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Publicly Available Assessment Report for a
Veterinary Medicinal Product

Eprecis 20 mg/ml solution for injection for cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0340/001/DC
Name, strength and pharmaceutical form	Eprecis 20 mg/ml solution for injection for cattle, sheep and goats
Active substance(s)	Eprinomectin
Applicant	Ceva Santé Animale 10 Av. de la Ballastiere 33500 Libourne France
Legal basis of application	"Hybrid" application in accordance with Article 13 (3.) of Directive 2001/82/EC as amended.
Date of authorisation	21/10/2020
Target species	Cattle (beef and dairy cattle), sheep and goats
Indication for use	Treatment of infestations by listed internal and external parasites sensitive to eprinomectin, prevention of reinfestations with various species of parasites.
ATCvet code	QP54AA04
Concerned Member States	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK, 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 slight 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

A. Qualitative and Quantitative Particulars

The product contains eprinomectin (20 mg/ml) and the excipients butylhydroxytluene (E321), dimethyl sulfoxide and glycerol formal stabilised.
The product is presented in 50 ml, 100 ml, 250 ml or 500 ml amber multilayer plastic vials with bromobutyl rubber stoppers and aluminium and plastic flip capsules.

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)

The application for marketing authorisation was submitted in accordance with Article 13 (3.) ("hybrid" application) of Directive 2001/82/EC as amended (" […] in the case of changes to the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration vis-à-vis the reference medicinal product […].") The reference product chosen by the applicant is Eprinex 0.5% w/v pour-on solution for beef and dairy cattle (Boehringer IngelheimVetmedica GmbH) for which the following differences, relative to the reference medicinal product, have been identified:
- change in pharmaceutical form (from pour-on solution to solution for injection)
- change in strength (quantitative change to the active substancefrom 5mg/ml to 20 mg/ml)
- change in route of administration (from pour-on use to subcutaneous use)

The product is intended to be injected to cattle, sheep and goats by subcutaneous route at the dose rate of 0.2mg of eprinomectin/kg bw (i.e.: 1 ml/100 kg BW) as single injection.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that eprinomectin acts by binding selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve or muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarisation of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels; the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels, and they do not readily cross the blood-brain barrier.

In support of this application, the applicant conducted an *in vivo* study in cattle in order to compare the bioavailability of the product and the reference product (*Eprinex 0.5% pour on solution for beef and dairy cattle*). Additionally, the applicant conducted *in vivo* studies in sheep to compare the bioavailability of the product with the reference product (*Eprinex Multi 5 mg/ml pour-on for beef and dairy cattle, sheep and goats*). Please refer to Section IV.A for more information.

Toxicological Studies

Information on toxicity of eprinomectin is sourced primarily from MRL summary reports published by EMA and JECFA.Given that the majority of the data presented has been reviewed by the CVMP in the context of the MRL assessment, it is accepted that the toxicity of eprinomectin has been adequately characterised. In brief:
·Eprinomectin has moderate acute toxicity with a LD50 value of 35mg/kg BW in the mouse and in the rat, using the intraperitoneal route.
·In the dog, a NOEL of 1mg/kg b.w. was established after repeated oral administration of eprinomectin for 6 or 53 weeks, based on mydriasis and focal neuronal degeneration in the brain.
·Repeated oral doses in pregnant rats and rabbits have not revealed any evidence of embryo- or foeto-toxic potential for eprinomectin.
·Eprinomectin did not show genotoxic activity in a battery of tests.
·Eprinomectin is not considered to have carcinogenic potential.

The applicant has provided a series of local effect studies conducted using the final formulation. Based on these studies, the formulation proposed for marketing is considered neither a skin irritant nor a skin sensitiser. However, the test item is considered an ocular irritant.

