SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dalpam 2 mg tabletten
Dalpam 5 mg tabletten
Dalpam 10 mg tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg diazepam.
Each tablet contains 5 mg diazepam.
Each tablet contains 10 mg diazepam.

Excipient(s) with known effect:
Each Dalpam 2 mg tablet contains 168.1 mg lactose monohydrate.
Each Dalpam 5 mg tablet contains 165.1mg lactose monohydrate.
Each Dalpam 10 mg tablet contains 160.1 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Dalpam 2 mg: white to almost white round, flat, 8 mm in diameter with "2" on one side and a break line on the other side.
Dalpam 5 mg: Tablet is white to almost white round, flat, 8 mm in diameter with "5" on one side and a break line on the other side.
Dalpam 10 mg: Tablet is white to almost white round, flat, 8 mm in diameter with "10" on one side and a break line on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Anxiety.
- Adjunct in the control of skeletal muscle spasm, including spasticity caused by upper motor neuron disorders (such as cerebral palsy).
- Alcohol withdrawal symptoms.
- Premedication before general anaesthesia or for sedation during minor surgical or investigative procedures.

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Standard dosage

For optimal effect, the dosage should be carefully individualised. Treatment should begin at the lowest effective dose appropriate to the particular condition.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.4). The patient should 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, especially in case the patient is symptom free. In general, treatment must not last longer than 8 to 12 weeks, including tapering off process.
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.

Adults:
Anxiety
- *Usual dose:* 2 mg to 5 mg diazepam two to three times daily.
- *Maximum dose:* In severe cases the dose may be incrementally increased up to 30 mg diazepam daily in 2 to 4 divided doses. Adjusted on an individual basis
- The lowest dose which can control symptoms should be used.
- Treatment should not be continued at the full dose beyond 4 weeks.
- Long-term chronic use is not recommended.
- 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.

Adjunct in the control of muscle spasm
- *Muscle spasm:* Up to 15 mg diazepam daily in 2 to 4 divided doses.
- *Management of upper motor neuron spasticity (such as cerebral palsy) in selected cases:* If necessary, the dose may be titrated up to a maximum of 60mg diazepam daily in 3 to 4 divided doses.

Alcohol withdrawal symptoms
- 5 mg to 20 mg diazepam repeated once within 2 to 4 hours if necessary, or 10 mg diazepam three to four times on the first day. After the first day, the dose is usually lowered to 5 mg diazepam three to four times daily as needed.
- In severe cases, a loading-dose method may be used with initial administration of 10 mg diazepam every hour until patient is lightly sedated and asymptomatic, usually reaching up to 50–80 mg. Treatment should take place in a hospital setting and the patient should be appropriately monitored.

Premedication before minor surgery
- 5 mg to 20 mg diazepam.

Special populations:
Individuals in the following patient groups should be checked regularly at the start of treatment. Monitoring during treatment is essential in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation, such as in children and adolescents, elderly patients and patients with impaired liver function.

Paediatric population
Children above 6 years of age and adolescents

The administration in children above 6 years of age and adolescents should only be for compelling medical reasons. The half-life may be extended in children. The dose level should be reduced and individual adjustments have to be performed.
- Usual dose: 0.1–0.3 mg/kg body weight per day in two to four divided doses. Treatment should be initiated with the lowest possible dose and increased gradually as necessary and tolerated.

/.../ is not recommended for children below 6 years of age due to possible swallowing difficulties. More suitable pharmaceutical forms may be available for younger children.

Elderly patients
Distribution, elimination and clearance are changed in elderly patients, resulting in an extended half - life. The dose level should therefore be reduced to 50% of the normal recommended dose.
These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation.
- *Initial dose*: 2 mg to 2.5 mg once or twice daily. Increased gradually as necessary and tolerated.

Impaired renal f unction
Dose adjustment is usually not necessary. However, caution should be exercised when treating renally impaired patients with diazepam.

Impaired liver function
The dose must be reduced for individuals with cirrhosis and impaired liver function. Patients with severe hepatic impairment must not be treated with diazepam due to risk of hepatic encephalopathy (see section 4.3).

