Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Lismay 222 mg/g + 444.7 mg/g Powder for Use in Drinking Water

Date Created: February 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Lismay 222 mg/g + 444.7 mg/g Powder for Use in Drinking Water, Powder for use in drinking water
Applicant	Laboratorios Maymo S.A., Via Augusta 302, Barcelona, 08017, Spain
Active substance	Lincomycin (lincomycin hydrochloride) Spectinomycin (spectinomycin sulfate tetrahydrate)
ATC Vetcode	QJ01FF52
Target species	Pigs
Indication for use	For the treatment and metaphylaxis of porcine proliferative enteropathy (ileitis) caused by Lawsonia intracellularis and associated enteric pathogens (Escherichia coli) susceptible to lincomycin and spectinomycin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	The application is for an MA submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of conclusion of the procedure	20/09/2021

I. SCIENTIFIC OVERVIEW

The application is for an MA submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC. The Spanish reference product is Linco-Spectin 100, 222/444.7 mg/g polvo para la administración en agua de bebida para porcino y pollos. It is noted that the Spanish reference product is also authorised in the UK as Linco-Spectin 100, 222/444.7 mg/g Powder for Use in Drinking Water for Pigs and Chickens, marketed by Zoetis UK Limited and authorised via mutual recognition on 22/02/1993. The applicant claimed that the proposed product is 'essentially similar' to the reference product, Linco-Spectin 100.

The proposed dose rates are 3.33 mg lincomycin and 6.67 mg spectinomycin per kg bodyweight per day, for 7 days (equivalent to 15 mg powder per kg bodyweight per day, for 7 days), administered in drinking water.

The proposed indication is for the treatment and metaphylaxis of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis* and associated enteric pathogens (Escherichia coli) susceptible to lincomycin and spectinomycin.

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, 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains Lincomycin (as lincomycin hydrochloride) and Spectinomycin (as spectinomycin sulfate tetrahydrate) and the excipients Sodium benzoate (E-211) and Lactose monohydrate.

The choice of the formulation and the absence 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. The manufacturing method consists of simple dry blending.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are Lincomycin (as lincomycin hydrochloride) and Spectinomycin (as spectinomycin sulfate tetrahydrate), both are established active substances described in the European Pharmacopoeia. 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 have been provided.

The active substances comply with their Ph. Eur. monographs and are supplied by manufacturers who are in receipt of Certificates of Suitability issued by the EDQM.

It is stated that both excipients comply with their respective Ph. Eur. Monographs.

For Lincomycin the container/closure system consists of the active substance being packaged in double polyethylene bags placed in a paperboard drum.

For Spectinomycin the container/closure system consists of the active substance being packaged in a polyethylene bag, in an aluminium foil bag placed in a fibre drum.

II.C.4. Substances of Biological Origin

For Spectinomycin certificates of suitability issued by the EDQM have been provided and 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.

For Lincomycin 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. Control tests on the finished product are those for: Appearance, Identification, Appearance of solution S, pH, Specific optical rotation, Related substances, Water, Sulfated ash, Assay and Acetone.

II.F. Stability

Stability data on the finished product have 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

This veterinary medicinal product does not require any special storage conditions.
Keep the container tightly closed. After use, fold over the top of the bag and secure with a clip.

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 6 months
Shelf life after dissolution according to directions: 24 hours.
Medicated drinking water should be refreshed or replaced every 24 hours.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological and Toxicological Studies

Due to the legal base of the application, the applicant was only required to provide toxicological and pharmacological data relevant to support the submitted user risk assessment (URA). Since this is an application for a generic product, and as the formulation is qualitatively and quantitatively the same as the reference product with regard to active substances (lincomycin and spectinomycin), is qualitatively comparable in terms of the excipients (and any quantitative differences are not considered to significantly affect the safety profile), has the same pharmaceutical form and posology, it was accepted that the hazard, exposure and risks to the user of the generic product, will be comparable to those of the reference product.