Observations in Humans

No human data are available as eprinomectin has been developed exclusively for use in veterinary medicine. However, other substances of the avermectin family have been used in humans, e.g.: ivermectin. In humans ivermectin is administered orally as a single dose of 200 micrograms/kg BW. Ivermectin is generally well tolerated; however, adverse effects can occur and are usually mild-to-moderate in nature and transient.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. The product includes as excipients buthyl hydroxy toluene (BHT), dimethyl sulfoxide (DMSO) and glycerol formal stabilised. These are common excipients and, in terms of potential hazard, are considered of minor importance compared to the active ingredient eprinomectin. It was shown that a potential risk for the user may arise following accidental oral, dermal, systemic or ocular exposure to the formulation. The SPC includes a number of user safety warnings in order to mitigate against such risks. Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product.

Environmental Risk Assessment

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

Phase II
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 x 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

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *species*	EC50	8.99	mg/l
Daphnia sp. immobilisation	EC50	2.66 x 10^{-4}	mg/l
Daphnia magna, reproduction (Tier B)	NOEC	9.9 x 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 sediment-dwelling organisms in case of direct 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 cattle, sheep and goats 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
- sediment-dwelling organisms in case of direct 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

Two studies were conducted in cattle to characterise depletion of residues from meat and milk following administration of the final formulation. Both studies were conducted in accordance with GLP and relevant guidance.

Studies were conducted in sheep to characterise depletion of residues from meat and milk following administration of the final formulation. These studies were conducted in accordance with GLP and the relevant guidance.

Studies were conducted in goats to characterise depletion of residues from meat and milk following administration of the final formulation. These studies were conducted in accordance with GLP and the relevant guidance.

The analytical methods used for determination of eprinomectin residues in tissues/milk were appropriately validated.

MRLs

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

Muscle	50 micrograms/kg
Liver	1,500 micrograms/kg

Kidney	300 micrograms/kg
Fat	250 micrograms/kg
Milk	20 micrograms/kg

Withdrawal Periods

Based on the residue data provided, the following withdrawal periods are justified.

Cattle: 63 days for meat and offal; zero hours for milk.
Sheep: 42 days for meat and offal; zero hours for milk.
Goats: 42 days for meat and offal; zero hours for milk.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

In order to adequately characterise the pharmacokinetics of eprinomectin, the applicant has conducted proprietary studies and has provided bibliographical data which are summarised as follows:

·In cattle following subcutaneous administration of eprinomectin at a dose of 0.2 mg/kg, plasma concentrations increased rapidly to reach a peak (mean C_{max}: 58.0 ± 17.80µg/L) between 24h and 72h after dosing (median T_{max}: 36h). Inlactating sheep, following subcutaneous administration at 0.2 mg/kg, plasmaconcentrations increased rapidly to reach a peak (mean C_{max}: 19.5µg/L ± 7.9 µg/L) between 10 h and 72 h after dosing (median T_{max}:33.6 h). In non-lactating sheep, following subcutaneous administration at 0.2mg/kg, plasma concentrations increased rapidly to reach a peak (mean C_{max}:11.3 µg/L ± 5.85 µg/L) between 12 h and 60 h after dosing (median T_{max}:26.7 h). In goats, following subcutaneous administration at 0.2 mg/kg, plasmaconcentrations increased rapidly to reach a peak (mean C_{max}: 20.7µg/L ± 12.85 µg/L) 36 h after dosing.

·In cattle, systemic exposure after subcutaneous administration at 0.2 mg eprinomectin/kg was approximately 2 times higher than that observed after pour-on administration of 0.5 mg/kg, whilst in non-lactating sheep, systemic exposure after subcutaneous administration at 0.2 mg eprinomectin/kg was approximately the same as that observed after pour-on administration of 1 mg/kg. However, eprinomectin is slower to deplete from plasma following topical administration compared to following subcutaneous administration: the elimination half-life following topical administration was calculated to be 115.06±29.01 hr compared to 65.33±23.51 hr following subcutaneous administrationin cattle, whilst in sheep it wascalculated to be 85.794±19.911 h compared to 78.546±51.037 h.
·Over the dose range 0.1 to 0.4mg/kg, eprinomectin exhibits linear pharmacokinetics. In addition, following repeated administration at intervals of one week, clinically relevant systemic accumulation was not evident.
·The absolute bioavailability of eprinomectin of the subcutaneous formulation was about 89% (range: 75% - 104%).
·Macrocyclic lactones have a high lipophilicity. They are distributed extensively throughout the body and concentrate particularly in adipose tissue.
·Eprinomectin is highly bound (greater than 99%) to plasma proteins.
·Eprinomectin is not extensively metabolised and is excreted primarily in faeces. There is very limited elimination of eprinomectin in milk.

