IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

PRODUCT SUMMARY

EU Procedure number	IE/V/0668/001/DC
Name, strength and pharmaceutical form	Lincoral-S 222 mg/g + 444.7 mg/g powder for use in drinking water
Active substance(s)	Lincomycin (as lincomycin hydrochloride monohydrate) and Spectinomycin (as spectinomycin sulfate tetrahydrate)
Applicant	Huvepharma NV
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	31/05/2023
Target species	Pigs, chickens
Indication for use	Pigs For the treatment and metaphylaxis of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis*, and associated enteric pathogens (*Escherichia coli*). The presence of the disease in the group must be established before the veterinary medicinal product is used. Chickens For the treatment and metaphylaxis of chronic respiratory disease (CRD) caused by *Mycoplasma gallisepticum* and *Escherichia coli* and associated with a low mortality rate. The presence of the disease in the group must be established before the veterinary medicinal product is used.
ATCvet code	QJ01FF52
Concerned Member States	AT, BE, BG, CY, CZ, DK, EE, EL, ES, HR, HU, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK
Withdrawn CMS during original decentralised procedure	DE, FR

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 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 222 mg of lincomycin (as lincomycin hydrochloride monohydrate) and 44.7 mg of spectinomycin (as spectinomycin sulfate tetrahydrate), and the excipient lactose monohydrate.
The container/closure system is 150 g thermos-sealed sachets made of polyethylene/aluminium/polyethylene/paper or 1.5 kg thermos-sealed bags made of polyethylene/aluminium/polyester.

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 substances are lincomycin (as lincomycin hydrochloride monohydrate) and spectinomycin (as spectinomycin sulfate tetrahydrate), 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 materials. Batch analytical data demonstrating compliance with these specifications has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 substances 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

This application has been submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC (a generic veterinary medicinal product).

The applicant has cited a suitable reference product, 'Linco-Spectin 100, 222/444.7 mg/g powder for use in drinking water for pigs and chickens' which has been authorised for in excess of ten years and can be accepted as a valid reference product in this generic application. 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 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.

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 contains lincomycin, which may be harmful to the unborn child. Pregnant women should use this veterinary medicinal product with great caution.

This veterinary medicinal product contains lincomycin, spectinomycin and lactose monohydrate, all of which can cause allergic reactions in some people. People with known hypersensitivity to lincomycin, spectinomycin or lactose monohydrate should avoid contact with the veterinary medicinal product.

The veterinary medicinal product may be harmful when inhaled before being diluted in drinking water. Care should be taken not to raise and inhale any dust.

This veterinary medicinal product may cause skin and eye irritation. Contact with skin and eyes should be avoided.

Handle this veterinary medicinal product with great care to avoid skin and ocular exposure.

Wear gloves, safety glasses and either a disposable half-mask respirator conforming to European Standard EN149 (FFP2 in general, FFP3 for pregnant women) or a non-disposable respirator to European Standard EN140 with a filter conform to EN143 during preparation of medicated water.

Wash hands and any exposed skin with soap and water immediately after use. In the event of eye contact, rinse the affected area with large amounts of clean water.

If you develop symptoms following exposure such as a skin rash or persistent eye irritation, seek medical advice immediately and show the package leaflet or the label to the physician.

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

Environmental Risk Assessment

Phase I

A Phase II ERA is required as the Phase I assessment showed that the $PEC_{soil\ initial}$ trigger value of 100 µg/kg is exceeded for both lincomycin and spectinomycin.

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	Lincomycin 1.2 x 10^{-4} Pa, 25°C Spectinomycin <1.2 x 10^{-4} Pa, 25°C
Water solubility	Lincomycin 505.7 g/L, pH 5, 20°C 362.2 g/L, pH 7, 20°C 382.6 g/L, pH 9, 20°C Spectinomycin 52.85 g/L, pH 5, 20°C 51.88 g/L, pH 7, 20°C 49.10 g/L, pH 9, 20°C
Dissociation constants in water (pKa)	Lincomycin 7.93, 20°C Spectinomycin No specific pH driven dissociation point identified experimentally.
n-Octanol/Water Partition Coefficient ($logK_{ow}$)	Lincomycin -3.724, pH 5, 20°C -3.789, pH 7, 20°C -3.825, pH 9, 20°C Spectinomycin ≥-4.307, pH 5, 20°C ≥-4.316, pH 7, 20°C ≥-4.277, pH 9, 20°C

