[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dormazolam 5 mg/ml solution for injection for horses (AT, BE, CZ, DE, EE, ES, FR, HR, HU, IE, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK)
Dormaquin vet 5 mg/ml solution for injection for horses (IS, NO, SE)
Midaquin Vet. 5 mg/ml solution for injection for horses (DK, FI)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Midazolam 5.0 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol (E1519)	10.0 mg
Sodium chloride	
Hydrochloric acid, dilute (ad pH)	
Sodium hydroxide (ad pH)	
Water for injections	

Clear, colourless solution.

3. CLINICAL INFORMATION

3.1 Target species

Horse (non food-producing).

3.2 Indications for use for each target species

Co-induction of anaesthesia with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia.

3.3 Contraindications

Do not use in animals with severe respiratory failure.
Do not use as a sole agent.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

In case of renal or hepatic dysfunction or respiratory depression there may be greater risk associated with the use of the veterinary medicinal product. Use only according to the benefit/risk assessment by

the responsible veterinarian.

The veterinary medicinal product is not intended for sole use; midazolam produces muscle relaxation and when used as a sole agent horses may be slightly sedated, but also restless or even agitated when they become ataxic/unstable.
Prolonged recovery time (prolonged recumbence and time to extubation) may be associated with use of the veterinary medicinal product.

The safety of repeated bolus dosing (at 0.06 mg/kg) at intervals of less than 4 days has not been established. Based on the pharmacokinetics of the active substance, care should be taken when administering repeated doses of midazolam within a 24-hour period to horses, particularly neonatal foals (i.e. foals less than 3 weeks old), obese horses and horses with hepatic impairment or conditions associated with reduced organ perfusion, due to the possibility of drug accumulation.

Care should be taken when administering the veterinary medicinal product to hypoalbuminaemic horses since these animals may have higher sensitivity to a given dose.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Midazolam is a CNS depressant and can cause sedation and induction of sleep. Care should be taken to avoid self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet to the physician, but DO NOT DRIVE as sedation and impaired muscular function may occur.

Midazolam and its metabolites may be harmful for the unborn child, and are secreted into breastmilk in small amounts, thereby exerting a pharmacological effect on the nursing child. Pregnant and breastfeeding women should, therefore, take great care when handling this veterinary medicinal product and, in the event of exposure, seek medical advice immediately.

Midazolam and benzyl alcohol may cause hypersensitivity reactions. People with known hypersensitivity to these substances should avoid contact with the veterinary medicinal product. Seek medical advice in case of hypersensitivity reactions.
This veterinary medicinal product can cause skin and/or eye irritation. Avoid contact with skin and eyes. In the case of contact with skin, wash with soap and water In the case of contact with the eyes, rinse the eyes immediately with plenty of water. If irritation persists, seek medical advice.

Wash hands after use.

To the physician:
Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria anterograde amnesia, and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma. Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. Respiratory and haemodynamic symptoms should be treated symptomatically.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Target species: Horse (non food-producing)

Common (1 to 10 animals / 100 animals treated):	Ataxia[a], incoordination. [a]

Uncommon (1 to 10 animals / 1,000 animals treated):	Respiratory depression[b], urination.[b]

[a]during recovery from anaesthesia
[b]upon induction of anaesthesia

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Laboratory studies in mice, rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. In humans, use of benzodiazepines during the late third trimester of pregnancy or during labour has been associated with adverse effects in the foetus/neonate, including mild sedation, hypotonia, reluctance to suck, apnoea, cyanosis and impaired metabolic response to cold stress. Midazolam is found in low quantities in the milk of lactating animals.

The safety of the veterinary medicinal product during pregnancy and lactation has not been established in the target species. Use only according to the benefit/risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Before using combinations of midazolam with other veterinary medicinal products, the product literature for the other products should be observed.
Midazolam potentiates the effect of some sedative and anaesthetic agents, reducing the dose required, including alpha-2-agonists (detomidine, xylazine), propofol and some inhalational agents.

Concurrent use of midazolam with antihistamines (H_2-receptor antagonists, e.g. cimetidine), barbiturates, local anaesthetics, opioid analgesics or CNS depressants may enhance the sedative effect.

