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

Anesketin 100 mg/ml Solution for Injection for Dogs, Cats and Horses
(Denmark, France, Germany, Netherlands, Spain, UK)

Nimatek 100 mg/ml Solution for Injection for Dogs, Cats and Horses
(Belgium)

Date Updated: January 2023

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0278/001
Name, strength and pharmaceutical form	Anesketin 100 mg/ml Solution for Injection for Dogs, Cats and Horses
Applicant	Eurovet Animal Health BV Handelsweg 25 Bladel 5531 AE The Netherlands
Active substance(s)	Ketamine Hydrochloride
ATC Vetcode	QN01AX03
Target species	Dogs, cats and horses
Indication for use	To be used as a sole agent for restraint and minor surgical procedures in the cat, where muscle relaxation is not required. To be used to induce anaesthesia: a) in combination with butorphanol and medetomidine in the dog and cat, b) in combination with xylazine in the horse, dog and cat, c) in combination with detomidine in the horse, d) in combination with romifidine in the horse.

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 hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	10th July 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, Denmark, France, Germany, The Netherlands, Spain.

I. SCIENTIFIC OVERVIEW

Anesketin 100 mg/ml Solution for Injection has been developed as a generic of Ketaset 100 mg/ml Solution for Injection. Bioequivalence with this product is claimed. The active substance is ketamine, as ketamine hydrochloride, which is a dissociative anaesthetic.

Anesketin is indicated as an anaesthetic both as a sole agent, for minor surgical procedures in the cat when muscle relaxation is not required, and in combination with other anaesthetic agents. The product can be used in conjunction with butorphanol and medetomidine in the dog and cat, xylazine in the dog, cat and horse and in conjunction with romifidine or detomidine in the horse. The product is administered by intramuscular, subcutaneous or intravenous injection.

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[1].

The product is safe for the user, the consumer of foodstuffs from treated animals (horses only) 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 benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains ketamine hydrochloride as active and the excipients chlorocresol, sodium hydroxide, hydrochloric acid and water for injections.

The container/closure system consists of clear Type I glass vials closed with bromobutyl rubber stoppers and aluminium caps. The vials are filled with 5 ml, 10 ml, 20 ml, 25 ml, 30 ml or 50 ml and each vial is presented in an individual cardboard carton. 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.

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. The product is manufactured by firstly dissolving the chlorocresol in the water for injection before adding and dissolving the ketamine hydrochloride. Following this step the pH is adjusted as necessary, the solution is sterilised, filled into the sterile vials and the vials are sealed.

C. Control of Starting Materials

The active substance is ketamine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur). A certificate of suitability has been provided for one active substance manufacturer and an Active Substance Master File (ASMF) for the other manufacturer. 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.

All excipients comply with their respective Ph. Eur monographs. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

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. The tests include identification and assay of the active substance, identification and assay of the preservative, pH test and appearance.

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.

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. A retest period of 4 years from one manufacturer of the active substance and a retest period of 5 years from the other manufacturer is justified.

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 shelf life of 3 years for the finished product is supported and an in-use shelf life of 28 days has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale is 3 years.
- Shelf life after first opening the immediate packaging is 28 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic hybrid application submitted according to Article 13(3) of Directive 2001/82/EC as amended and bioequivalence with the reference can be assumed because of the nature of the product, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic hybrid application submitted according to Article 13(3) of Directive 2001/82/EC as amended and bioequivalence with the reference can be assumed because of the nature of the product, results of toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main routes of exposure are through accidental self-injection and accidental spillage onto skin.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- This is a potent drug. Particular care should be taken to avoid accidental self-administration.
- People with known hypersensitivity to ketamine or any of the excipients should avoid contact with the veterinary medicinal product.
- Avoid contact with the skin and eyes. Wash any splashes from skin and eyes immediately with large amounts of water.
- Adverse effects on the foetus cannot be excluded. Pregnant women should avoid handling the product.
- In case of accidental self-injection, or if symptoms occur after ocular/oral contact, seek medical advice immediately and show the package leaflet or the label to the physician, but DO NOT DRIVE.

Advice to doctors:

Do not leave patient unattended. Maintain airways and give symptomatic and supportive treatment.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that as the product is an anaesthetic and as such will only be used in a very limited number of animals, the risk of exposure to the environment is very low.

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

The applicant has not conducted any residue depletion studies but has provided several references, including the MRL report. This is sufficient for a generic

hybrid application and the references indicate ketamine is rapidly absorbed and excreted; therefore a 1 day withdrawal period in horses is acceptable.

Withdrawal Periods

Horse
Meat and offal: 1 day
Milk: 24 hours

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic hybrid application submitted according to Article 13(3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been accepted because of the nature of the product, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

The applicant has provided references to support the substitution of the preservative benzethonium chloride in the reference product with chlorocresol. The applicant has opted to use chlorocresol as a preservative, which is a commonly used preservative in veterinary medicine, instead of benzethonium chloride. The applicant has demonstrated that this alteration does not significantly influence the rate or extent of absorption of the active substance, ketamine hydrochloride.

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

IV.B Clinical Studies

As this is a generic hybrid application submitted according to Article 13(3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been accepted because of the nature of the product, results of clinical studies are not required.

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 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.

•	27 November 2022	Update of the product information to QRD version 9.0 and implementation of changes requested after PSUR assessment
•	11 January 2019	Change in QPPV
•	30 August 2018	Change in RMS from UK to NL.
•	05 June 2018	Renewal – UK as RMS
•	06 September 2017	Deletion of manufacturing site for an active substance. Submission of an updated Ph. Eur. certificate of suitability for an active substance from an already approved manufacturer.
•	09 May 2017	Changes to the labelling and/or package leaflet. Changes to the labelling and/or package leaflet.
•	19 August 2015	Changes to the labelling and package leaflet.
•	21 May 2014	Change in storage conditions of the finished product by the addition of ‘Keep the vial in the outer carton in order to protect from light’, minor editorial changes to the SPC and replacement of ‘detomidine’ in Section 4.9 of the SPC with ‘romifidine’.
•	26 April 2013	Change of QPPV name and contact details.