User Safety

The same user warnings as agreed for the reference product are employed with an additional 'A' phrase (the concerned risk), pertaining to the skin, respiratory and eye irritation potential of the product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The applicant's user recommendations are as follows:

- People with known hypersensitivity to lincomycin, spectinomycin or soybean millfeed should avoid contact with the veterinary medicinal product.
- This product may cause skin, respiratory and eye irritation.
- Care should be taken not to raise and inhale any dust.
- Contact with skin and eyes should be avoided.
- Personal protective equipment consisting of approved dust masks (either a disposable half mask respirator conforming to European Standard EN149 or a non-disposable respirator conforming to European Standard EN 140 with a filter EN 143), gloves and safety glasses should be worn when handling and mixing the product.
- Wash hands and any exposed skin with soap and water immediately after use.
- If symptoms such as skin rash, persistent cough or persistent eye irritation appear after exposure, seek medical advice immediately and show the package leaflet or label to the physician.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The applicant has provided a comprehensive Phase I exposure evaluation. The Phase I assessment concluded that a Phase II risk assessment, was required because initial PECs exceeded the trigger value (100 µg/kg).

As the product will be used to treat intensively reared species, the environment may be exposed to the product via manure being spread onto agricultural land. The aquatic environment may also be exposed because of run-off and leaching.

Phase II Tier A:
A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physicochemical properties, environmental fate and effects. Studies were carried out using the active substances, lincomycin and spectinomycin, unless indicated otherwise.

In addition, as a combination product, the applicant has combined the exposure calculations for both lincomycin and spectinomycin and then compared it with the most sensitive environmental effect concentration determined for either compound.

Physicochemical properties

Study type	**Guideline**	**Result**	
		Lincomycin	**Spectinomycin**
Water solubility	OECD 105	927 mg/l (25ºC)	4.07E+005 mg/l (25ºC)
Dissociation constants in water pKa	OECD 112	pka 7.9	pka 7.0 pka 8.6
Melting Point/Melting Range	OECD 102	925ºC	184 to 194ºC
Vapour Pressure	OECD 104	1.34 x 10^{-17} mmHg (25ºC) 1.79 x 10^{-15} mPa (25ºC)	8.21E^{-013} mmHg (25ºC)
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	Log Pow = 0.3	Log Pow = -2.02

As the log K_{OW}s are <4, which suggests that lincomycin and spectinomycin have a low potential to partition to lipids, an evaluation for the potential for bioaccumulation, secondary poisoning and for these substances to be persistent, bioaccumulative and toxic (PBT) substances was not required.

Environmental fate

Study type	Guideline	Result	
		Lincomycin	**Spectinomycin**
Soil Adsorption/Desorption	OECD 106	Koc range = 18.8 to 26.1 ml/g	Koc range = 623 to 2209 ml/g
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} range = 8.2 to 11.1 days	DT_{50} range (parent) = 2.0 to 5.7 days DT_{50} range (metabolites) = 43.8 to 539.0 days

