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

Tranquinervin 10 mg/ml solution for injection for horses (AT, BE, BG, CY, CZ, EL, FR, HR, HU, LU, NL, PT, RO, SI, SK, UK)

Tranquinervin Vet 10 mg/ml solution for injection for horses (EE, IS, LT, LV, NO, PL, SE)

Date Created: May 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0321/002/DC
Name, strength and pharmaceutical form	Tranquinervin 10 mg/ml Solution for Injection for Horses
Applicant	Le Vet Beheer B.V. Wilgenweg 7 3421 TV Oudewater The Netherlands
Active substance	Acepromazine (equivalent to 13.55 mg acepromazine maleate)
ATC Vetcode	QN05AA04
Target species	Horses
Indication for use	*Anaesthetic Premedication*: Following acepromazine administration, the amount of anaesthetic necessary to induce anaesthesia is considerably reduced. *Tranquilisation*: Acepromazine tranquilisation (ataraxy) involves a modification of temperament which is not associated with hypnosis, narcosis or marked sedation. This is achieved with low doses of acepromazine. At low doses, acepromazine reduces anxiety which is beneficial for use in horses prior to shoeing or transportation. *Sedation*: At higher dose rates acepromazine is an effective sedative, as an adjunct to, or replacement for, physical restraint e.g. dentistry, handling and shoeing. The relaxant effects aid examination of the penis in horses and the treatment of tetanus and choke

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	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	20th December 2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, France, Greece, Hungary, Iceland, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden.

I.SCIENTIFIC OVERVIEW

This is an application for a generic product, Tranquinervin 10 mg/ml solution for injection for horses, in in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is ACP injection 10 mg/ml solution for injection, authorised in the UK since 1992. The proposed product was considered to be qualitatively and quantitatively the same as the reference product.

The product is indicated for:

Anaesthetic Premedication: Following acepromazine administration, the amount of anaesthetic necessary to induce anaesthesia is considerably reduced.

Tranquilisation: Acepromazine tranquilisation (ataraxy) involves a modification of temperament which is not associated with hypnosis, narcosis or marked sedation. This is achieved with low doses of acepromazine. At low doses, acepromazine reduces anxiety which is beneficial for use in horses prior to shoeing or transportation.

Sedation: At higher dose rates acepromazine is an effective sedative, as an adjunct to, or replacement for, physical restraint e.g. dentistry, handling and shoeing. The relaxant effects aid examination of the penis in horses and the treatment of tetanus and choke.

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.[1] The product is safe for the user and for the environment, when used as recommended. 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains acepromazine 10 mg (equivalent to 13.55 mg acepromazine maleate) and the excipients phenol, sodium hydroxide (pH for adjustment), maleic acid (pH for adjustment) and water for injections.

The container/closure system consists of clear Type I glass vials 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 mixing followed by filling and terminal sterilisation.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substance is acepromazine, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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

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.

An Active Substance Master File was provided and all excipients used in the manufacture of Tranquinervin are supplied in accordance with the relevant Ph. Eur monographs. Certificates of analysis were provided for each excipient.

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 include those for appearance, relative density, volume, pH, and sterility, identification of acepromazine, identification of phenol, assay of acepromazine and assay of phenol.

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.

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.
A retest period of 4 years was agreed. Stability data on the finished product were provided on a single batch of finished product.

The claim of 56 day stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at +25°C/60% RH. Results from these data dictated the agreed shelf-life and storage precautions as cited in the SPC.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 30 months
- Shelf life after opening of 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)

As this is a generic application according to Article 13 (1), and a biowaiver absolving the applicant from the need to provide bioequivalence tests with a reference product on the basis of essential similarity was accepted, the results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users / the environment / consumers.

III.A Safety Documentation

Observations in Humans

Bibliographical data were provided which show that likely effects in humans which are:

- Hypertension and epilepsy at oral doses of 200 mg/day daily for 6 weeks
- CNS and respiratory depression along with hypertension at doses of 950 mg and 1250 mg acepromazine (adult suicide attempts)
- Sedation, tachycardia and evidence of poor perfusion after a dose of 6.25-8.3 mg/kg orally (accidental ingestion by a child)

User Safety

A user risk assessment was provided in compliance with the relevant guideline which states that the formulation is identical to the reference and a summary on toxicity of the excipients was also provided. At the concentrations in the product and the amounts likely to be accidentally injected, none are of toxicological concern.

The applicant has updated user safety information on the SPC compared to that of the reference product.
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:

- This product contains a potent sedative; care should be taken, when handling and administering the product, to avoid accidental self-exposure.
- In case of accidental self-injection, seek medical advice immediately and show the package insert or label to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur. Symptomatic treatment may be required.
- If accidental eye contamination occurs, flush gently with fresh running water for 15 minutes. Medical advice should be sought if irritation persists.
- In the event of accidental skin contamination, contaminated clothing should be removed and the area washed with large amounts of soap and water. Medical advice should be sought if irritation persists.
- Wash hands and exposed skin thoroughly after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The VICH decision tree provided correctly concludes that environmental assessment stops in Phase I. The disposal advice in the SPC and product literature is satisfactory and the product is not expected to pose a risk for the environment when used as recommended.
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13(1) and bioequivalence with a reference product has been accepted on the basis of essential similarity, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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 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 **(Application number)**	**Approval date**
Introduction of a new Pharmacovigilance system which has been assessed by the EMA for another product of the same MAH NL/V/xxxx/WS/021	12 July 2019
RMS change from UK to NL	21 March 2019