiredness (see section 4.8).

The effect can be observed immediately after the start of treatment and it can last for several days following discontinuation due to the long half-life of diazepam.

4.8 Undesirable effects

The most common adverse reactions are fatigue, drowsiness and muscle weakness and are usually dose-related. These phenomena mostly occur at the beginning of treatment and usually disappear with continued administration.

Nervous system disorders
Ataxia, dysarthria, slurred speech, headache, tremor, dizziness, decreased alertness. Anterograde amnesia may occur at therapeutic doses, increasing the risk of this reaction at higher doses. Amnesic effects may be associated with inappropriate behaviors.

Psychiatric disorders
Paradoxical reactions such as restlessness, agitation, irritability, disorientation, aggressiveness, nervousness, hostility, anxiety, delirium, fits of anger, nightmares, abnormal dreams, hallucinations, psychosis, hyperactivity, inappropriate behavior, and other behavioral disturbances have been described. If this occurs, treatment should be discontinued. These reactions are more likely to occur in the pediatric population and in elderly patients.
In addition, a state of confusion, emotional and mood disturbances, depression, and changes in libido have been observed.
rbances, depression, and changes in libido have been observed.

Dependence
Continued administration of the product (even at therapeutic doses) may lead to the development of physical dependence: withdrawal from treatment may lead to the development of withdrawal or rebound phenomena. Cases of benzodiazepine abuse have also been reported in polydrug abusers (see section 4.4).

Injury, poisoning and procedural complications
Cases of falls and fractures have been observed in patients taking benzodiazepines. The risk of this adverse reaction is higher in patients taking other sedative medications and/or alcohol concomitantly and in elderly patients.

Gastrointestinal disorders
Nausea, dry mouth or hypersalivation, constipation, and other gastrointestinal disturbances.

Eye disorders
Diplopia, blurred vision.

Vascular disorders
Hypotension, circulatory depression.

Investigations
Irregular heart rate, very rarely increased transaminases and increased blood alkaline phosphatase.

Renal and urinary disorders
Incontinence, urinary retention.

Skin and subcutaneous tissue disorders
The most common skin reactions are rash, urticaria, pruritus, rash erythematosus. Most of the cases were not serious.

In most cases associated with severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme), concomitant medication and patients with impaired general condition were considered important confounders.

Ear and labyrinth disorders
Vertigo.

Cardiac disorders
Cardiac insufficiency, including cardiac arrest.

Hepatobiliary disorders
Very rarely jaundice.

Respiratory, thoracic, and mediastinal disorders

Respiratory depression, including respiratory failure.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms
Benzodiazepines frequently cause drowsiness, ataxia, dysarthria, and nystagmus. Diazepam overdose is rarely life-threatening if only this medication is taken, but it can result in areflexia, apnoea, hypotension, cardiorespiratory depression, and coma. If coma occurs, it usually lasts only a few hours but can be prolonged and cyclical, especially in elderly patients. Severe overdose can lead to central circulatory and respiratory depression (cyanosis, loss of consciousness leading to respiratory failure, cardiac arrest) and coma. Admission in the intensive care unit is required. In the recovery phase of an overdose, severe agitation has been reported.

Respiratory depressant effects are more severe in those patients with respiratory disease.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Treatment
The patient's vital signs should be monitored and supportive measures established based on their clinical status. In particular, some patients may require symptomatic treatment to alleviate the cardiorespiratory effects or effects on the central nervous system caused by overdose.

To prevent further absorption of the drug, an appropriate method should be used, e.g. treatment with activated charcoal within the first 1-2 hours. If activated charcoal is used, it is imperative to keep the airways open in drowsy patients. As an exceptional measure, gastric lavage could be considered in cases of overdose due to concomitant ingestion of several medications.

If CNS depression is severe, the use of flumazenil (Anexate), a benzodiazepine antagonist, should be considered. It should only be administered under close monitoring. It has a short half-life (about one hour), so patients who are given flumazenil should be monitored after its effects have worn off. Flumazenil should be used with extreme caution in combination with medications that lower the seizure threshold (e.g., tricyclic antidepressants). Refer to the relevant product information for flumazenil for more information on the correct use of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivatives, ATC code: N05BA01

Diazepam is a benzodiazepine tranquilizer with anxiolytic, sedative, muscle relaxant, and anticonvulsant effects. It can cause anterograde amnesia even at therapeutic doses. Its action is increased by the generation of active metabolites (mainly desmethyldiazepam). The central actions of benzodiazepines are mediated by an enhancement of GABAergic neurotransmission

at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is potentiated by positive allosteric modulation resulting in an increase in the action of released GABA on the transmembrane transsynaptic chloride ion flux.