Environmental effects

Terrestrial

Species (Guideline)		Result	Active Substance
Nitrogen transformation (OECD 216)		No impact at the concentration studied	Lincomycin
			Spectinomycin
Plants (OECD 208)	*Avena sativa*	EC50 = 79 mg/kg NOEC = 25.5 mg/kg	Lincomycin
	Phaseouls aureus	EC50 = 18 mg/kg NOEC = 7.7 mg/kg	
	Cucumis melo	EC50 = 8.2 mg/kg NOEC = 7.7 mg/kg	
	Cucurbita pepo	EC50 = 6.4 mg/kg NOEC = 2.6 mg/kg	
	Cucumis sativus	**EC50 = 1.94 mg/kg** **NOEC = 0.85 mg/kg**	
	Avena sativa	EC50 = 79 mg/kg NOEC = 25.5 mg/kg	
	Alium cepa	EC50 = 4.64 mg/kg NOEC 1.04 mg/kg	
	Zea mays	EC50 = 62.1 mg/kg NOEC 28.2 mg/kg	
	Brassica napa	EC50 = 62.1 mg/kg NOEC = 3.13 mg/kg	
	Brassica napa	**EC50 = 2.32 mg/kg*** **NOEC = 0.74 mg/k*g**	Spectinomycin
	Brassica napus	EC50 = 8.94 mg/kg NOEC = 0.99 mg/kg	
	Beta vulgaris	EC50 = 12.9 mg/kg NOEC = 8.89 mg/kg	
	Pisum sativum	EC50 = 49 mg/kg NOEC = 19 mg/kg	
	Hordeum vulgaris	EC50 >1555 mg/kg NOEC >1555 mg/kg	
	Triticum aestivum	EC50 >1555 mg/kg NOEC >1555 mg/kg	

	Alium cepa	EC50 = 46.8 mg/kg NOEC 13.3 mg/kg	
	Helianthus annuus	EC50 = 61.3 mg/kg NOEC 13.3 mg/kg	
	Solanum lycopersicum	EC50 = 64.1 mg/kg NOEC = 30.0 mg/kg	
Earthworm *Eisenia foetida* (OECD 222)	NOEC (mortality) = 329 mg/kg** NOEC (weight) = 329 mg/kg** NOEC (reproduction) = 329 mg/kg**		Lincomycin
	NOEC (mortality) = 310 mg/kg** NOEC (weight) = 310 mg/kg** NOEC (reproduction) = 310 mg/kg**		Spectinomycin

Aquatic

Species (Guideline)	Result	Active Substance
Cyanobacteria *Anabaena flos-aquae* (OECD 201)	EC_{50} (growth) = 260 µg/l EC_{10} (growth) = 107.1 µg/l NOEC (growth) = 19.2 µg/l	Lincomycin
	EC_{50} (growth) = 304.20 µg base/l EC_{10} (growth) = 56.17 µg base/l NOEC (growth) = 58.4 µg base/l	Spectinomycin
Aquatic invertebrates *Daphnia magna* (OECD 202)	EC_{50} >100 mg base/l	Lincomycin
	EC_{50} >100 mg base/l	Spectinomycin
Fish *Danio rerio* (OECD 203)	LC_{50} >100 mg base/l	Lincomycin
	LC_{50} >100 mg base/l	Spectinomycin

Exposure assessment (Predicted exposure concentration)
Worst-case PEC values (Weaner pig) for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

Scenario	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Lincomycin	202.54	99.41	33.14
Spectinomycin	405.68	8.05	2.68

Risk Characterisation (Risk Quotient)
Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal.

Tier A

- Initially an unacceptable risk to groundwater was determined. As the $PEC_{groundwater}$ is higher than the trigger value of 0.1 µg/l for both compounds, refinement using more sophisticated modelling (FOCUS PEARL) was conducted. This resulted in an acceptable risk to groundwater:

- Lincomycin PECgw (FOCUS PEARL Okehampton): 0.0 µg/l
- Spectinomycin PECgw (FOCUS PEARL Okehampton): 0.793 µg/l

- Acceptable risk to soil microorganisms. The substances did not have significant impacts at the relevant concentrations studied.
- Acceptable risk to earthworms (combined lincomycin plus spectinomycin): RQ<1.
- Unacceptable risk to plants (combined): RQ>1. Tier B refinement required.
- Unacceptable risk to algae (combined): RQ<12.8. Tier B refinement required.
- Acceptable risk to daphnia (combined): RQ<1.
- Acceptable risk to fish (combined): RQ<1.

Tier B and C

As the RQ value for algae and plants were >1 further assessment of the environmental risk was required.