In combination with other agents (e.g. opioid analgesics, inhalational anaesthetics), an increase in respiratory depression may be observed.

Erythromycin and azole antifungals (fluconazole, ketoconazole) inhibit the metabolism of midazolam, resulting in increased plasma midazolam concentrations and increased sedation.

Drugs that induce CYP450 mediated metabolism, such as rifampin, may decrease plasma concentrations and effects of midazolam.

3.9 Administration routes and dosage

For intravenous use.

Once the horse is properly sedated, anaesthesia is induced by intravenous injection of:
Midazolam at a dose of 0.06 mg per kg body weight, corresponding to 1.2 ml solution per 100 kg, in combination with ketamine at a dose of 2.2 mg per kg body weight. Midazolam and ketamine may be combined and administered in the same syringe.
To ensure a correct dosage, body weight should be determined as accurately as possible.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

The symptoms of overdose are mainly an intensification of the pharmacological effects of midazolam: drowsiness, and muscle relaxation.

In case of accidental midazolam overdose, restlessness or agitation in combination with prolonged muscle weakness may develop when the ketamine effect of the combined midazolam-ketamine anaesthesia subsides.

Following a dose of 0.18 mg midazolam per kg bodyweight (3 times overdose) in combination with ketamine (2.2 mg/kg intravenously) after premedication with detomidine (20 µg/kg intravenously) the following effects attributable to midazolam were observed: poor recovery (more attempts to stand, more ataxia), a slight decrease of the haematocrit, respiratory depression - evidenced by a slight decrease of the respiratory rate, a lower pO_2, a metabolic alkalosis and a slight increase of arterial pH - and a prolonged recovery. A dose of 0.3 mg midazolam per kg bodyweight (5 times overdose) using the same combination resulted in a violent recovery, i.e. horse trying to stand up, whilst still having profound muscle weakness.

The benzodiazepine antagonist flumazenil can be used to reverse effects associated with an overdose of midazolam, although clinical experience in horses is limited.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

To be completed in accordance with national requirements after conclusion of the procedure.

3.12 Withdrawal periods

Not authorised for use in horses intended for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN05CD08

4.2 Pharmacodynamics

Midazolam is an imidazobenzodiazepine, differing structurally from other benzodiazepines by the presence of an imidazole ring fused at positions 1 and 2 of the benzodiazepines nucleus. Midazolam exhibits similar pharmacologic actions as other benzodiazepines. The subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed by the benzodiazepines thus producing the mild sedative (in horses), skeletal muscle relaxant, and anticonvulsant effects seen. Benzodiazepine agonists act by enhancing the inhibitory synaptic neurotransmission mediated by gamma-aminobutyric acid (GABA), through binding to the benzodiazepine binding site on the $GABA_A$-receptor, a ligand-gated chloride channel consisting of five subunits. Sensitivity to benzodiazepines is conferred by the presence of a γ subunit. Four types of benzodiazepine-sensitive $GABA_A$-receptors can be further distinguished on the basis of the presence of α1, α2, α3 or α5 subunits. The α1 $GABA_A$ receptors are mainly expressed in cortical areas and thalamus, α2 and α5 $GABA_A$ receptors are largely expressed in the limbic system, and α3 $GABA_A$ receptors are selectively expressed in noradrenergic and serotonergic neurons of the reticular activating system.

Studies with genetically modified mice have shown that the sedative and partly the anticonvulsant actions of benzodiazepines are mediated by the α1-type $GABA_A$ receptors, whereas the anxiolytic effects of benzodiazepine-receptor ligands appear to be mediated via $GABA_A$ receptors containing the α2 subunit. The myorelaxant effect of benzodiazepines also seems to be mediated by benzodiazepine-sensitive $GABA_A$ receptors other than the α1-type.

In acidic conditions (pH less than 4), the benzepine ring of midazolam is open, resulting in increased water solubility. However, at physiological pH, the ring closes and midazolam becomes lipophilic, which accounts for its rapid onset of action. When midazolam is used in combination with ketamine for co-induction of anaesthesia, time to achievement of lateral recumbency is approximately 1 minute and time to intubation is approximately 1.5 minutes.