Tolerance in the Target Species of Animals

The applicant evaluated the general and local tolerance of the test item in cattle in a GLP study which followed the general recommendations of VICH GL43. Based on the findings of the study, it is accepted that systemic tolerance to the product is good/acceptable when administered 3 times at weekly intervals at up to 5 times the recommended treatment dose. However, local reactions at the site of injection are very common. These reactions are characterised by moderate to severe swelling followed by induration. Swelling may last for up to one week, with induration persisting for in excess of two weeks. Swelling may be associated with mild to moderate pain.

Regarding reproductive safety, it is accepted, based on bibliographic data provided, that eprinomectin is not a teratogen when investigated in laboratory animals and had no negative impact on reproductive parameters in cattle when administered topically at a dose of 1.5 mg eprinomectin/kg (3X the recommended topical dose). Given that topical administration of 1.5 mg eprinomectin/kg had no effect on pregnant or breeding cattle and that systemic availability following subcutaneous administration of 0.2 mg eprinomectin/kg will likely be less that that achieved following topical administration of 1.5 mg eprinomectin/kg, it is accepted that 0.2 mg eprinomectin/kg administered by the subcutaneous route will not pose a risk to pregnant or breeding cattle. A restriction on use in pregnant or breeding cattle is not required.

The applicant evaluated the general and local tolerance of the test item in sheep in a GLP study which followed the general recommendations of VICH GL43. Based on the findings of the study, it is accepted that systemic tolerance to the product is good/acceptable when administered 3 times at weekly intervals at up to 5 times the recommended treatment dose. However, local reactions at the site of injection are very common. These reactions are characterised by slight to moderate swelling, typically resolving within 16-18 days.

The applicant evaluated the general and local tolerance of the test item in goats in a GLP tissue residue study which partially followed the general recommendations of VICH GL43. Based on the findings of the study, it is accepted that systemic tolerance to the product is good/acceptable when a single treatment is administered at the recommended dose and by the recommended route of administration. However, local reactions at the site of injection are very common. These reactions are characterised by slight to moderate swelling, typically resolving within 16-18 days.
The applicant has not addressed reproductive safety in either sheep or goats and a warning regarding use in these species during pregnancy has been included in the product literature.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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 bodyweight, 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.
If there is a risk for re-infection, the advice of a veterinarian should be sought regarding theneed for and frequency of repeat administration.

Cattle: Resistance to other macrocyclic lactones has been reported in parasite species in cattle within the EU. Therefore, use of this 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.
Sheep and goats: Resistance to eprinomectin in parasite species in goats and sheep has been reported within the EU. Therefore, use of this 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.

