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

Vetroxy LA 200 mg/ml solution for injection for cattle, sheep and pigs (UK, EE, LV, HU, NL, EL, PL)
Vetroxy vet 200 mg/ml solution for injection for cattle, sheep and pigs (SE)

Date Created:
May 2018

Updated: November 2023

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0253/001/DC
Name, strength and pharmaceutical form	Vetroxy LA 200 mg/ml Solution for Injection for Cattle, Sheep and Pigs
Applicant	Bimeda Animal Health Ltd. Unit 2/3/4 Airton Close, Tallaght, Dublin 24 Ierland
Active substance(s)	Oxytetracycline dihydrate
ATC Vetcode	QJ01AA06
Target species	Cattle, Sheep and Pigs
Indication for use	Treatment of infections caused by oxytetracycline susceptible bacteria in cattle, sheep and pigs as follows: Cattle: • Pasteurellosis and respiratory tract infections caused by *Mannheimia haemolytica* or *Pasteurella multocida*. • Umbilical infections and septic arthritis caused by *Trueperella pyogenes*, *Escherichia coli* or *Staphylococcus aureus*. • Clinical Mastitis caused by *Trueperella pyogenes*, *Escherichia coli*, *Staphylococcus aureus, Streptococcus agalactiae* or *Streptococcus uberis*. • Metritis caused by *Escherichia coli* Sheep: • Pasteurellosis and respiratory tract infections caused by *Mannheimia haemolytica* or *Pasteurella multocida*. • Umbilical infections and septic arthritis caused by *Trueperella pyogenes*- or

	Escherichia coli. • Clinical Mastitis caused by *Trueperella pyogenes*, *Escherichia coli* or *Staphylococcus aureus.* • Erysipelas caused by *Erysipelothrix rhusiopathiae*. • The product can also be used for treatment and metaphylaxis of enzootic abortion in sheep caused by *Chlamydophila abortus*. Pigs: • Pasteurellosis and respiratory tract infections caused by *Mannheimia haemolytica* or *Pasteurella multocida*. • Umbilical infections and septic arthritis caused by *Trueperella pyogenes*, *Escherichia coli* or *Staphylococcus aureus*. • Clinical Mastitis caused by *Escherichia coli.* • Erysipelas caused by *Erysipelothrix rhusiopathiae*. • Atrophic rhinitis caused by *Bordetella bronchiseptica* or *Pasteurella multocida*.

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).

- The CBG-MEB veterinary department website: https://www.diergeneesmiddeleninformatiebank.nl/nl/

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	19 October 2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Estonia, Greece, Hungary, Latvia, Poland, Sweden, United Kingdom (Northern Ireland)

I. SCIENTIFIC OVERVIEW

This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC (as amended). Alamycin LA 200 mg/ml Solution for Injection authorised in the UK since 1993. The application was exempt from the conduct of *in vivo* bioequivalence studies is claimed in accordance with section 7.1(b) of EMA/CVMP/016/00-Rev.2.

The product is indicated for the treatment of infections caused by oxytetracycline susceptible bacteria in cattle, sheep and pigs as follows:

Cattle:

- Pasteurellosis and respiratory tract infections caused by *Mannheimia haemolytica* or *Pasteurella multocida*.
- Umbilical infections and septic arthritis caused by *Trueperella pyogenes*, *Escherichia coli* or *Staphylococcus aureus*.
- Clinical Mastitis caused by *Trueperella pyogenes*, *Escherichia coli*, *Staphylococcus aureus, Streptococcus agalactiae* or *Streptococcus uberis*.
- Metritis caused by *Escherichia coli*

Sheep:

- Pasteurellosis and respiratory tract infections caused by *Mannheimia haemolytica* or *Pasteurella multocida*.
- Umbilical infections and septic arthritis caused by *Trueperella pyogenes*- or *Escherichia coli*.

- Clinical Mastitis caused by *Trueperella pyogenes*, *Escherichia coli* or *Staphylococcus aureus.*
- Erysipelas caused by *Erysipelothrix rhusiopathiae*.
- The product can also be used for treatment and metaphylaxis of enzootic abortion in sheep caused by *Chlamydophila abortus*.

Pigs:

- Pasteurellosis and respiratory tract infections caused by *Mannheimia haemolytica* or *Pasteurella multocida*.
- Umbilical infections and septic arthritis caused by *Trueperella pyogenes*, *Escherichia coli* or *Staphylococcus aureus*.
- Clinical Mastitis caused by *Escherichia coli.*
- Erysipelas caused by *Erysipelothrix rhusiopathiae*.
- Atrophic rhinitis caused by *Bordetella bronchiseptica* or *Pasteurella multocida*.

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, 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 [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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 200 mg oxytetracycline (equivalent to 216 mg oxytetracycline dihydrate) and the excipients sodium formaldehyde magnesium oxide light, dimethylacetamide, disodium edetate, ethanolamine (for pH adjustment), hydrochloric acid, concentrated (for pH adjustment) and water for injections.

The container/closure system consists of amber type II glass vials of 100 ml sealed with a bromobutyl rubber stopper with aluminium overseals. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence 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 a simple mixing and sterilisation process.

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 oxytetracycline an established active substance described in the European Pharmacopoeia (Ph. Eur). 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.