4.3 Pharmacokinetics

Distribution
The disposition of midazolam following intravenous administration to horses is characterized by very rapid and relatively extensive distribution (V_D is 0.62 L/kg after administration of the recommended dose). Midazolam is highly protein bound (94 - 97%) and rapidly crosses the blood-brain barrier.

Metabolism
Midazolam undergoes biotransformation by hepatic microsomal oxidation followed by conjunction with glucuronic acid.

Elimination
Midazolam is eliminated almost exclusively by metabolic processes. The drug has a medium blood clearance (0.52 L/kg/h after administration of the recommended dose) and an elimination half-life of approximately 3.48 hours in horses.
The principal route of excretion is through the kidneys, mainly as glucuronidated metabolites.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products, except for ketamine 100mg/ml solution for injection.

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 4 years
Shelf-life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
This veterinary medicinal product does not require any special temperature storage conditions.

5.4 Nature and composition of immediate packaging

Colourless type I glass vials of 5 ml, 10 ml, 20 ml and 50 ml closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box.
Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD month YYYY}.

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dormazolam 5 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Midazolam 5.0 mg

3. PACKAGE SIZE

5 ml
10 ml
20 ml
50 ml

4. TARGET SPECIES

Horse (non food-producing)

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intravenous use.

7. WITHDRAWAL PERIODS

Not authorised for use in horses intended for human consumption.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once broached use within 28 days
Once broached use by:

9. SPECIAL STORAGE PRECAUTIONS

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

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Glass vials of 5, 10, 20 or 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dormazolam

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Midazolam 5 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days.
Once broached, use by:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Dormazolam 5 mg/ml solution for injection for horses

2. Composition

Each ml contains:
Active substance:
Midazolam 5.0 mg

Excipient(s):
Benzyl alcohol (E1519) 10.0 mg

Clear, colourless solution.

3. Target species

Horse (non food-producing).

4. Indications for use

Co-induction of anaesthesia with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia.

5. Contraindications

Do not use in animals with severe respiratory failure.
Do not use as a sole agent in horses.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

6. Special warnings

Special precautions for safe use in the target species:
In case of renal or hepatic dysfunction or respiratory depression there may be greater risk associated with the use of the veterinary medicinal product. Use only according to the benefit/risk assessment by the responsible veterinarian.

The veterinary medicinal product is not intended for sole use; Midazolam produces muscle relaxation; when used as a sole agent horses may be slightly sedated, but also restless or even agitated when they become ataxic/unstable.

Prolonged recovery time (prolonged recumbence and time to extubation) may be associated with use of the veterinary medicinal product.

The safety of repeated bolus dosing (at 0.06 mg/kg) at intervals of less than 4 days has not been established. Based on the pharmacokinetics of the active substance, care should be taken when administering repeated doses of midazolam within a 24-hour period to horses, particularly neonatal foals (i.e. foals less than 3 weeks old), obese horses and horses with hepatic impairment or conditions associated with reduced organ perfusion, due to the possibility of drug accumulation.

Care should be taken when administering the veterinary medicinal product to hypoalbuminaemic horses since these animals may have higher sensitivity to a given dose.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Midazolam is a CNS depressant and can cause sedation and induction of sleep. Care should be taken to avoid self-injection. In case of accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet to the physician, but DO NOT DRIVE as sedation and impaired muscular function may occur.

Midazolam and its metabolites may be harmful for the unborn child, and are secreted into breastmilk in small amounts, thereby exerting a pharmacological effect on the nursing child. Pregnant and breastfeeding women should, therefore, take great care when handling this veterinary medicinal product and, in the event of exposure, seek medical advice immediately.

Midazolam and benzyl alcohol may cause hypersensitivity reactions. People with known hypersensitivity to these substances should avoid contact with the veterinary medicinal product. Seek medical advice in case of hypersensitivity reactions.
This veterinary medicinal product can cause skin and/or eye irritation. Avoid contact with skin and eyes. In the case of contact with skin, wash with soap and water In the case of contact with the eyes, rinse the eyes immediately with plenty of water. If irritation persists, seek medical advice.
Wash hands after use.

Advice to physicians: Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria anterograde amnesia, and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma.
Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. Respiratory and haemodynamic symptoms should be treated symptomatically.

