United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Rominervin 10 mg/ml Solution for Injection for Horses

Date Created: October 2018

PuAR correct as of 21/03/19 when RMS was transferred to NL. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0661/001/DC
Name, strength and pharmaceutical form	Rominervin 10 mg/ml Solution for Injection for Horses
Applicant	Le Vet Beheer B.V. Wilgenweg 7 3421 TV Oudewater The Netherlands
Active substance(s)	Romifidine hydrochloride
ATC Vetcode	QN05CM93
Target species	Horses
Indication for use	Sedative to facilitate handling, examination, minor surgical interventions and minor procedures. For premedication prior to administration of injectable or inhalation anaesthetics. Romifidine can also be used with synthetic opiates (e.g. butorphanol) to provide deeper sedation/analgesia.

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	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	1st August 2018.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, authorised according to Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Sedivet 10 mg/ml Solution for Injection for Horses, marketed in the UK since October 1991.

The product is indicated as a sedative to facilitate handling, examination, minor surgical interventions and minor procedures, in horses. It is also indicated for premedication prior to administration of injectable or inhalation anaesthetics.

Romifidine can also be used with synthetic opiates (e.g. butorphanol) to provide deeper sedation/analgesia. The product is for intravenous only, at a dose range of 0.04 - 0.12 mg romifidine hydrochloride/kg bodyweight. This equates to 0.4 – 1.2 ml of product per 100 kg bodyweight, and provides a dose-related response. Refer to the Summary of Product Characteristics (SPC), for full detail on the depth and duration of sedation required. When romifidine is used in combination with butorphanol for deeper sedation and analgesia, a dose of 0.04 mg – 0.12 mg romifidine HCl/kg bodyweight (0.4 – 1.2 ml product per 100 kg bodyweight) should be used followed by butorphanol.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used

as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy [1] 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 10 mg/ml romifidine hydrochloride, equivalent to 8.76 mg/ml romifidine, and the excipients chlorocresol, sodium chloride, hydrochloric acid, diluted (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injection.

The container/closure system consists of various presentations of colourless Type I glass vials, closed with a coated bromobutyl rubber stopper and aluminium cap. 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 presented in 10 ml, 20 ml or 50 ml glass vials.

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 mixing process followed by pH adjustment and subsequent filling into vials and appropriate sterilisation.

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 romifidine hydrochloride, an established active substance, produced under a suitable specification. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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. Suitable Certificates of Analysis were provided.

[1] Efficacy – The production of a desired or intended result.

All excipients are monographed within the European Pharmacopoeia (Ph. Eur). Packaging materials for the active substance conform to EC Regulation 10/2011. Packaging materials for the finished product comply with relevant Ph. Eur monographs.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, colour, pH, density, volume, sterility identification and assay of active substance, and assay for related substances.

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.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 30 months

Shelf life after first opening the immediate packaging: 56 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

Pharmacological Studies

Due to the nature of the application, pharmacological and toxicological studies were not required, other than to support the User Risk Assessment (URA).

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:

- In the case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.
- Avoid skin, eye or mucosal contact.
- Wash the exposed skin immediately after exposure with large amounts of water.
- Remove contaminated clothes that are in direct contact with skin.
- In the case of accidental contact of the product with eyes, rinse thoroughly with fresh water. If symptoms occur, seek the advice of a physician.
- If pregnant women handle the product, special caution should be observed not to self-inject as uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.

Advice to the physician:

Romifidine is an alpha2-adrenoreceptor agonist, symptoms after absorption may involve clinical effects including dose-dependent sedation, respiratory depression, bradycardia, hypotension, a dry mouth, and hyperglycaemia. Ventricular arrhythmias have also been reported. 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.

Phase I:

The product will be used to treat a small number of animals, and as such environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because pharmaceutical equivalence was successfully claimed with the reference product, which has a 6 day withdrawal period.

MRLs

The active substance romifidine is included in Table 1 (allowed substances) of Regulation No. 37/2010 with a 'No MRL required' status.
The excipients chlorocresol, sodium chloride and hydrochloric acid are also included in Table 1 of Regulation No. 37/2010 with a 'No MRL required' status.

Withdrawal Periods

Based on the data provided, withdrawal periods were established as follows:

- Meat and offal: 6 days.
- Not authorised for use in animals producing milk for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, no data were required to be submitted for this section. The SPC carries details on the pharmacodynamic and pharmacokinetic properties of romifidine.

Pharmacodynamics

Romifidine is an alpha-2-agonist of the imino-imidazolidine class, exerting sedative and analgesic effects. Its sedative effect is induced by stimulation of alpha-2-adrenoreceptors in the central nervous system.

After administration of romifidine, blood pressure increases. Subsequently, blood pressure decreases due to the effect on peripheral presynaptic receptors and decrease of sympathetic tone resulting in vasodilatation.

Pharmacokinetics

Approximately 20% of romifidine is bound to plasma proteins. Romifidine is found predominantly in the kidney and muscle, whereas the liver contains only traces of the parent compound.

Following intravenous injection, romifidine is rapidly eliminated: approximately 80% of the administered dose is eliminated via urine and the remainder via the faeces

Tolerance in the Target Species

Tolerance studies were not required because the proposed product was considered therapeutically identical to the reference product. Appropriate data were added to the SPC.

IV.II. Clinical Documentation

Studies were not required because the proposed product was considered therapeutically identical to the reference product. Appropriate data were added to the SPC.

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.

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