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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: Spain)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

**Apravet 552 IU/mg powder for use in drinking
water/milk**

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0252/001/DC
Name, strength and pharmaceutical form	Apravet 552 IU/mg powder for use in drinking water/milk
Applicant	Huvepharma NV Uitbreidingstraat 80, 2650 Antwerpen (Belgium)
Active substance(s)	Apramycin sulfate
ATC Vet code	QA07AA92
Target species	Pigs (weaned piglets), cattle (pre-ruminant calves), chickens (broilers) and rabbits.
Indication for use	<p>Pigs (weaned piglets): Treatment of bacterial enteritis caused by <i>Escherichia coli</i> susceptible to apramycin.</p> <p>Pre-ruminant calves: Treatment of bacterial enteritis caused by <i>Escherichia coli</i> and clinical outbreaks due to <i>Salmonella enterica</i> subsp. <i>enterica</i> serovar Dublin (<i>Salmonella</i> Dublin) susceptible to apramycin. Treatment should be based on prior confirmation of the <i>Salmonella</i> serovars involved or at least the availability of epidemiological data confirming the presence of this serovar.</p> <p>Chickens: Treatment of colibacillosis caused by <i>Escherichia coli</i> susceptible to apramycin.</p> <p>Rabbits: Treatment and metaphylaxis of bacterial enteritis caused by <i>Escherichia coli</i> susceptible to apramycin. The presence of the disease in the herd must be established before the product is used.</p>

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	01/08/2018
Date product first authorised in the Reference Member State (MRP only)	NA
Concerned Member States for original procedure	CMS: AT, BE, BG, CY, CZ, DE, DK, EE, EL, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK.

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range:

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.



II. QUALITY ASPECTS

A. *Qualitative and quantitative particulars*

The product contains 552 IU of apramycin sulfate per mg as active substance. No other ingredients are included.

The container/closure systems are 1 000 000 IU multilayer sachet, 50 000 000 IU HDPE bottle and 1 000 000 000 IU multilayer bag. The particulars of the containers and controls performed are provided and conform to the regulation.

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 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 apramycin sulfate, an established active substance is described in the British 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 information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. The provided information is considered appropriate.

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 have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. 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 (2 years) when stored under the approved conditions.

Appropriate data have been provided to support the in-use shelf-life of the product. The claim of the stability after reconstitution in water/milk is based on the demonstration of stability for a batch diluted according to directions.

G. Other Information

Not applicable.



III. SAFETY AND RESIDUES ASSESSMENT

As this is a generic application according to Article 13.1 of the Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of safety and residue tests are not required.

The safety and residue aspects of this product are identical to 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 / the environment / consumers.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of toxicological studies are not required.

The safety aspects of this product is/are identical to the reference product

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 the same as those of the reference product and are adequate to ensure safety of the product to users.

Environmental Risk Assessment

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PEC_{soil} initial = 3547.8 µg/kg) is greater to 100 µg/kg and no mitigations exist that alter the PEC_{soil}.

Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005-Rev.1). The data were considered to be complete and acceptable.

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	OECD 105	> 2 g/ml	
Dissociation constants in water pKa	OECD 112	pKa = 7.428 (at 20°C ± 1°C)	
n-Octanol/Water Partition Coefficient logP _{ow}	OECD 107 or 117 or 123	Log Pow (pH5) = -2.01 Log Pow (pH7) = -2.33 Log Pow (pH9) = -1.02	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	LUFA 2.1 Koc = 169,204.1 ml/g LUFA 2.2 Koc = 1,807,537.36 ml/g LUFA 2.3 Koc = 2,757,575.63 ml/g LUFA 2.4 Koc = 6,297,467.2 ml/g LUFA 6S Koc = 4,390,220.48 ml/g Average Koc = 2206444.70 ml/g Geomean Koc = 1,877,308.08 l/kg	
Aerobic and Anaerobic Transformation in Soil	OECD 307	LUFA 2.1 DT50 > 1000 days (20°C, SFO) LUFA 2.2 DT50 > 1000 days (20°C, HS) LUFA 2.3 DT50 > 439.3 days (20°C, SFO) LUFA 5M DT50 > 1000 days (20°C, SFO) DT ₅₀ , 12°C. geo. mean of 4x soils or worst case if < 4 soils = 2138.6 days	

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks*
Cyanobacteria, growth inhibition test/ <i>Anabaena flosaquae</i>	OECD 201	EC50	700	µg/l	Apramycin base; static (nom)
<i>Daphnia</i> sp. immobilisation	OECD 202	EC50	>57000	µg/l	Apramycin base, static test (nom)
Fish, acute toxicity/ <i>species</i>	OECD 203	LC50	>55300	µg/l	Apramycin base, static test (nom)
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216		< 25% effect at 162 mg/kg	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	333400	µg/kg	6 species: (<i>Brassica napus</i> , <i>Glycine max</i> , <i>Cucumis sativus</i> , <i>Lycopersicon esculentum</i> , <i>Lolium perenne</i> , <i>Allium cepa</i>)
Earthworm/ <i>Enchytraeidae</i> reproduction	OECD 220/222	EC10 or NOEC	791100	µg/kg	

*add information on analytical verification of test substance (nominal (n) or measured (m)), on exposure (e. g. semi-static, flow-through, sediment spiked, etc.), on test substance (salt, base), and on test medium (e. g. Corg content)

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005-Rev.1)

Using the assessment factors (AF) in these VICH guidelines, predicted no effect concentrations (PNEC) were calculated and compared with the PEC values. This results in a risk quotient (RQ) for each compartment as follows:

Compartment	PNEC	PEC	RQ
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surface water			
Algae	7.0 µg/L	0.54 µg/L	0.08
Daphnia	57 µg/L	0.54 µg/L	0.009
Fish	55.3 µg/L	0.54 µg/L	0.01
Groundwater	NA		NA
PECgw initial		0.12 µg/l (Broiler, worse case)	
PECgw refined (Average concentration closets to the 80th percentile)		0.000 µg/l	
Soil microorganisms: Nitrogen transformation test	<25% difference in N transformation at 162 mg/kg	NA	NA
Soil			
Earthworms	79110 µg/kg	16126.4 µg/kg	0.20
Plants	33340 µg/kg	16126.4 µg/kg	0.48

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

PBT assessment

PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	BCF	log Kow < 4	not B
Persistence	DT _{50, compartment, 12 °C}	> 1000 days	vP
Toxicity	NOEC or CMR	> 0.01	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

Since this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC and bioequivalence with the reference product has been demonstrated, the applicant is not required to provide the results from residue depletion studies.

MRLs

The active substance Apramycin is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions
Apramycin	Apramycin	Bovine	1000 µg/kg 1000 µg/kg 10000 µg/kg 20000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption
	Not applicable	Ovine, porcine, chicken, rabbit	No MRL required	Not applicable	For oral use only. Not for use in animals from which milk or eggs are produced for human consumption.

Withdrawal Periods

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, the same withdrawal periods are justified:

Pigs:

Meat and offal: Zero days.

Calves:

Meat and offal: 28 days.

Chickens:

Meat and offal: Zero days.

Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

Rabbits:

Meat and offal: Zero days.



IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Apravet is eligible to biowaiver as requirements in section 7.1.C and section VI.2 (Appendix I) of Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) are fulfilled.



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.

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