College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Nerfasin vet. 20 mg/ml, solution for injection for cattle, horses, dogs and cats

NL/V/157/001

AND

Nerfasin vet. 100 mg/ml, solution for injection for cattle and horses

NL/V/157/002

Created: July 2014
Updated: February 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/157/001-002/DC
Name, strength and pharmaceutical form	Nerfasin vet. 20 mg/ml, solution for injection for cattle, horses, dogs and cats Nerfasin vet. 100 mg/ml, solution for injection for cattle and horses
Applicant	Le Vet B.V. Wilgenweg 7 3421TV Oudewater, the Netherlands
Active substance(s)	Xylazine Hydrochloride
ATC Vetcode	QN05CM92
Target species	Cattle, Horses, Dogs, Cats
Indication for use	Sedation. Premedication in combination with an anaesthetic.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Nerfasin vet. 20 mg/ml: generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended. Nerfasin vet. 100 mg/ml: hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	22 February 2012
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	AT, BE, CZ, DK, EL, ES , FI, FR, HU, IE, IS, IT, LU, NO, PL, PT, SE, SK, UK

I. SCIENTIFIC OVERVIEW

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; the slight 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 of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains xylazine hydrochloride, at respectively 20 mg and 100 mg xylazine per ml and excipients methyl parahydroxybenzoate, sodium hydrogencarbonate, hydrochloric acid and (in the 20 mg/ml product only) sodium chloride.

The solutions are packed in clear, colourless type II glass bottles with volumes of 10, 30 (with 25 ml content) and 50 ml, fitted with bromobutyl 20 mm stoppers and aluminium 20 mm caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and preservative are justified.

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance is xylazine hydrochloride an established active substance described in the European Pharmacopoeia. 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.

Two suppliers are used. For one supplier a Certificate of Suitability has been provided, and for the other supplier the ASMF procedure is applied.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

Not applicable.

F. 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.

G. 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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The claim of a 28 day stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at 25°C. The claimed storage condition ‘Do not refrigerate or freeze’ has been justified.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that xylazine hydrochloride is a potent α2-agonist and classified as a sedative/analgesic with muscle relaxant properties.

After intramuscular administration, absorption is rapid in the target animal, though bioavailability is incomplete, variable and species-dependent. The onset of action is within minutes. The duration of the effect is dose-dependent, but may last for approximately 2 hours. Xylazine is rapidly distributed. The rapid elimination of xylazine is probably related to extensive metabolism rather than to a rapid renal excretion of unchanged xylazine.

Toxicological Studies

The applicant has provided bibliographical data which show that no toxicological NOELs could be established since available studies were not complete enough to establish definite NOELs for repeated-dose toxicity.

Based on case reports of pregnant animals treated with xylazine or other α2-agonists, it is concluded that xylazine may induce early parturition or abortion (by uterine contractility).

Xylazine is considered not to be mutagenic and/or carcinogenic. The 2,6-xylidine metabolite of xylazine is considered to be genotoxic and carcinogenic. However, this metabolite was not found in cattle tissue, milk and urine. Metabolism of xylazine to 2,6-xylidine in humans is unknown.

Observations in Humans

The applicant has provided information which shows that accidental self-injection may lead to effects such as hypotension, bradycardia, respiratory depression, central nervous system depression and hyperglycaemia. Ventricular arrhythmias have also been reported. In pregnant women uterine contractions and decreased foetal blood pressure may occur after systemic exposure.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that exposure to the product may occur via accidental self-injection and/or spilling of droplets of the product from the needle.

The risk of accidental self-injection is considered acceptable as this product is used by highly skilled professionals. Based on a quantitative estimate of the carcinogenic risk assuming that the metabolite 2,6-xylidine is formed in humans, this risk was found to be negligible. This product can be used safely when contaminated skin areas are immediately washed after dermal exposure. Pregnant women should handle this product with special caution as uterine contractions and decreased foetal blood pressure may occur.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product and are in line with the CVMP opinion on alpha2-agonists.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because Nerfasin vet. 20 mg/ml is identical to its reference product Rompun 2%, including identical dosage regimens (i.e. the amount of the product injected). Nerfasin vet. 100 mg/ml differs with respect to the concentration of the active substance xylazine. However, an identical quantity of xylazine is injected as the injection volume proportionally decreases with the strength, anticipating equal residues.

MRLs

Xylazine hydrochloride is listed in Annex I of Council Regulation 2377/90. The marker substance is xylazine hydrochloride.

MRLs are listed below:

	Bovine	Equidae
Muscle	No MRL needed	No MRL needed
Liver	No MRL needed	No MRL needed
Kidney	No MRL needed	No MRL needed
Fat / skin	No MRL needed	No MRL needed
Milk	No MRL needed	No MRL needed

Withdrawal Periods

Based on the data provided above, a withdrawal period of 1 day for meat in bovine and equidae and 0 days for bovine milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

As the application for Nerfasin vet. 20 mg/ml is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated based on essential similarity, tolerance and efficacy studies are not required. The product literature accurately reflects the type and incidence of adverse effects which might be expected and the efficacy claims for this product are equivalent to those of the reference product.

With regard to the hybrid application for Nerfasin vet. 100 mg/ml tolerance and efficacy studies were submitted (see below).

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted controlled target animal tolerance studies using the recommended dose and two injection rates in the target species cattle and horse. An authorised reference product containing the same active substance, Rompun 2%, was used as a control.

The study in horses was designed as a randomised, 3-period crossover study with a 7 day wash out period. Doses were administered by intravenous route on a single occasion. Parameters evaluated were heart rate and clinical abnormalities. Minimal adverse effects were seen following administration of the 1.0 mg xylazine per kg body weight in 5 or 10 seconds. No differences between product and reference product were observed for the safety parameters.

The study in cattle was designed as a randomised 2-period crossover safety and efficacy study with a 7 day wash out period. Doses were administered by intramuscular route on a single occasion. Parameters evaluated were heart rate, respiratory rate, ataxia and reaction to stimuli. The study revealed no difference between the product and the reference product.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted the following studies.

A single dose, blinded, randomised, 3-way, crossover, comparative efficacy and tolerance study on 3 xylazine containing formulations intravenously administered

to 12 healthy horses was performed in 2010 in the Netherlands. Efficacy parameters studied were position of the head and reaction to stimuli. Safety parameters studies were heart rate, ataxia and local reactions. Differences between test products and reference product (Rompun 2%) were minimal or non-existent with regard to efficacy and safety.

A single dose, blinded, randomized, 3-way crossover, comparative efficacy and tolerance study on 3 xylazine containing formulations intravenously administered to 12 healthy cattle was performed in 2010 in the Netherlands. Efficacy parameters studied were degree of instability and response to stimuli. Safety parameters studies were respiratory rate and heart rate. No differences were observed between test products and reference product (Rompun 2%) with regard to efficacy and safety parameters or side-effects.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

Summary of change	**Section updated**	**Approval date**
Update SPC/product information regarding antidotes without an established MRL (NL/V/0157/001-002/IB/001)	N/A	28 October 2014
Renewal (NL/V/0157/001-002/R/001)	N/A	10 May 2017
Change of DDPS	N/A	24 July 2019