Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Dormazolam 5 mg/ml Solution for Injection for Horses (AT, BE, CZ, EE, HR, HU, LT, LU, LV, PO, PT, RO, SI, SK, UK)

Dormaquin vet 5 mg/ml solution for injection for horses (IS, NO, SE)

Date Created: November 2018

PuAR correct as of 04/04/2019 when RMS was transferred to PT. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0674/001/MR
Name, strength and pharmaceutical form	Dormazolam 5 mg/ml Solution for Injection for Horses, Solution for injection
Applicant	Le Vet Beheer B.V., Wilgenweg 7, 3421 TV Oudewater, The Netherlands
Active substance(s)	Midazolam
ATC Vetcode	QN05CD08
Target species	Horses
Indication for use	Intravenous co-induction of anaesthesia with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of conclusion of the mutual recognition procedure	4th July 2018
Date product first authorised in the Reference Member State (MRP only)	21st August 2017
Concerned Member States for original procedure	Austria, Belgium, Croatia, Czech Republic, Estonia, Hungary, Iceland, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden

I. SCIENTIFIC OVERVIEW

This was a 'full' application for a product containing midazolam, an active substance new in the target species, horses. As Dormazolam 5 mg/ml Solution for Injection for Horses is to be used in a minor species, the product was granted MUMS (Minor Use Minor Species) status. The product is indicated for horses only, for the intravenous co-induction of anaesthesia with ketamine, for smooth induction and intubation and profound muscle relaxation during anaesthesia. The dose rate is 0.06 mg/kg bodyweight (1.2 ml/100 kg bodyweight), in combination with ketamine at a dose of 2.2mg/kg bodyweight. Midazolam and ketamine may be combined and administered in the same syringe.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. The product is not authorised for horses intended for human consumption. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 5 mg/ml midazolam and the excipients benzyl alcohol, sodium chloride, hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment) and water for injections.

The container/closure system consists of 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. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple weighing, mixing and adjustment process, followed by suitable filtration, filling into vials, sterilisation and packing.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is midazolam, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice, and certificates of suitability provided.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

For the excipients and packaging, certificates of suitability were provided. All excipients are monographed in the Ph. Eur.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the Transmissible Spongiform Encephalopathy (TSE) Guideline present or used in the manufacture of this product. Suitable TSE tables were provided.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: appearance, pH, relative density, particulate contamination, identification of active substance and related substances and microbiological quality.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. The retest period is 5 years when stored appropriately. Substantial data indicate that the product is stable for 4 years when packaged for sale, with an in-use shelf-life of 28 days.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 4 years.
Shelf-life after first opening the immediate packaging: 28 days.
Keep the vial in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

The applicant provided a full dossier for this section of the application. The applicant referred to EMEA/CVMP/SWP/66781/2005 to provide Safety and Residue Data Requirements for Veterinary Medicinal Product for minor species. It was noted that the document was under revision as EME/CVMP/66781/2005-Rev. 1.

Pharmacological Studies

Pharmacodynamics

Bibliographical data has been provided which show that midazolam, (a benzodiazepine), acts by binding the GABA[3] BZ receptor. GABA is the principal

[3] GABA – gamma-aminobutyric acid.

inhibitory neurotransmitter in the central nervous system, (CNS). Benzodiazepines in general potentiate the effects of GABA receptors. Midazolam is a CNS depressant with amnesic, anticonvulsant, anxiolytic, hypnotic, muscle relaxant and sedative properties. In dogs, midazolam was seen to have minimal effects on cardiovascular action, and had no effect on blood pressure in rats. However, when used in conjunction with a barbiturate, a dose-related drop in blood pressure was observed.

Pharmacokinetics

References were provided citing results from respective studies in humans, horses, dogs, mice and rats. Midazolam is rapidly absorbed both intra-muscularly and intravenously, with the majority of the active substance being bound to plasma. Following biotransformation, the active substance is eliminated almost entirely in the urine.

Toxicological Studies

The applicant provided bibliographical data

- Single Dose Toxicity

References were provided from studies on rats and mice, describing the acute toxicity of midazolam. Oral toxicity (LD50*) was low as compared to intravenous administration. Following oral exposure, diazepam and midazolam exhibited similar potency. However, diazepam administered alone appeared to be several times more potent than midazolam following intravenous administration.