- Terrestrial plant PNEC values have been recalculated using NOEC values for terrestrial plants using a revised assessment factor of 10.
- Unacceptable risk to plants (combined): RQ>1. Results for lincomycin show that the risk quotients are slightly >1 for cucumber and onion. All other values were <1, including two species of the same genus as cucumber. Results for spectinomycin demonstrate the risk quotient to be >1 for Brassicaceae. No risk has been detected for the other families assayed.
- FOCUS SWASH modelling reduced the $PEC_{surfacewater}$ but this veterinary medicinal product, under the proposed dose rate, does potentially represent a risk for the environment for algae in surface water in some scenarios. However, the evaluation performed at Tier C using data from more than 15 field studies from scientific literature indicated that lower concentrations for lincomycin than those estimated from FOCUS should be expected under field conditions, decreasing the RQ values <1. In consequence, these field data demonstrate that a risk associated to the use of lincomycin should not be expected to occur on aquatic organisms under field conditions.

Due to the risk characterisation, the following environmental properties information were included on the product literature:

Environmental Properties
Lincomycin and spectinomycin may be toxic for terrestrial plant species including crop species such as Cruciferous vegetables (Brassicaceae). Lincomycin may be toxic for aquatic organisms such as, cyanobacteria.

Although spectinomycin is not persistent in the environment, some degradation products produced in the environment from spectinomycin might be classified as persistent or very persistent.

Disposal Advice
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

Lincomycin is toxic for aquatic organisms (such as cyanobacteria). Do not contaminate surface waters or ditches with the veterinary medicinal product or used container, to avoid adverse effects on aquatic organisms.

III.B.2 Residue documentation

Residue Studies

No residue depletion studies were conducted because the proposed product is 'essentially similar' to the reference product, Linco-Spectin 100 and bioequivalence with the refence product is claimed.

MRLs

Spectinomycin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for muscle, liver, kidney and skin/fat. The marker substance is spectinomycin.

MRLs for spectinomycin are listed below:

	Porcine
Muscle	300 µg/kg
Liver	1000 µg/kg
Kidney	5000 µg/kg
Fat / skin	500 µg/kg

Lincomycin hydrochloride is listed in Table 1 of Regulation 37/2010 and MRLs have been established for muscle, liver, kidney and skin/fat. The marker substance is lincomycin.

MRLs for Lincomycin hydrochloride are listed below:

	Porcine
Muscle	100 µg/kg
Liver	500 µg/kg
Kidney	1500 µg/kg
Fat / skin	50 µg/kg

The excipients, sodium benzoate and lactose monohydrate, are included in Table 1 of the annex to Commission Regulation (EU) No 37/2010 or are considered as not falling within the scope of Council Regulation 470/2009.

Withdrawal Periods

The proposed withdrawal period is the same as that agreed for the reference product: Zero days for meat and offal in pigs.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As this is an application for a generic product, submitted according to Article 13(1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, no pharmacodynamic or pharmacokinetic data were required to be submitted.

The applicant claimed that the product is 'essentially similar' to the reference product, Linco-Spectin, and therefore did not conduct an *in vivo* bioequivalence study.

The applicant claimed a waiver from the requirement for an *in vivo* bioequivalence study in accordance with criteria 7.1c and d of the current EMA guideline on the conduct of bioequivalence studies for veterinary medicinal products.

The applicant conducted a literature review regarding the current status of lincomycin and spectinomycin resistance in the target pathogen *Lawsonia intracellularis* and concluded that no updates to the product literature are necessary. It was noted that substantial spectinomycin resistance has been detected in pathogenic *E. coli* isolates from pigs in Europe; however, this is mitigated by an appropriate warning in the SPC.

The proposed SPC is the same as that of the reference product with the omission of chickens as a target species.

Tolerance in the Target Species

Owing to the legal basis of the application, no target species tolerance data have been submitted.

Resistance

Owing to the legal basis of the application, no resistance data have been submitted.

IV.II. Clinical Documentation

Owing to the legal basis of the application, no clinical data have been submitted.

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 is favourable.

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)