IV.B Clinical Studies
Laboratory Trials

It is noted that the applicant had requested and received Scientific Advice from the European Medicines Agency on data requirements to support efficacy and aspects of target animal safety. As part of this scientific advice, the CVMP agreed certain approaches to establishing efficacy and this advice has been taken into account in the assessment of the efficacy file.
Eprinomectin has been authorised in the Community since 1997 for use in cattle as a pour-on formulation for topical application at a dose of 0.5 mg/kg (Eprinex® Pour-on). Consequently, it is argued that the efficacy profile/spectrum of activity of eprinomectin is well established. Efficacy of the pour-on formulation is supported by reference to information in the published domain.
A study was conducted to characterise the eprinomectin plasma pharmacokinetic profile following administration of eprinomectin to cattle by the intravenous, subcutaneous and topical routes. Based on the outcome of this comparative pharmacokinetic study, systemic exposure after subcutaneous administration at 0.2 mg eprinomectin/kg was approximately 2 times higher than that observed after pour-on administration of 0.5 mg/kg without any dose normalisation. Given the higher systemic availability, it is expected that the test product at the proposed dose of 0.2 mg eprinomectin/kg will be at least as effective as the authorised reference product, Eprinex Pour-on Solution, for the treatment of lungworm (*Dictyocaulus viviparous*) and gastrointestinal nematodes.
The efficacy of eprinomectin against lungworm and common gastrointestinal nematodes when administered by the subcutaneous route at a dose of 0.2 mg/kg is further supported by a study reported in the scientific literature and a single confirmatory study conducted using the formulation proposed for marketing. Although only a single confirmatory study using the product proposed for marketing was conducted by the applicant, the study did evaluate efficacy against the dose-limiting nematode species and adequate efficacy (in accordance with guideline requirements) was confirmed. Given the well-established efficacy of the active substance and the other data presented in support of efficacy, a single confirmatory study is considered adequate.
In addition to the nematode indication it is also accepted, based on the data/argumentation presented, that the claim for efficacy against sucking lice (*Linognathus vituli*, *Haematopinus eurysternus*, *Solenopotes capillatus*), horn flies (*Haematobia irritans*), *Sarcoptes scabiei var. bovis* and *Hypoderma* spp. has been adequately justified (bibliographic data and, based on the comparative pharmacokinetic study, efficacy for these parasite species can be extrapolated from the authorised pour-on product, Eprinex.
In addition to the indication for treatment of infestation, available data support a claim for the prevention of reinfestation with certain nematodes for periods up to 14 days. The duration of persistent effect (14 days) was accepted based on the findings of the comparative pharmacokinetic study. In that study, the mean plasma concentration at 336h (14 days) following subcutaneous administration was less than the mean plasma concentration detected following topical administration. However, the mean/range of plasma concentrations at 336h following subcutaneous administration (3.80 microgram/L [0.63 – 10.54]) exceeds the mean/range of plasma concentrations at 480h (20 days) following topical administration (1.64 microgram/L [0.64-3.02]). Given that the authorised pour-on product claims persistent efficacy against a range of target nematodes for 21-28 days following treatment, it follows that systemic exposure over this time frame is adequate for effect (that is, plasma concentrations in the range 0.64-3.02 microgram/L correlate with adequate efficacy). Therefore, it can be accepted that the systemic exposure at 14 days following administration of the injectable eprinomectin product will be adequate for effect against the claimed nematode species.
Eprinomectin has been authorised in the Community since 2016 for use in sheep and goats as a pour-on formulation for topical application at a dose of 1.0 mg/kg (Eprinex Multi 5 mg/ml pour-on for beef and dairy cattle, sheep and goats). Consequently, it is argued that the efficacy profile/spectrum of activity of eprinomectin is well established. Efficacy of the pour-on formulation is supported by reference to information in the published domain.
In sheep, a study was conducted to characterise the eprinomectin plasma pharmacokinetic profile following administration of eprinomectin by the subcutaneous and topical routes. Based on the outcome of this comparative pharmacokinetic study, systemic exposure after subcutaneous administration at 0.2 mg eprinomectin/kg was approximately the same as that observed after pour-on administration of 1.0 mg eprinomectin/kg. Additionally, studies conducted in goats in which 0.2 mg eprinomectin/kg was administered by the subcutaneous route, demonstrated comparable plasma concentrations as those observed following subcutaneous administration of 0.2 mg eprinomectin/kg in sheep. Given the comparable systemic availability, it is expected that the test product at the proposed dose of 0.2 mg eprinomectin/kg will be as effective as the authorised product, Eprinex Multi 5 mg/ml pour-on for beef and dairy cattle, sheep and goats, for the treatment of lungworm (*Dictyocaulus filaria*) and gastrointestinal nematodes *(Teladorsagia circumcincta (pinnata/trifurcata*), *Haemonchus contortus*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Nematodirus battus*, *Cooperia curticei, Chabertia ovina, Oesophagotomum venulosum) in sheep and goats*.

Field studies:

No field studies have been presented. Given that the active substance is well established, the CVMP in the context of a scientific advice procedure agreed that field studies investigating efficacy would not be required where the findings of the comparative pharmacokinetic study confirmed comparable, or superior, systemic availability for the injectable formulation compared to the authorised pour-on formulation.

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:
None.