5.2 Pharmacokinetic properties

Absorption
As a single oral dose, diazepam is rapidly and almost completely absorbed (>90%) in the gastrointestinal tract, reaching maximum plasma concentration 30-90 minutes after oral administration. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in C_{max} of 20 % in addition to a 27 % decrease in AUC (range 15 % to 50 %) when administered with food.

Steady state is reached in about 5 days; while for the metabolite desmethyl-diazepam it takes about twice as long to reach a steady state. Average steady-state diazepam levels after a daily administration are about twice as high as peak levels of the drug after the first dose.

Distribution
Diazepam and its metabolites are widely distributed in tissues, despite their high binding to plasma proteins (98-99%), mainly albumin and, to a lesser extent, to the α1 acid glycoprotein. Diazepam and its metabolites cross the blood-brain barrier. The average steady-state volume of distribution ranges from 0.88 to 1.1 L/kg when derived from plasma concentration measurements. Both the binding to both proteins and the volume of distribution of desmethyl-diazepam are similar to those of diazepam.

High protein binding limits the extent of absorption of diazepam into cerebrospinal fluid (CSF). Following multiple dosing, the metabolite desmethyl-diazepam, unlike diazepam, can accumulate significantly in the CSF. Diazepam has very rapid absorption and equilibrium with brain tissue, with equilibrium concentrations in the brain higher than those in plasma. The overall action profile of receptor occupancy was consistent with the action profile of the sum of brain concentrations of diazepam plus metabolites.

Metabolism
Diazepam is metabolized in the liver to metabolites with pharmacological activity, mainly desmethyl-diazepam, which accounts for 50-60% of the total clearance of diazepam; 3-hydroxylation also accounts for 27% of the total clearance of diazepam, giving rise to the oxidation metabolites temazepam and oxazepam. Oxazepam and temazepam are also conjugated with glucuronides.
After multiple doses of diazepam, plasma concentrations of desmethyl-diazepam/diazepam were 1.1 ± 0.2; temazepam/diazepam 0.11 ± 0.05 and oxazepam/diazepam 0.09 ± 0.03.
The metabolism of diazepam is mediated by cytochrome P450 isoenzymes; mainly CYP2C19 and CYP3A are responsible for the metabolite desmethyl-diazepam, and CYP3A in the formation of temazepam and oxazepam.

Because CYP2C19 is polymorphic, rapid metabolizers and slow metabolizers of diazepam can be distinguished. Poor metabolizers showed significantly lower clearance (12 vs 26 mL/min) and longer elimination half-life (88 vs 41h) of diazepam than rapid metabolizers after a single oral dose. In addition, poor metabolizers had lower clearance, higher AUC, and longer elimination half-life for the metabolite desmethyl-diazepam.
There seem to be differences in this polymorphism between different ethnicities.

Elimination
The plasma concentration of diazepam decreases biphasic over time when administered orally: an initial phase of rapid and extensive distribution is observed, followed by a phase of prolonged terminal elimination. The elimination half-life is in the range of 24-48 hours for diazepam and 40-100 hours for the active metabolite desmethyl-diazepam. The clearance of diazepam is 20-40 ml/min.

The drug is almost completely metabolized and only negligible amounts of unchanged diazepam are eliminated in the urine. The main metabolite in urine is oxazepam-glucuronide.

Pharmacokinetics in special situations:

Elderly patients
Due to the decrease in plasma proteins with age, the free fraction of diazepam is elevated compared to younger patients. Age affects metabolism, decreasing it, as well as a decrease in clearance of free drugs. This results in a 2-4fold increase in elimination half-life (more strongly observed in males than females). Therefore, the degree of accumulation of free diazepam in elderly people during multiple dosing will be greater than in younger adults (see section 4.2).

Hepatic impairment
The bioavailability of diazepam and its major metabolite desmethyl-diazepam is altered in hepatic impairment. These changes are mainly due to impaired hepatic metabolism; along with plasma protein binding changes.
In acute viral hepatitis, the half-life of diazepam is increased approximately 2-fold, but slowly returns to normal at recovery. In patients with alcoholic cirrhosis, a more marked increase (2- to 5-fold) in elimination half-life is observed. Reduced clearance of diazepam and desmethyl-diazepam leads to their increased long-term accumulation and increased pharmacological effects (see section 4.2).