- Repeated Dose Toxicity

References were provided for this section. In mice, rats, rabbits and dogs, evidence of hepatotoxicity was observed as a result of daily sub-chronic or chronic oral exposure. Additional adverse effects were noted, including change to body weight, liver enzyme activity, leucocyte cell count, endocrine/pituitary gland and kidney weight. Dose-related, transient effects related to the pharmacological effect of the active substance were also noted. No suitable toxicological reference values for use in risk characterisation were established from published literature.

- Reproductive Toxicity, including Teratogenicity

Due to a lack of suitable, controlled studies on midazolam in pregnancy, the SPC describes the results of available data and recommends:

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

- Mutagenicity

Three proprietary studies and several references were presented for this section. Overall, it was accepted the midazolam did not causes mutagenic complications in the studies provided.

- Carcinogenicity

In light of the active substance having no known analogue to known carcinogens, and there was no evidence of mutagenicity, no long term carcinogenicity studies were required.

Studies of Other Effects

The applicant has provided bibliographical data which contributed to consideration of the product with regard to user safety. (See 'User Safety'). It was noted that the metabolites of midazolam exhibit less pharmacological activity than that observed in the parent compound.

Observations in Humans

Substantial amounts of bibliographical data were provided to support this section. Midazolam is widely and rapidly distributed, crosses the placenta and is expressed at low levels in breast milk. Risk mitigation for specific scenarios and routes of administration for midazolam are presented in the SPC. (See 'User Safety'.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- 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 breast milk in small amounts, thereby exerting a pharmacological effect on the nursing neonate. Pregnant and breastfeeding women should, therefore, take great care when handling this product and, in the event of exposure, seek medical advice immediately.
- People with known sensitivity to midazolam or the excipients should avoid contact with the veterinary medicinal product.

- This product contains benzyl alcohol and can cause skin irritation. Avoid contact with skin. In the case of contact with skin, wash with soap and water. If irritation persists, seek medical advice. Wash hands after use.
- The product can cause eye irritation. Avoid contact with eyes. If the product comes into contact with the eyes, rinse the eyes immediately with plenty of water and seek medical attention if irritation persists.

- 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.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines. Assessment stopped at Question 5 of the Phase I decision tree, as for the purposes of ERA, horses are considered to be a food-producing species. Additionally, the product will only be administered to individual animals.

Withdrawal Periods

The product is not authorised for use in horses intended for human consumption.

IV. CLINICAL DOCUMENTATION

Under MUMS permissions cited in EMEA/CVMP/EWP/117899/2014, literature references were permitted to support dose determination. These data were significant for the field study. The key difference between single-dose products cited in published literature and the multi-dose proposed product is the presence of the preservative benzyl alcohol in the proposed product. No excipients within the proposed product were deemed likely to interfere with the action of the product. Therefore, a waiver from the need to provide bioequivalence studies could be accepted under section 7.1a) of Guideline EMA/CVMP/016/00-Rev. 2.

V.I. Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical data describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Pharmacodynamics
The applicant provided multiple references noting the effects of the active substance in horses. Generally, it is noted that midazolam has effects on skeletal muscle and is an anti-convulsant. Data also suggest that midazolam has a limited sedative effect in horses.

Pharmacokinetics
The applicant provided multiple references noting the pharmacokinetic effects of midazolam in horses. Because the active substance is eliminated both renally and hepatically, provision of a suitable warning was key for section 4.5 of the SPC:

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

As limited data were found to support detail on plasma-binding in the horse, but this is known to be high in humans (96%), another key warning was added to section 4.5 of the SPC:

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

The SPC should be referred to for further specific information and warnings on use of the product.

Tolerance in the Target Species

The applicant has conducted a controlled target animal tolerance study, to assess both the pharmacokinetics and tolerance of the proposed product in horses.

This was a single-dose, four-period, four sequence, cross-over design with a wash-out period of 4 days between treatments. Eight horses, both male and female, from 2 to 9 years with bodyweights of between 372 kg – 545 kg were enrolled in the study.

