



MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD



agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

**ENTEROSTREP SP 500 mg/g powder for use in drinking water
for rabbits**

CORREO ELECTRÓNICO

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[temporallP000571.docx](#) [HH-INF-PUB-002-002.docx](#) [plantilla PuAR-PRM-PDC may09.doc](#)

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PARA CONEJOS - 2859 ESP - Informe público de evaluación

NAME ENTEROSTREP

SP VETERINARIA

Date: 02/11/2017

ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

Application for Mutual Recognition Procedure

Publicly available assessment report

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0285/001/MR
Name, strength and pharmaceutical form	ENTEROSTREP SP 500 mg/g powder for use in drinking water for rabbits
Applicant	SP VETERINARIA S.A.
Active substance(s)	Dihydrostreptomycin sulfate
ATC Vet code	QJ01GA90
Target species	Rabbit
Indication for use	Reduction of clinical signs and mortality due to epizootic rabbit enteropathy.



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PARA CONEJOS - 2859 ESP - Informe público de evaluación

NAME > ENTEROSTREP

SP VETERINARIA

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ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (<http://www.hma.eu>).



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Publicly available assessment report

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) (Directive 2001/82/EC as amended by Directive 2004/28/EC)
Date of completion of the original mutual recognition procedure	20/09/2017
Date product first authorised in the Reference Member State (MRP only)	30/07/2013
Concerned Member States for original procedure	PT

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 risk/benefit analysis is in favour of granting a marketing authorisation.



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ENTEROSTREP SP 500 mg/g POLVO PARA ADMINISTRACION EN AGUA DE BEBIDA
PARA CONEJOS - 2859 ESP - Informe público de evaluación<PRODUCT

NAME>ENTEROSTREP-

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ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

Application for Mutual Recognition Procedure

Publicly available assessment report

II. QUALITY ASPECTS

A. Composition

The product contains 500 mg/g of dihydrostreptomycin and the excipients lactose monohydrate and silica colloidal anhydrous.

The container/closure system is a bag made of polypropylene, aluminium and polyethylene complex, closed by thermo-sealing. The particulars of the containers and controls performed are provided and conform to the regulation.

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 from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance is Dihydrostreptomycin sulfate, an established active substance 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.

D. 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.

E. <Control on intermediate products> (pharmaceuticals)

N/A

F. Control Tests on the Finished Product



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PARA CONEJOS - 2859 ESP - Informe público de evaluación<PRODUCT

NAME>ENTEROSTREP-

SP VETERINARIA

Date: 02/11/2017

ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

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Publicly available assessment report

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.

G. Stability

Stability data on the active substance have 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 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.

The in-use shelf-life of the product after first opening is supported by the data provided.

H. Genetically Modified Organisms

J. Other Information



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Application for Mutual Recognition Procedure

Publicly available assessment report



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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (for pharmaceuticals only)

The documentation submitted by the applicant supports an appropriate safety level of the veterinary medicine under evaluation. Warnings and precautions as listed on the product literature are adequate to ensure safety to the user, the environment and the consumers.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographic information on the pharmacodynamics properties, focusing on the mechanism of action and on the antimicrobial activity. The applicant has also provided bibliographical data on the relevant pharmacokinetic properties.

Toxicological Studies

The applicant has submitted data on single dose and chronic toxicity, reproductive toxicity, including information regarding the teratogenic, mutagenic and carcinogenic potential, special studies and observations in humans, in compliance with the relevant guidelines.

- Single Dose Toxicity

The applicant has provided bibliographical data which show a low acute toxicity of dihydrostreptomycin following an oral administration (LD₅₀ 9000-25000 mg/kg b.w./day).

- Repeated Dose Toxicity

The NOEL was determined as 40 mg/kg bw/day

- Reproductive Toxicity, including Teratogenicity:

The applicant has submitted bibliographic information showing that dihydrostreptomycin does not exert any teratogenic nor genotoxic effect.

The documentation on the laboratories studies performed in mice, guinea pigs and rabbit did not show any teratogenic effect. Studies performed on several food-producing animals did not show embryotoxic effects. Additionally, the active substance did not exert toxic effects on the females.

- Mutagenicity

There is not conclusive evidence in this regard, although contradictory results on a chromosomic aberration *in vitro* study have been reported.

- Carcinogenicity:

The applicant submits bibliographic information pointing out the lack of carcinogenic potential. The NOEL was set at the highest dose (5 mg/kg b.w./day), based on the weight decrease observed

**ENTEROSTREP SP 500 mg/g POLVO PARA ADMINISTRACION EN AGUA DE BEBIDA
PARA CONEJOS - 2859 ESP - Informe público de evaluación<PRODUCT**

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Date: 02/11/2017

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Application for Mutual Recognition Procedure

Publicly available assessment report



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User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that the use of this product in the conditions stated in the SPC does not pose a risk for the environment. No warnings regarding the risks for the environment are therefore required.