A certificate of suitability was provided which has additional testing requirements for any unspecified impurity detected by the test for related substances of the monograph, with a limit of not more than 0.1%.

Each of the excipients complies with the relevant, current Ph. Eur. monograph, except for sodium formaldehyde sulfoxylate dihydrate and ethanolamine, for which no Ph. Eur. monograph exists. Sodium formaldehyde sulfoxylate

dihydrate complies with the USPNF monograph and ethanolamine complies with the BP monograph.

The container-closure for oxytetracycline dihydrate is stated on the certificate of suitability as two polyethylene bags placed in a paper bag.

II.C.4. Substances of Biological Origin

The applicant has submitted a declaration confirming that all starting materials and manufacture are in compliance with the requirements of the *Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)*. Separate TSE declarations are provided from each of the suppliers of the excipients.

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, particulate contamination, colour, pH, identification and assay of the active substance, impurities and sterility.

II.F. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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 data show that the product remains within the specification for 24 months at 25°C/60%RH and therefore support a shelf life of 2 years when stored below 25°C.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: 28 days
Do not store above 25ºC.

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

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

This is an application for a generic product, according to Article 13(1) of Regulation 2001/82/EC, as amended, therefore no pharmacology or toxicology data were provided.

III.A Safety Documentation

User Safety

A user risk assessment (URA) was provided in compliance with the relevant guideline which shows that the product may cause sensitisation and can be irritating to eyes and skin. The URA also shows that the excipient dimethylacetamide may damage unborn children.

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:

- The excipient dimethylacetamide may damage unborn children; therefore, women of child bearing age must be very careful to avoid exposure via spillage onto the skin or accidental self-injection when administering the product. If you are pregnant, think you may be pregnant or are attempting to conceive, you should not administer the product.
- This product may cause allergy-type reactions in sensitised people.
- Those with known hypersensitivity to tetracyclines should avoid contact with the product.
- This product may cause skin and eye irritation. Avoid contact of the skin and eyes with the product. In case of accidental spillage onto skin or eyes, rinse the affected area with large amounts of water.
- Take care to avoid accidental injection. In case of self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

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

Phase I:

The Phase I exposure assessment concludes at question 17, since the PECsoil-initial values have been calculated and are all found to be lower than 100 µg/kg; a Phase II assessment is only required if the calculations exceed this limit. The ERA therefore concludes at Phase I.

III.B.2 Residues documentation
Residue Studies

No residue depletion studies were conducted because the application was for a generic product, according to Article 13(1) of Regulation 2001/82/EC, as amended

MRLs

Oxytetracycline is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues and milk.

MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Oxytetracycline	Sum of parent drug and its 4-epimer	All food producing species	600 300 100 100 200	Kidney Liver Muscle Milk Eggs	None

Withdrawal Periods

The same withdrawal periods as authorised for the reference product are proposed for the generic product:

Cattle:
Meat and offal: 31 days
Milk: 10 days

Sheep:
Meat and offal: 9 days
Milk: 7 days

Pigs:
Meat and offal: 18 days

Maximum recommended dose at any one site:
Cattle: 20 ml
Pigs: 10 ml
Sheep: 5 ml

IV CLINICAL DOCUMENTATION

The application is for a generic product and has been submitted under Article 13(1) of Directive 2001/82/EC, as amended. Therefore, no clinical data were required to be provided.

Resistance

The bibliography provided suggests that oxytetracycline resistance has been identified in many veterinary pathogens; however, the prevalence of resistance varies widely between different locations. Adequate warnings and precautions appear on the product literature. For veterinary isolates, the susceptible breakpoint is ≤ 2µg/ml for bovine respiratory pathogens and ≤ 0.5µg/ml for swine pathogens. For other isolates, the breakpoint for sensitive organisms in humans is used, which is ≤4µg/ml for all organisms, except streptococci, which is ≤2µg/ml (CLSI, 2007).

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(s) 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 Summary of Product Characteristics (SPC) for this product is available on the website:

https://www.diergeneesmiddeleninformatiebank.nl/nl/

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)	**Section updated in Module 3**	**Approval date**
Update of Certificate of Suitability from an already approved manufacturer (UK/V/0611/001/IA/001)	N/A	23 November 2017
RMS change from UK to NL, procedure number change from UK/V/0611/001 to NL/V/0253/001, NL changed from CMS to RMS and the UK from RMS to CMS.	N/A, Module 1 updated	15 March 2018
MAH transfer from Cross Vetpharm Group to Bimeda Animal Health Limited. (National, in NL)	N/A, Module 1 updated	(Nationally approved) 28 November 2018
Update DDPS and change of site of batch release to Bimeda Animal Health Ltd (IE/V/xxxx/IA/118/G)	N/A, batch release site in product information leaflet updated	6 September 2019
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site (IE/V/XXXX/IA/195/G)	N/A	4 March 2021
Change in QPPV and/or QPPV contact details and/or back-up procedure (NL/V/0253/001/IA/003)	N/A	19 March 2021
Renewal (NL/V/0253/001/R/001)	N/A	13 November 2021

Submission of a new Ph. Eur. Certificate of suitability of the active substance 'oxytetracline dihydrate' (NL/V/0253/001/A/004)	N/A	2 July 2022
Change in site of batch release Additional Site of Secondary assembly NL/V/0253/001/VNRA 10975	N/A	4 November 2023