All animals were anaesthetised with 0.02 mg/kg detomidine, followed by ketamine at 2.2 mg/kg for induction. In addition, as a co-inductor, horses received either a single intravenous dose of midazolam, (0.06mg/kg, 0.18 mg/kg or 0.30 mg/kg, corresponding to x1, x3 and x 5 the recommended dose). Some horses were not dosed with midazolam, (x0). Midazolam was administered before ketamine. Animals were allocated to four groups, (x0, x1, x3, x5) of 2 animals according to bodyweight and sex and a randomisation schedule for 8 animals using a block size of 2 was used. Animals in each group were allocated randomly to 1 of 4 groups. The study was not blinded. A series of parameters were measured in order to ascertain the effectiveness of administrations. From the results, a dose of 0.06 mg/kg was seen to be the most efficacious. At x5 the recommended dose, violent reaction on return to consciousness was noted in one animal, and the dose was not repeated in the other animals. The x3 dose produced prolonged recovery. The effects of over-dosing are noted in the SPC at sections 4.6 and 4.10.

IV.II. Clinical Documentation

Dose Determination Studies

In addition to other data, six key literature references were submitted for this section. These data supported the premise that the addition of midazolam for co-induction of anaesthesia with ketamine and the proposed doses of 0.06 mg/kg and 2.2 mg/kg respectively.

Field Trial

Study title	An efficacy study on a midazolam containing formulation for use as a co-induction agent with ketamine for anaesthesia in healthy equidae undergoing field castration
Objectives	To evaluate the effectiveness and safety of midazolam given as a co-induction agent with ketamine after detomidine premedication in horses anaesthetised for surgical intervention
Test site(s)	Stud farms (UK)
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Dormazolam 5 mg/ml Solution for Injection for Horses, administered at a dose of 0.06 mg per kg bodyweight (0.6 ml per 50 kg bodyweight).
Control product/placebo	Placebo solution for injection administered at 0.6 ml per 50 kg bodyweight.
Animals	39 horses aged 12-51 months, various Welsh breeds, all castrated males estimated bodyweights ranging from 100 to 400 kg. Exclusion criteria: Females, males with undescended testicles, clinical condition which may interfere with study, medication which may interfere with study.
Outcomes/endpoints	Primary endpoint: Quality of induction scored using a Visual Analog Scale (VAS) based on: movement and staggering, limb rigidity, degree of muscle relaxation once recumbent.
Randomisation	Randomisation was carried out by sequential allocation of previously prepared ampoules of test product or placebo. Test substance and placebo ampoules were randomised in blocks of 6 (3 midazolam, 3 placebo) and numbered from 1-42 by means of computer programme research randomiser https://www.randomizer.org. The horses were numbered in the order they were presented for surgery and therefore automatically randomised to test or placebo group.
Blinding	Both the proposed product and the placebo were aqueous solutions and appeared identical. They were indistinguishable for all personnel involved in the animal phase.
Method	Clinical examination, weighing, temperament grading. Pre-medication with detomidine at 20 µg/kg.* IV induction of anaesthesia combining midazolam and ketamine. Placebo group: Placebo and ketamine. Intubation and animal placed in dorsal recumbancy.

	Routine castration surgery performed. Detomidine/ketamine supplied in further incremental doses if required. Horse returned to lateral recumbancy following the procedure. Efficacy and clinical parameters evaluated. *10 horses required a higer detomidine dose, but these were all deviations from the established protocol.
Statistical method	Normality of the data was evaluated using the Shapiro-Wilkinson test. Individually scored SDS data were analysed using the Fisher exact test. Physiological data and VAS scores (mean of the two assessors) were analysed using the unpaired Students' t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data to compare the two groups. Changes with time (trend analysis) of the physiological data within each group were analysed using the paired t-test for normally distributed differences or the signed rank test for non-normally distributed differences. Where applicable 95% confidence intervals were calculated and $p<0.05$ was considered significant.
RESULTS	
Participant flow	Forty horses were initially included, but one was excluded after premedication as only one descended testicle noted. Thirty nine animals finally included in the study: 20 treated with midazolam and 19 with placebo.
Outcomes for endpoints	Induction quality was significantly better in the group receiving Dormazolam instead of placebo, (mean score 83) compared with placebo (mean score 71, $p=0.0011$).
Adverse events	No major adverse effects occurred.
DISCUSSION	The applicant conducted a pivotal field study investigating the use of midazolam as a co-induction agent with ketamine for anaesthesia in healthy horses undergoing field castration. In this study, significant clinical differences in induction quality, ease of intubation, and degree of muscular relaxation were observed in the group receiving the proposed product. This supported the proposed dose of 0.06mg/kg midazolam IV for co-induction of anaesthesia.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)