III.B Residues documentation

Residue Studies

The applicant has conducted residue depletion studies in compliance with the relevant guidelines. The animals were divided in different groups and slaughtered at different times after the administration. The results show that the residues detected in the different tissue samples are below the MRL before the withdrawal time. The residues were quantified using a fully validated analytical method consisting in a high-resolution liquid chromatography in reverse phase with a mass spectrometry detector.

MRLs

The active substance is included in the Regulation 470/2009 as a pharmacological active substance with the following MRLs:

Active substance	Marker residue	Animal	MRL (µg/Kg)	Tissue
Dihydrostreptomycin	Dihydrostreptomycin	Rabbits	500	Muscle
			500	Liver
			500	Fat
			1000	Kidney

The excipients, colloidal anhydrous silica and lactose monohydrate, contained in the product under evaluation are out of the scope of Regulation 37/2010.

Withdrawal Periods

Based on the data provided, a withdrawal period of 8 days for rabbit meat and offal is justified. The withdrawal time established is considered adequate to grant the consumers safety.

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PARA CONEJOS - 2859 ESP - Informe público de evaluación<PRODUCT

NAME>ENTEROSTREP-

SP VETERINARIA

Date: 02/11/2017

ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

Application for Mutual Recognition Procedure

Publicly available assessment report

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show the pharmacodynamics of the active substance, focusing in the description of the mechanism of action and the antimicrobial activity. Dihydrostreptomycin is an aminoglycoside and it is used in infections of the digestive tract caused by aerobic Gram-negative bacteria.

No specific PK study in the target species has been conducted. However, the applicant has provided bibliography demonstrating that the active substance is very scarcely absorbed in animals when administered orally (less than 1%) and high concentrations of the drug remain in the gastrointestinal tract.

Tolerance in the Target Species of Animals

The applicant has evaluated the local and systemic tolerance of the product. Studied parameters included blood analysis and necropsy of a small number of animals from each treatment level. No relevant adverse reactions were observed in any of the recommended dosage range.

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

Resistance

The bacterial mechanisms of development of resistance to aminoglycosides and specifically to streptomycin and dihydrostreptomycin have been described. This information is included in the SPC of the product.

IV.B Clinical Studies

Field Trials

The applicant has conducted a field study according to the principles of Good Clinical Practice (VICH GL9).

The results obtained support the indications and posology reflected in the summary of product characteristics.



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PARA CONEJOS - 2859 ESP - Informe público de evaluación<PRODUCT

NAME>ENTEROSTREP-

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ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

Application for Mutual Recognition Procedure

Publicly available assessment report

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.



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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 veterinary Heads of Agencies website (www.hma.eu).

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.

<None>

or

Complete this section for extensions to the same VPA range or defined, significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- Changes to pharmacokinetic data leading to a change in the SPC
- Changes to toxicological data leading to a change in the SPC
- Changes to user safety warnings
- Changes to ecotoxicological information as given in the SPC or changes to disposal warnings
- New residue studies in new target species or tissues
- Reassessment of residue data or new studies resulting from changes to MRL
- Changes to withdrawal period
- Changes to target species
- Changes to target species tolerance data leading to change in warnings/precautions for target species
- New or changed indications

Significant changes in administrative or quality data include any Type II change, which affects the initial report. The following Type IA or IB changes may also apply:

- Name of product [Type IA: 2]
- Name of active substance [Type IA: 3]
- MAH [Type IA: 1]
- Composition of the medicinal product [Type IB: 18, Type IA/B: 25, 34, 35, 39]
- Container/closure system [Type 1/B: 26, 28, 29, 36, 41, 43]
- Method of preparation [Type 1B: 33]
- Active substance specification [Type IB: 25]
- CEP [Type IA/B: 15]
- Re-test period or storage conditions of active substance [Type IB: 17]
- Excipient specifications [Type 1A/B: 25]
- Packaging materials [Type 1A/B: 28, 29, 36, 41, 43]
- TSE [Type 1A: 16, 22]



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NAME > ENTEROSTREP

SP VETERINARIA

Date: 02/11/2017

ENTEROSTREP SP 500 mg/g POLVO PARA ADMINIS

Application for Mutual Recognition Procedure

Publicly available assessment report

- Shelf-life or storage conditions of the finished product [Type 1B: 42]

Quality changes

Summary of change (Application number)	Section updated in Module 3	Approval date
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	Section updated in Module 3	Approval date
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	



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