Overweight patients
Various studies have shown that the kinetics are changed in overweight patient s, compared to those of a normal weight. Overweight patients require significantly longer treatment times than patients of normal weight before the maximum effect of the drug occurs in long-term treatment. Similarly the therapeutic effect and undesirable effects, including withdrawal symptoms, can occur for longer periods following the discontinuation of more long-term treatment of overweight patients (see section 5.2).

4.3 Contraindications

Dalpam is contra-indicated for patients with:
- Hypersensitivity to benzodiazepines or to one or more of the excipients (see section 6.1).
- Myasthenia gravis.
- Sleep apnoea syndrome.
- Severe hepatic insufficiency.
- Severe respiratory insufficiency.

4.4 Special warnings and precautions for use

Concomitant use of alcohol/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).

The concomitant use of benzodiazepines with buprenorphine has been associated with significant respiratory depression, particularly when buprenorphine is used by the intravenous route. A number of

overdose deaths have occurred when addicts have intravenously abused buprenorphine, with benzodiazepines concomitantly.

Medical history of alcohol or drug abuse
Diazepam should be used with extreme caution in patients with a history of alcohol or drug abuse.

Risk from concomitant use of opioids
Concomitant use of Dalpam 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 Dalpam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Dalpam 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).

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
Treatment with diazepam can result in mental or physical dependency. The risk increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse or in patients with marked personality disorders. 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 will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

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.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2) depending on the indication. 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. In

general, treatment must not last any longer than 8-12 weeks, including the tapering off process. Extension beyond these periods 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.

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.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions (such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects) have been reported from the use of benzodiazepines. Such reactions ar e possibly seen more often in the treatment of children and elderly patients and should result in the discontinuation of treatment.

Specific patient groups
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 has not been established.

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.

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

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.

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

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

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

Dalpam contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Increase sedative effects and depression of respiratory and cardiovascular functions may occur if diazepam is used with other centrally acting agents, such as antipsychotics anxiolytics/sedatives, antidepressants, hypnotics, anticonvulsants, narcotic analgesics, anaesthetics for general anaesthesia and sedating antihistamines or alcohol.

Coadministration of diazepam with valproic acid increases the risk of psychosis.

The combination of buprenorphine with benzodiazepines can potentiate respiratory depression of central origin (see section 4.4).

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as /…/ 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).

Theophylline can decrease the effects of benzodiazepines.

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.
As shown in vitro, the reaction of hydroxylation is mainly mediated by CYP3A isoenzyme, while N-demethylation is mediated by CYP3A and CYP2C19. The results from in vivo studies in human volunteers have confirmed those observed in vitro.
Subtracts of CYP3A4 and/or CYP2C19 can potentially change the pharmacokinetics of diazepam. Drugs such as atazanavir, cimetidine, ketoconazole, fluvamine, fluoxetine, omeprazole, disulfiram, isoniazide, propranolol and rifampicine inhibit CYP3A and CYP2C19 and can provoke increased and prolonged sedation.

Cisapride can temporary increase of the sedative effects of benzodiazepines when orally administered after an accelerated absorption.

Ritonavir may increase plasma concentrations of diazepam and increase the risk of sedation and respiratory depression. Therefore, a reduced dose of diazepam might be needed in concomitant use.

The metabolism of phenytoin may be affected by diazepam.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Any woman wishing to become or suspects that she is pregnant should be urged to contact her doctor concerning stopping the treatment.

Pregnancy

There are limited amount of data from the use of diazepam in pregnant women.
If, for compelling medical reasons, diazepam is administered during the last trimester of pregnancy, or at high dose levels around the time of birth, effects can be expected in the neonate, such as hypothermia, hypotonia ("Floppy Infant Syndrome"), irregularities in the heart rate, poor suckling and moderate respiratory depression, due to the substance's pharmacological effect.
In addition, infants born to mothers who have taken benzodiazepines regularly during the last stage of pregnancy may develop a physical dependence and be at risk of developing withdrawal symptoms following the birth.

Studies in animals have shown reproductive toxicity (see section 5.3).

Diazepam should only be used in pregnant women on compelling indication.

