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Publicly Available Assessment Report for a Veterinary Medicinal Product

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NIMATEK 100 mg/ml, Solution for injection for dogs, cats and horses

PRODUCT SUMMARY

EU Procedure Number	IE/V/0475/001 (formerly UK/V/0513/001)
Name, Strength, Pharmaceutical Form	NIMATEK 100 mg/ml, Solution for injection for dogs, cats and horses
Active Substances(s)	Ketamine
Applicant	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel Netherlands
Legal Basis of Application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Target Species	Cats,Dogs,Horses
Indication For Use	The product may be used to induce anaesthesia: a) in conjunction with butorphanol and medetomidine in the dog and cat, b) in conjunction with xylazine in the dog, cat and horse, c) in conjunction with detomidine in the horse, d) in conjunction with romifidine in the horse. Based on a benefit/risk assessment performed by the veterinarian the product may also be used as a sole agent for restraint and minor surgical procedures where muscle relaxation is not required in the domestic cat.
ATC Code	QN01AX03
Date of completion of the original decentralised procedure	26 March 2014 (UK) 09 May test2014 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original	Austria, Finland, Ireland (now RMS), Italy, Norway, Poland, Portugal, Sweden UK added via RMS change

procedure	

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

Nimatek 100 mg/ml Solution for Injection for Dogs, Cats and Horses has been developed as a generic hybrid of Ketaset 100 mg/ml Solution for Injection, which has been authorised in the UK since April 1990. Bioequivalence is claimed with the reference product but due to a change in the listed indications the product is a generic hybrid.
The product contains ketamine and is indicated for use as a dissociative anaesthetic agent. It should be administered via intramuscular, subcutaneous or intravenous injection. The product is contraindicated in animals with known hypersensitivity, severe cardiac de-compensation, high blood pressure, glaucoma and hepatic or renal failure. The product should not be used as the sole agent in the horse or dog.
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 reactions observed are indicated in the SPC[1].
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 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 the active substance and the excipients chlorocresol, sodium hydroxide, hydrochloric acid and water for injections.

The container/closure system consists of a clear, colourless Type I glass vial 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 of product and packaged in a cardboard carton. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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. The product is manufactured by adding chlorocresol then ketamine hydrochloride to the water for injection and stirring until dissolved. Sodium hydroxide and hydrochloric acid are then added as necessary to adjust the pH. Under a nitrogen atmosphere the solution is filtered and filled into the vials, which are sealed and subsequently sterilised.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 ketamine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.). A Ph. Eur. Certificate of Suitability has been provided for one manufacturer and an Active Substance Master File (ASMF) has been provided for the second manufacturer of the active substance. 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 the excipients comply with their respective Ph. Eur. monographs and are tested upon receipt. Certificates of analysis have been provided.

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 those for identification and assay of the active and preservative, appearance, clarity, pH, density and sterility.

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. A retest interval of 5 years has been established for one manufacturer and a retest interval of 4 years for the second manufacturer.

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. Data have been provided for batches stored at 25°C/60%RH for 24 months and 40°C/75%RH for 18 months. A shelf life of 3 years is supported.

In-use stability studies were also provided. Samples taken 2 and 4 weeks after broaching were examined against the shelf life specification. An in-use shelf life of 28 days has been determined.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life

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

Special precautions for storage

- Keep the vial in the outer carton in order to protect from light.

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 product has been determined, the 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 product has been determined, the 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 dermal, ocular and accidental self-injection. The product is expected to only be handled by veterinary surgeons, and possibly nurses.

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 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 the product will only be used in a small number of animals and therefore poses minimal risk to the environment. 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
A bibliography has been provided to support the withdrawal period for horses. Pharmacokinetic data have been provided which demonstrate the rapid absorption of ketamine from the injection site. Peak plasma concentrations of ketamine are reached within 10 minutes of injection.

Ketamine is then distributed very quickly to the central nervous system and peripheral tissues. The half-life for distribution is in the horse is 3 minutes. Rapid metabolism then occurs in the liver before elimination of ketamine and its main metabolite, norketamine.

The elimination half-life of ketamine is between 40 and 60 minutes and after 10 half-lives (approximately 7 hours) the percentage still present in the body is <0.1%. Both ketamine and norketamine are almost completely eliminated within the first day after administration. In all the animal species tested and reported in the literature the rapid absorption, distribution, metabolism and elimination of ketamine mean it is not a problem substance regarding residue levels.

Less data has been submitted regarding the milk withdrawal period for ketamine in horses. However studies in cattle found that even 1 hour after administration ketamine was below the limit of detection (8 µg/kg) in cow's milk when using the same dose as horses. This amount is much lower than the amount that could produce pharmacological effects in humans. As the horse is a minor milk-producing species further data are not required.

MRLs
All the ingredients in this product are listed in Table 1 of Regulation 37/2010. No MRL is required for the active or any of the excipients.

Withdrawal Periods
Horse: Meat and offal: 1 day
Milk: 1 day
Cat: Not applicable.
Dog: Not applicable.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies
Pharmacology
The applicant has provided information that indicates the change of preservative compared to the reference product, benzethonium chloride to chlorocresol, should not affect the bioavailability of ketamine as neither preservative will interact with ketamine. Based on this information and as this is a generic hybrid application, submitted according to Article 13 (3) of Directive 2001/82/EC as amended,

bioequivalence can be assumed and therefore pharmacological studies are not required.

Tolerance in the Target Species of Animals

Bibliographical information has been provided as evidence that chlorocresol is safe for use in the target species. Chlorocresol is widely used as a preservative in human and veterinary medicines with antimicrobial activity against Gram positive and negative bacteria as well as fungi. At concentrations of 0.1 – 0.2% chlorocresol is bacteriostatic.

The MRL summary report for chlorocresol was summarised. Toxicity studies in rats and rabbits indicate a low toxicity following oral administration (LD_{50}[1] values >1830 mg/kg in rats) and no evidence of systemic toxicity was observed following topical administration to rabbits. Repeat dose oral administration for 28 days in rats resulted in a NOEL[2] of 200 mg/kg/day and no histopathological changes or effects on clinical chemistry were noted. Chlorocresol has not been found to be teratogenic or mutagenic.

A study which compared the reference product toxicity with the test product toxicity was also submitted. The results indicated that the substitution of benzethonium chloride with chlorocresol would not be detrimental to the safety profile of the test product.

Data on the safety of ketamine were not submitted during the application but as this is a generic hybrid application and the safety profile of ketamine (in a 100 mg/ml injectable solution) has already been established this was not required. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Laboratory Trials

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 determined, the results of laboratory trials are not required.

[1] LD_{50} – The dose which is lethal for 50% of the population
[2] NOEL – No observable effect level

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.