IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Tetracure 200 mg/ml solution for injection for cattle, sheep and pigs

PRODUCT SUMMARY

EU Procedure Number	IE/V/0440/001/DC (formerly UK/V/0546/001/DC)
Name, Strength, Pharmaceutical Form	Tetracure 200 mg/ml solution for injection for cattle, sheep and pigs
Active Substances(s)	Oxytetracycline
Applicant	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road Tallaght Dublin 24 Ireland
Legal Basis of Application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target Species	Cattle, pigs, sheep
Indication For Use	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.
ATC Code	QJ01AA06
Date of completion of the original decentralised procedure	17 December 2015 (UK) 05 February 2016 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Denmark, France, Germany, Ireland, Spain UK added as a result of change of RMS

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

This was a generic application in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Alamycin LA 200 mg/ml Solution for Injection, authorised in the UK since October 1993.
The product is for use in cattle for the following indications: 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*.
For sheep, the product is used to treat 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*.
In pigs, the product is used to treat 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. QUALITY ASPECTS

II.A. Composition

The product contains 200 mg/ml oxytetracycline (as dihydrate) and the excipients sodium formaldehyde, sulphoxylate dehydrate, 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 and packaged individually into outer cartons. 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The method of manufacture consists of the mixing of ingredients, and a number of heating and cooling stages. The solution is finally diluted to volume with water for injection.

II.C. Control of Starting Materials
The active substance is oxytetracycline (as dihydrate), 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, and quality is controlled by a certificate of suitability. 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 are monographed in the Ph. Eur, apart from sodium formaldehyde and sulfoxylate dehydrate, which is monographed in the United States National Formulary. The vials in which the product is sold are monographed in the Ph. Eur.

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. Tests on the finished product include those for appearance, colour, pH, identification of the active substance and any associated impurities, extractable volume and sterility.

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. A retest period of 2 years when stored in double polyethylene bags, within a paper bag was established.
Stability tests on the proposed product were performed on batches stored under VICH[1] conditions at 25°C/60%RH and 40°C/75%RH. Photostability studies were not performed therefore a suitable warning to protect from light is included in the SPC and product literature.

H. Genetically Modified Organisms
Not applicable.

J. Other Information
Do not store above 25ºC. Keep the vial in the outer carton in order to protect from light. Shelf life of the veterinary medicinal product as packaged for sale: 2 years. Shelf life after first opening the immediate packaging: 28 days.
[1] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been accepted, 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 and consumers.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The chief risks are from self-injection of the product and hypersensitivity reaction to the active substance, with some potential for the occurrence of eye and skin irritation. The user warnings are the same as those of the reference product, with additional warnings added with regard to action to be taken in the event of an adverse event during use. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- This product may cause sensitisation.
- People with known hypersensitivity to tetracyclines, such as oxytetracycline, 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

A Phase I environmental risk assessment was submitted. The product will in general be used on a herd basis in intensively reared cattle, sheep and pigs, and when used as directed, is not likely to pose an adverse threat to the environment. A Phase II environmental risk assessment was not required.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted as the proposed product is of the same pharmaceutical form as the reference product and contains the same active ingredient at the same concentration. There is a minor difference in the list of excipients, as hydrochloric acid is present in the proposed product and not in the reference product. This difference in formulation is permissible, and the conclusion that the rate of depletion of residues is not affected is accepted.

MRLs

Active substance: Oxytetracycline. Marker residue: Sum of parent drug and its 4-epimer.
MRLs are listed below:

All food producing species	MRLs (µg/kg)
Muscle	100
Liver	300
Kidney	600
Eggs	200
Milk	100

Withdrawal Periods

Based on the data assessed/provided, the following withdrawal periods were accepted:

Cattle:

Meat and offal: 31 days
Milk: 10 days

Sheep:

Meat and offal: 9 days
Milk: 7 days

Pigs:

Meat and offal: 18 days

IV. CLINICAL ASSESSMENT

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

IV.I. Pre-Clinical Studies

Pharmacology

No data were required for this section. A waiver from bioequivalence studies was granted according to 7.1(b) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), which states: 'For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipients(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance.'

Tetroxy Vet 200 mg/ml Solution for Injection for Cattle Sheep and Pigs fulfils these criteria:

- Tetracure and Alamycin LA are both aqueous solutions;
- Both products contain oxytetracycline at a concentration of 200 mg/ml;
- The addition of HCl to Tetracure as a pH adjuster is acceptable, as there is no significant effect on absorption of the active substance.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been accepted, target animal safety studies are not required. The SPC and product literature carry suitable warnings.

Resistance

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been accepted, resistance data were not required. The SPC and product literature carry suitable warnings.

IV.II. Clinical Documentation

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been accepted, 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(s) is favourable.