Renal impairment
In chronic renal failure, the clearance of diazepam, as indicated by clearance of the unbound drug, was similar to that of healthy volunteers; Therefore, steady-state concentrations of diazepam not bound to any daily dose should not be on average different between patients with renal impairment and healthy individuals. Due to changes in plasma protein binding and tissue distribution of diazepam, its elimination half-life was shortened in renal disease from (mean ± SD) 92 ± 23 hours at control to 37 ± 7 hours in subjects with renal impairment.

Pregnancy and breastfeeding
Diazepam and desmethyl-diazepam easily cross the placental barrier. The foetus can also perform N-demethylation of diazepam. Long-term treatment leads to accumulation of both compounds in the foetus with high levels in the foetus's heart, lungs, and brain.

The plasma protein binding of diazepam decreases during pregnancy, particularly during the last trimester, in part due to decreased serum albumin concentration. Pharmacological effects may be increased following single-dose administration (see section 4.6).

Diazepam metabolized more slowly by term and preterm infants than older infants (> 5 months) and adults, leading to a prolonged half-life (much more pronounced in preterm infants).

Diazepam and its metabolites are excreted in breast milk. Concentrations of diazepam in milk are only 10% of concentrations in maternal blood. Normalized for body weight, about 5% of the mother's dose reaches the baby. After multiple administrations with daily doses of more than 10 mg, the amounts transferred may be large enough to show effects on the infant (see section 4.6).

Overweight patients
Several studies have shown that the pharmacokinetics in obese patients are different from those in normal weight patients. In a study in which subjects were given 2 mg diazepam in the evening for 30 days, accumulation was delayed and the half-life for the accumulated amount of diazepam was prolonged in obese subjects compared with normal weight subjects (7.8 days vs. 3.1 days). The accumulated amount of the active metabolite desmethyldiazepam was similarly prolonged. The half-life for plasma elimination of diazepam was prolonged to 82 hours in obese subjects. The altered pharmacokinetics during long-term treatment of obese patients is probably related to the volume of distribution.

These data indicate that overweight patients require significantly longer treatment than normal weight patients before the maximum effect of the drug is achieved during long-term treatment. Similarly, therapeutic effect and side effects, including withdrawal symptoms, may persist for a longer period of time after discontinuation of long-term treatment in overweight patients.

5.3 Preclinical safety data

Carcinogenicity
The carcinogenic potential of oral diazepam has been studied in several rodent species. An increased incidence of liver tumours has been shown in male mice given diazepam on the diet. No significant increase in tumour incidence was observed in female mice, rats, hamsters, or gerbils.
Contradictory results are derived from mutagenesis studies.
Other studies have shown no carcinogenic activity.

Genotoxicity
Several studies have shown weak evidence of mutagenic potential at high concentrations of the drug, considered much higher than the doses used in humans.

Impaired fertility
Fertility studies conducted in rats receiving oral diazepam at doses of 100 mg/kg/day before and during mating and during gestation and lactation showed a decrease in the number of pregnancies and in the number of live offspring.

Reproductive toxicity
Studies in rats and rabbits receiving 80-300 mg/kg/day and 20-50 mg/kg/day respectively revealed no teratogenic effects in offspring. In contrast, diazepam is teratogenic in mice at doses of 45-50 mg/kg, 100 mg/kg and 140 mg/kg/day as well as in hamsters at 280 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Simethicone emulsion (contains, benzoic acid (E210))
Polysorbate 80 (E433)
Potassium sorbate (E202)
Glycerol (E422)
Microcrystalline cellulose
Carmellose sodium
Ethanol (E1510)
Erythrosine (E127)
Sucrose

Raspberry flavor (contains propylene glycol (E1520))
Purified water

6.2 Incompatibilities

No applicable.

6.3 Shelf life

18 months
Discard 30 days after first opening.

6.4 Special precautions for storage

Store below 25°C.
Do not refrigerate or freeze

6.5 Nature and contents of container

Amber glass bottle with child-resistant polypropylene closure.
Each pack contains one bottle containing 100 ml oral suspension,

Dosing Device: A 1ml syringe with 0.01 ml intermediate graduation, a 10 ml syringe with 0.1 ml intermediate graduation, bottle adaptor and a 25 ml measuring cup with 2.5 ml intermediate graduation.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Syri Pharma Limited
1 Windmill Lane
Dublin 2, D02 F206
Ierland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 132835

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 6 november 2025

10. DATE OF REVISION OF THE TEXT