Breast-feeding
Diazepam is excreted in breast milk. Diazepam should not be used during breast-feeding.

Fertility
Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There is no human data.

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

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	Very rare	Leukopenia
Immune system disorders	Very rare	Anaphylaxis.
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.[1] Emotional poverty, decreased alertness and depression.[2]
Nervous system disorders	Very common	Drowsiness
	Common	Ataxia, impaired motor ability, tremor.
	Uncommon	Anterograde amnesia.[3] 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, thoratic and mediastinal disorders	Uncommon	Respiratory depression
	Rare	Respiratory arrest, increased bronchial secretion.
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, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, aggression, disrupted sensory perception, muscle spasms, general

		malaise, loss of appetite, paranoid psychosis, delirium and epileptic attacks).[4]
Investigations	Very rare	Elevation of transaminases.

[1] 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).
[2] Pre-existing depression may be unmasked during benzodiazepine use.
[3] May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).
[4] The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

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

4.9 Overdose

In every case of overdose it should be assessed whether multiple agents are involved, for example in an attempted suicide. Symptoms of overdose are more pronounced in the presence of alcohol or drugs causing a depression in central nervous system.

Symptoms:
Symptoms of mild overdose include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, dysarthia, hypotension and hypotonia. 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.

Treatment:
Following overdose with oral benzodiazepines, induction of vomiting can be considered (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. Activated charcoal can be given to reduce absorption in the early stages of intoxication. Further treatment is symptomatic and supportive. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

The use of flumazenil, a specific benzodiazepine-receptor antagonist, can be considered for the complete or partial reversal of the sedative effects of benzodiazepines. Flumazenil should only be administered under closely monitored conditions. Due to the short half-life of flumazenil, symptoms of benzodiazepine intoxication can recur after a short period of time. Therefore, monitoring of the patient's clinical state remains essential. For some patient groups treatment with flumazenil might be useful, especially with regard to preventing the need for artificial respiration. This applies for example to patients with pre-existing respiratory disorder or threatening respiratory insufficiency, elderly patients and children.
Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose.

Attention should be given to induction of withdrawal symptoms and convulsions, especially in the case of long-term benzodiazepine users and mixed intoxication with agents that lower the threshold for seizures (e.g. tricyclic antidepressants).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action:
Diazepam is an agonist that binds specifically to benzodiazepine receptors in the brain, thus enhancing the normal transmission of the signal substance GABA. GABA inhibits the transmission of important signal substance, by which means a neuronal inhibition is achieved. The muscle -relaxant effect is mediated via spinal synaptic reflexes.

Pharmacodynamic effects:
Diazepam is an anxiolytic that acts by subduing the anxiety symptoms of agitation, restlessness and tension. Diazepam also has a sedative and muscle-relaxant effect.

5.2 Pharmacokinetic properties

Absorption
Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30-90 minutes after oral ingestion.

Distribution
Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (see section 4.6). The steady state volume of distribution is 0.8-1.0 l/kg. The distribution half-life is reached in 3 hours.

Biotransformation
Diazepam is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam.

Elimination
The decline in the plasma concentration-time profile after oral administration is biphasic, an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase (half -life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly in their conjugated forms. The clearance of diazepam is 20-30 ml/min.

Special populations
The elimination half-life may be prolonged in the new-born, in the elderly and in patients with liver disease. In renal failure, the half-life of diazepam is not clinically significantly changed.

5.3 Preclinical safety data

Not reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised maize starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC blisters and HDPE tablet containers with white PE caps.

Pack sizes:
Al/PVC blisters
10, 20, 25, 28, 30, 50, 60 and 100 tablets

HDPE container
100, 500 and 1000 tablets

Not all pack sizes may be marketed.

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

Neogen NV
Square Marie Curie 50
1070 Anderlecht
België

8. MARKETING AUTHORISATION NUMBER(S)

Dalpam 2 mg tabletten	RVG 118082
Dalpam 5 mg tabletten	RVG 118083
Dalpam 10 mg tabletten	RVG 118084

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 09 februari 2017
Datum van laatste verlenging: 5 december 2021

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 13 mei 2021