IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Eprecis 5 mg/ml pour-on solution for cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0343/001/DC
Name, strength and pharmaceutical form	Eprecis 5 mg/ml pour-on solution for cattle, sheep and goats
Active substance(s)	Eprinomectin
Applicant	CEVA Santé Animale, 10, Avenue de la Ballastière, 33500 Libourne, FRANCE.
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	03/03/2021
Target species	Cattle (beef and dairy cattle), sheep and goats
Indication for use	Treatment of infections by listed endo and ecto-parasites sensitive to eprinomectin, and the prevention of reinfection against listed endoparasites.
ATCvet code	QP54AA04
Concerned Member States	BE, DK, FR, DE, HU, IT, NL, PL, PT, ES, UK

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

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 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

A.Qualitative and Quantitative Particulars

The product contains eprinomectin (5 mg/ml) and the excipients butylhydroxytluene (E321), all-rac-α-Tocopherol (E307) and propylene gycol dicaprylocaprate.
The product is presented in a 250 ml translucent high density polyethylene (HDPE) bottle with 10 ml dispenser and removable aluminium/PE seals and PE screw caps or alternatively a 1L, 2.5 L or 5L white HDPE bottle, with a removable aluminium/PE seal and a polypropylene (PP) screw cap.

The choice of the formulation is 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 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 substance is eprinomectin an established 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 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 substance 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)

III.A Safety Testing

Pharmacological Studies

This application was submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended (that is, a "generic" application). The reference product used in support of cattle as a target species is *Eprinex 0.5% w/v Pour-On Solution for Beef and Dairy Cattle* (Boehringer Ingelheim Vetmedica GmbH, VPA 10454/033/001), which has been authorised in the Community for greater than 10 years. The addition of sheep and goats as target species is supported by the reference product *Eprinex Multi 5 mg/ml pour-on solution for beef and dairy cattle, sheep and goats* (Boehringer Ingelheim Vetmedica GmbH, VPA 10454/034/001) which is accepted as being part of the same global marketing authorisation as Eprinex 0.5 % w/v pour-on solution for beef and dairy cattle.

On the basis of appropriate comparative analysis, it is accepted that the test and reference products are of the same type of solution and contain the same concentration of the active substance and comparable excipients in similar amounts.

Accordingly, the omission of bioequivalence studies can be considered justified as per EMEA/CVMP/016/00-Rev3("Guideline on the conduct of bioequivalence studies for veterinary medicinal products"), Chapter 7.1 (b):

"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 and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance."

As bioequivalence with an authorised reference product is accepted, the applicant is not required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials. Both the test and reference products can be expected to have the same safety and efficacy profile.

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.

User Safety

Given that the test and reference products are of the same type of solution, contain the same concentration of the active substance, comparable excipients in similar amounts and have the same intended use, it is argued that the user safety profile will be the same for both products and that the user safety statements agreed for the reference product can be applied to the test product. The following user safety statements are proposed for inclusion in the SPC:

This veterinary medicinal product may be irritating to the skin and eyes.

·Avoid contact with the eyes and skin.

·Operators should wear rubber gloves, boots and waterproof coat when applying the veterinary medicinal product.

·If accidental skin contact occurs, wash the affected area immediately with soap and water.

·If accidental eye exposure occurs, flush eyes immediately with water.

Should irritation persist, seek medical advice.

·Do not smoke, eat or drink while handling the veterinary medicinal product.

·Wash hands after use. Should clothing become contaminated, remove as soon as possible and launder before re-use.

Do not ingest.

In the event of ingestion, wash out mouth with water and seek medical advice and show the package leaflet or the label to the physician.

·People with known hypersensitivity to the active substance or to any of the excipients should avoid contact with the veterinary medicinal product.

Eprinomectin can be transferred to breast milk. Therefore, breast-feeding users should handle the product with great care.

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

Environmental Risk Assessment

A Phase II ERA is required as the target species are reared on pasture, and eprinomectin is an endo- & ectoparasiticide.

A Phase II Tier A and B assessment was conducted the results of which are summarised below.

Physico-chemical properties	
Study type	**Result**
Vapour pressure	2.38×10^{-30} Pa, 25°C
Water solubility	11 mg/l
Dissociation constants in water pKa	No dissociation at environmentally relevant pH (pH 3 - 12)
n-Octanol/Water Partition Coefficient logP_{ow}	logP_{ow} = 5.7

Environmental fate	
Soil Adsorption/Desorption	Koc = 12,839 ml/g
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 43.1 days (20°C)

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *species*	EC50	8.99	mg/l
Daphnia sp. immobilisation	EC50	2.66×10^{-4}	mg/l
Daphnia magna, reproduction (Tier B)	NOEC	9.9×10^{-5}	mg/l
Fish, acute toxicity/ *Species*	LC50	0.566	mg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25%	
Terrestrial Plants, growth test	EC50	0.05	mg/kg dry soil
Earthworm/*Eisenia foetida* reproduction	NOEC	46.6	µg/kg
Sediment dwelling organism/*C. riparius*	NOEC	0.92	µg/kg
Dung fly larvae/*Musca autumnalis*	EC50	62.1	µg/kg_{dwt}
Dung beetle larvae/*Aphodius constans*	EC50	1,830	µg/kg_{dwt}
Bioaccumulation in fish/*Oncorhyncus mykiss*	BCF	73	

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.

Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.

The risk characterisation resulted in risk quotients below 1 for the groundwater and soil compartments indicating that the product will not pose a risk to those compartments when used as recommended.

The results of the assessment for the surface water, and dung compartments indicate that a risk for the environment potentially exists for aquatic organisms in case of direct exposure arising from run off and excretion, and dung dwelling organisms exposed to dung produced by treated pasture animals. Consequently, the following risk mitigation measures are required for this product:

Eprinomectin is very toxic to dung fauna and aquatic organisms, is persistent in soils and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of eprinomectin (and products of the same anthelmintic class) in cattle, sheep and goats.

The risk to aquatic ecosystems will be further reduced by keeping treated animals away from water bodies for two to five weeks after treatment.

PBT Assessment

An assessment of the compound in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.

The log Kow of eprinomectin was demonstrated to be 5.7.

The compound is not considered to be either PBT or vPvB.

Conclusion

The applicant has provided a comprehensive data package on the environmental fate and toxicity of eprinomectin. Based on the data provided in the ERA the risk assessment highlights potential risks for:

- dung dwelling organisms exposed to dung produced by treated pasture animals, and
- aquatic organisms in case of direct exposure arising from run off and excretion.

The risks identified are as expected for this class of compound (macrocyclic lactones). Therefore suitable risk mitigation measures and advice were included in the SPC for this product.

III.B Residues Documentation

Residue Studies

As this is a generic application according to Article 13(1), no residue depletion studies were conducted/presented. Given that the test and reference products are of the same type of solution, contain the same concentration of the active substance, comparable excipients in similar amounts and have the same intended use, the residue depletion profile will be the same for both products and the withdrawal periods agreed for the reference product can be applied to the test product.

MRLs

Eprinomectin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All ruminants
Muscle	50 µg/kg
Liver	1500 µg/kg
Kidney	300 µg/kg
Fat	250 µg/kg
Milk	20 µg/kg

Withdrawal Periods

Based on the argumentation presented, the following withdrawal periods are justified:
Cattle: Meat and offal: 15 days; Milk: zero hours.
Sheep: Meat and offal: 2 days; Milk: zero hours.
Goats: Meat and offal: 1 day; Milk: zero hours.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

This application was submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended (that is, a "generic" application). The reference product used in support of cattle as a target species is Eprinex 0.5% w/v Pour-On Solution for Beef and Dairy Cattle (Boehringer Ingelheim Vetmedica GmbH, VPA 10454/033/001). The addition of sheep and goats as target species is supported by the reference product Eprinex Multi 5 mg/ml pour-on solution for beef and dairy cattle, sheep and goats (Boehringer Ingelheim Vetmedica GmbH, VPA 10454/034/001) which is accepted as being part of the same global marketing authorisation as Eprinex 0.5 % w/v pour-on solution for beef and dairy cattle.
Based on the information provided, bioequivalence with the authorised reference product is accepted (the test and reference products are of the same type of solution, contain the same concentration of the active substance, comparable excipients in similar amounts and have the same intended use). Accordingly, the applicant is not required to provide the results of safety and residue tests or of pre-clinical and clinical trials.
Given that bioequivalence is accepted, both the test and reference products can be expected to have the same profile in terms of both target animal safety and efficacy. The proposed indications and posology reflect those agreed for the authorised reference product.

Resistance

Adequate warnings and precautions appear on the product literature:
Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:
- Too frequent and repeated use of anthelmintics from the same class, over an extended period of time.
- Underdosing, which may be due to underestimation of body weight, misadministration of the product, or lack of calibration of the dosing device (if any).

Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Test). Where the results of the test(s) strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used.
To date no resistance to eprinomectin (a macrocyclic lactone) has been reported in cattle while resistance to eprinomectin has been reported in sheep and goats within the EU. However resistance to other macrocyclic lactones has been reported in nematode populations in cattle, sheep and goats within the EU. Therefore, use of this veterinary medicinal product should be based on local (regional, farm) epidemiological information about susceptibility of nematodes and recommendations on how to limit further selection for resistance to anthelmintics.

Tolerance in the Target Species of Animals
Target animal safety studies specific to the test product have not been presented with the application. Given that bioequivalence is accepted (the test and reference products are of the same type of solution and contain the same concentration of the active substance and comparable excipients in similar amounts), both the test and reference products can be expected to have the same profile in terms of target animal safety.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies
The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. No proprietary efficacy studies have been carried out. The applicant has confirmed that the proposed product has the same qualitative and quantitative composition to that of the reference product. Consequently, efficacy studies relating to the test product 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

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 HPRA website.

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.

Changes:
Safety/Efficacy Changes

Summary of change (Application number)	**Approval date**
Addition of target species – sheep and goats (IE/V/0343/001/DX/001)	03/03/2021