IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

PRODUCT SUMMARY

EU Procedure number	IE/V/0773/001/DC
Name, strength and pharmaceutical form	Cyclofin 300 mg/ml + 20 mg/ml solution for injection for cattle
Active substance(s)	Oxytetracycline (as oxytetracycline dihydrate) Flunixin (as flunixin meglumine)
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531 AE Bladel Netherlands
Legal basis of application	Generic application in accordance with Article 18 of Regulation (EU) 2019/6.
Date of completion of procedure	03/05/2023
Target species	Cattle
Indication for use	For the treatment of acute respiratory disease caused by *Mannheimia haemolytica* and *Pasteurella multocida* where an anti-inflammatory and anti-pyretic effect is required.
ATC vet code	QJ01AA56
Concerned Member States	AT, BE, FR, DE, IT, NL, PL, PT, ES
Withdrawn CMS during original decentralised procedure	UK(NI) The company decided to withdraw the application. At the time of withdrawal the MS considered that the data provided did not allow to conclude on a positive benefit-risk balance as potential serious risk to public health was raised.

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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 relevant articles of Regulation (EU) 2019/6. 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

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 cattle; the reactions observed are indicated in the SPC.
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.

II. QUALITY ASPECTS

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A. Qualitative and Quantitative Particulars

The product contains oxytetracycline (300 mg/ml) and flunixin (20 mg/ml) as the active substances and the excipients glycerol formal, polyethylene glycol 200, magnesium oxide, light, sodium formaldehyde sulphoxylate, ethanolamine and water for injections.
The container/closure system consists of Type II clear glass vials of 100 ml with 20 mm bromobutyl rubber stoppers and aluminium caps.
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 at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are oxytetracycline (as oxytetracycline dihydrate) and flunixin (as flunixin meglumine), established substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with the specifications has been provided.
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.

D. Control on Intermediate Products

Not applicable.

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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substances has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (generic veterinary medicinal product).
The applicant has cited a suitable reference product, 'Hexasol LA solution for injection' which has been authorised for in excess of ten years and can be accepted as a valid reference product in this generic application. The applicant claimed a waiver from the requirement to provide *in vivo* bioequivalence data based on compliance with conditions set out in section 7.1 of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products. This waiver was accepted.
As bioequivalence with a suitable reference product has been accepted, the results of safety tests are not required. The safety aspects of this product are considered to be the same as the reference product.
Warnings and precautions as listed on the product literature are similar to those of the reference product and are adequate to ensure safety of the product to users, consumers and the environment.

III. SAFETY ASSESSMENT

III.A Safety Testing

Pharmacological Studies

No pharmacodynamic or pharmacokinetic data were presented. Given the legal basis of this application, and accepted bioequivalence with the reference product, omission of these data was accepted.

Toxicological Studies

No toxicological study data were presented. Given the legal basis of this application, and accepted bioequivalence with the reference product, omission of these data was accepted.

User Safety

The applicant provided a user risk assessment in accordance with relevant guidance. The following user safety warnings are included in the SPC:

This veterinary medicinal product may be harmful after accidental self-injection. In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician.
This veterinary medicinal product may be irritating to the skin and/or eye. Avoid skin and/or eye contact. Latex or nitrile gloves should be worn during application. In case of accidental contact with skin or eyes, rinse with copious amounts of water. If irritation persists, seek medical advice.
This veterinary medicinal product may cause hypersensitivity reactions due to the presence of oxytetracycline, flunixin, polyethylene glycol or ethanolamine. People with known hypersensitivity to tetracyclines, non-steroidal anti-inflammatory drugs (NSAIDs) or one of the excipients should avoid contact with the veterinary medicinal product. If allergic symptoms develop, such as a skin rash, swelling of the face, lips or eyes or difficulty in breathing, you should seek medical attention immediately and show the package leaflet or label to the doctor.
Laboratory studies in rats with the excipient glycerol formal have shown evidence of teratogenic and foetotoxic effects.
Pregnant women, and women of childbearing age should use the veterinary medicinal product with particular caution to avoid accidental self-injection.

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

Environmental Risk Assessment

Phase I

The environmental risk assessment returned PEC_{soil} calculations of less than 100 µg/kg for use in intensively reared cattle.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted because no difference in residue depletion between the candidate and reference products was anticipated. Based on acceptance of this conclusion, the withdrawal period of the reference product was extrapolated to the candidate product.

MRLs

Oxytetracycline and flunixin are listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows (MRLs listed are applicable to cattle):

	Oxytetracycline (sum of parent drug and its 4-epimer)	**Flunixin**
Muscle	100 µg/kg	20 µg/kg
Liver	300 µg/kg	300 µg/kg
Kidney	600 µg/kg	100 µg/kg
Fat		30 µg/kg
Milk	100 µg/kg	40 µg/kg (5-Hydroxy-flunixin)

Withdrawal Periods

Based on the data provided, the following withdrawal periods are justified:
Meat and offal: 28 days

Not authorised for use in cattle producing milk for human consumption.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals
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 application according to Article 18 of Regulation (EU) 2019/6, 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

Not applicable.