Environmental fate	
Soil Adsorption/Desorption	Lincomycin Kfoc = 44.9 ml/g Spectinomycin Kfoc = 34.8 ml/g
Aerobic and Anaerobic Transformation in Soil	Lincomycin DT_{50} = 4.26 days (20°C) Spectinomycin DT_{50} = 72 days (20°C)
Transformation in Manure (species)	Lincomycin Pigs DT_{50} = >2585.7 days (10°C) Poultry DT_{50} =29.2 days (25°C) Spectinomycin Pigs DT_{50} = >2585.7 days (10°C) Poultry DT_{50} =2.8 days (25°C)

Effect studies - Lincomycin			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Anabaena flos-aquae*	EC50	0.356	mg/l
Cyanobacteria, growth inhibition test/ *Anabaena flos-aquae* (Tier B)	NOEC	0.0073	mg/l
Daphnia sp. immobilisation	EC50	91.7	mg/l
Fish, acute toxicity/ *Danio rerio*	LC50	91.7	mg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25%	
Terrestrial Plants, growth test	EC50	3.930	$mg/kg_{dry\ weight}$
Terrestrial Plants, growth test (Tier B)	NOEC	0.920	$mg/kg_{dry\ weight}$
Earthworm/*Eisenia foetida*	NOEC	916.5	$mg/kg_{dry\ weight}$

reproduction			

Effect studies - Spectinomycin			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Anabaena flos-aquae*	EC50	0.418	mg/l
Cyanobacteria, growth inhibition test/ *Anabaena flos-aquae* (Tier B)	NOEC	0.0678	mg/l
Daphnia sp. immobilisation	EC50	79.5	mg/l
Fish, acute toxicity/ *Danio rerio*	LC50	>77.2	mg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25%	
Terrestrial Plants, growth test	EC50	16.64	$mg/kg_{dry\ weight}$
Terrestrial Plants, growth test (Tier B)	NOEC	3.86	mg/kg
Earthworm/*Eisenia foetida* reproduction	NOEC	48.3	$mg/kg_{dry\ weight}$

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 results of the assessment for the surface water, groundwater and soil compartments indicate that a risk for the environment potentially exists and consequently, the following warnings are required for this product:

The use of the veterinary medicinal product poses a risk to aquatic and terrestrial organisms, groundwater ecosystem and to human health through consumption of groundwater. The veterinary medicinal product should not come in contact with water bodies.

PBT Assessment

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

The log Kow of lincomycin was demonstrated to be -3.724. Lincomycin is not considered to be either PBT or vPvB.

The log Kow of spectinomycin was demonstrated to be -4.316. Spectinomycin is not considered to be either PBT or vPvB.

It was noted that spectinomycin is classified as very persistent in the environment.

Conclusion

Based on the data provided in the ERA, a risk to the aquatic and terrestrial environment and groundwater cannot be excluded. Therefore suitable advice was included in the SPC for this product.

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

Lincomycin and spectinomycin are listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	Lincomycin	**Spectinomycin**
Muscle	100 µg/kg	300 µg/kg
Fat	50 µg/kg	500 µg/kg
Liver	500 µg/kg	1,000 µg/kg
Kidney	1500 µg/kg	5,000 µg/kg
Milk	150 µg/kg	200 µg/kg
Eggs	50 µg/kg	Not for use in animals from which eggs

		are produced for human consumption.

Withdrawal Periods
Based on the data provided, the following withdrawal periods are justified:
Pigs:
Meat and offal: Zero days.
Chickens:
Meat and offal: 5 days.
Not for use in birds producing or intended to produce eggs for human consumption.

Animals must not be slaughtered for human consumption during treatment.

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 13 of Directive 2001/82/EC, and bioequivalence with a suitable reference product has been accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.
The applicant submitted two palatability studies in the target species, pigs and chickens. It was concluded that the palatability of the candidate product was not inferior to that of the reference product in the target species.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

On the basis of the original data submitted, the HPRA considered that the product demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory benefit/risk profile and therefore granted a marketing authorisation.

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.