Pregnancy and lactation:
Pregnancy and lactation:

Laboratory studies in mice, rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. In humans, use of benzodiazepines during the late third trimester of pregnancy or during labour has been associated with adverse effects in the foetus/neonate, including mild sedation, hypotonia, reluctance to suck, apnoea, cyanosis and impaired metabolic response to cold stress. Midazolam is found in low quantities in the milk of lactating animals.

The safety of the veterinary medicinal product during pregnancy and lactation has not been established in the target species. Use only according to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Before using combinations of midazolam with other veterinary medicinal products, the product literature for the other products should be observed.
Midazolam potentiates the effect of some sedative and anaesthetic agents, reducing the dose required, including alpha-2-agonists (detomidine, xylazine), propofol and some inhalational agents.

Concurrent use of midazolam with antihistamines (H_2-receptor antagonists, e.g. cimetidine), barbiturates, local anaesthetics, opioid analgesics or CNS depressants may enhance the sedative effect.

In combination with other agents (e.g. opioid analgesics, inhalational anaesthetics), an increase in respiratory depression may be observed.

Erythromycin and azole antifungals (fluconazole, ketoconazole) inhibit the metabolism of midazolam, resulting in increased plasma midazolam concentrations and increased sedation.

Drugs that induce CYP450 mediated metabolism, such as rifampin, may decrease plasma concentrations and effects of midazolam.

Overdose:
The symptoms of overdose are mainly an intensification of the pharmacological effects of midazolam: drowsiness, and muscle relaxation.

In case of accidental midazolam overdose, restlessness or agitation in combination with prolonged muscle weakness may develop when the ketamine effect of the combined midazolam-ketamine anaesthesia subsides.

Following a dose of 0.18 mg midazolam per kg bodyweight (3 times overdose) in combination with ketamine (2.2 mg/kg intravenously) after premedication with detomidine (20 µg/kg intravenously) the following effects attributable to midazolam were observed: poor recovery (more attempts to stand, more ataxia), a slight decrease of the haematocrit, respiratory depression - evidenced by a slight decrease of the respiratory rate, a lower pO_2, a metabolic alkalosis and a slight increase of arterial pH - and a prolonged recovery. A dose of 0.3 mg midazolam per kg bodyweight (5 times overdose) using the same combination resulted in a violent recovery, i.e. horse trying to stand up, whilst still having profound muscle weakness.

The benzodiazepine antagonist flumazenil can be used to reverse effects associated with an overdose of midazolam, although clinical experience in horses is limited.

Special restrictions for use and special conditions for use:
To be completed in accordance with national requirements after conclusion of the procedure.

Major incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products, except for ketamine 100mg/ml solution for injection.

7. Adverse events

Target species: Horse (non food-producing)

Common (1 to 10 animals / 100 animals treated):	Ataxia[a], incoordination[a].
Uncommon (1 to 10 animals / 1,000 animals treated):	Respiratory depression[b], urination.[b]

[a]during recovery from anaesthesia
[b]upon induction of anaesthesia

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}

8. Dosage for each species, routes and method of administration

For intravenous use.

Once the horse is properly sedated, anaesthesia is induced by intravenous injection of:

Midazolam at a dose of 0.06 mg per kg body weight, corresponding to 1.2 ml solution per 100 kg, in combination with ketamine at a dose of 2.2 mg per kg body weight.
To ensure a correct dosage, body weight should be determined as accurately as possible.

9. Advice on correct administration

Midazolam and ketamine may be combined and administered in the same syringe.

10. Withdrawal periods

Not authorised for use in horses intended for human consumption.

11. Special storage precautions

Keep out of the sight and reach of children.
Keep the vial in the outer carton in order to protect from light.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
Shelf life after first opening the container: 28 days
This veterinary medicinal product does not require any special temperature storage conditions.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Marketing authorisation number(s):
To be completed nationally.

Packaging:
Colourless Type I glass vials of 5 ml, 10 ml, 20 ml and 50 ml closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box.
Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{MM/YYYY}

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
To be completed nationally.

Manufacturer responsible for batch release:
Produlab Pharma B.V.
Forellenweg 16
4941 SJ Raamsdonksveer
The Netherlands

17. Other information