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PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

AMPHEN 200 mg/ml
Suspension for use in drinking water for pigs

PRODUCT SUMMARY

EU procedure number	FR/V/0460/001/DC
Name, strength and pharmaceutical form	AMPHEN 200 mg/ml suspension for use in drinking water for pigs
Applicant	Huvepharma N.V. Uitbreidingstraat 80 B-2600 Antwerp
Active substance(s)	Florfenicol
ATC vetcode	QJ01BA90
Target species	Pigs
Indication for use	Treatment and metaphylaxis at the group level of swine respiratory diseases associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*. The presence of the disease in the group must be established before the product is used.

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Huvepharma N.V.	DCP
Publicly available assessment report	

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application	Hybrid application in accordance with Article 19(1) of Regulation (EC) 2019/6 as amended.
Date of completion of the original decentralised procedure	20/12/2023
Concerned Member States for original procedure	AT, BE, BG , CY, CZ, DE, DK, EE, EL, ES, HR, HU, IE, IT, LT, LU, LV, NL, PL, PT, RO, SK, SI, UK(NI)
Concerned Member States for subsequent recognition procedure	

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the observed reactions observed are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

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

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains Florfenicol as active substance at the concentration of 200 mg/mL.

The product contains the following excipients : Hypromellose, Docusate sodium, Sodium benzoate, Hydrochloric acid concentrated, Simethicone emulsion and Purified water.

The container/closure system is adequate and described in the SPC.

The choice of the formulation and the presence/absence of preservative are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

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

The VMP is manufactured in accordance with the European Pharmacopoeia (Ph. Eur.) and relevant European guidelines.

C. Production and control of starting materials

The active substance is florfenicol, 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 have been provided.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this VMP.

D. Control tests carried out on isolated intermediates during the manufacturing process

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 VMP.

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 tests

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 VMP throughout its shelf life when stored under the approved conditions.

G. Other information

Not applicable

3. SAFETY DOCUMENTATION (safety and residues tests)

This is a hybrid application according to Article 19, which is similar to a reference product and rely in part on the results of the appropriate safety and residue studies for this reference product, and in part on new data.

The toxicological aspects of this VMP are identical to the reference VMP.

Warnings and precautions as listed on the product literature are similar to those of the reference VMP and are adequate to ensure safety of the product to users / the environment / consumers.

A. Safety tests

Pharmacological studies

See part IV.

Development of resistance and related risk in humans

The applicant has provided bibliographical information regarding <level of resistance in target pathogens which show<s> that that the prevalence of resistance remains very low across the EU.

Warnings and precautions as listed on the product literature are adequate to ensure prudent and responsible use of the VMP.

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 VMP.

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 PECsoil initial is greater to 100 µg/kg and no mitigations exist that alter the PECsoil.

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 (EMEA/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	1.4 g/L (20°C)	
Dissociation constants in water pKa	OECD 112	pKa at 20°C = 6.72	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	logK_{ow} at pH 5, 7, 9 = 0.29, 0.24, 0.26	

Environmental fate			
Soil Adsorption / Desorption	OECD 106	Lufa 2.1 (pH 4.7, 0.63% OC, 4.1 % clay) Koc = 19.44 Lufa 2.4 (pH 6.1, 0.65% OC, 25.9 % clay) Koc = 14.79 Lufa 6S (pH 7.3, 1.70% OC, 41.2 % clay) Koc = 20.29 LRA E1 (pH 5.29, 2.98% OC, 15.9 % clay) Koc = 10.67 LRA J1 (pH 7.34, 5.35% OC, 26.5 % clay) Koc = 11.04 Geo mean value = 14.7	
Aerobic and Anaerobic Transformation in Soil	OECD 307	**Soil** / **pH** / **OC (%)** / **Best fit model** / **X2 %** / **DT50* (days)** Lufa 2.1 / 4.7 / 0.63 / DFOP / 4.7 / 88.3 Lufa 2.2 / 5.6 / 1.61 / DFOP / 4.6 / 18.6 Lufa 2.3 / 6.1 / 0.65 / DFOP / 6.0 / 29.1 Lufa 6S / 7.3 / 1.70 / DFOP / 4.4 / 25.2 Geo mean / 33.1 *DT_{50}, 20°C., DFOP (k2), geo mean = 33.1d (parent + TP > 10%) DT_{50}, 12°C., DFOP(k2), geo. mean = 70.8d (parent +TP>10%) <u>Transformation products >10%:</u> Unk-SD-1 (florfenicol amine): max. 54.6% (d14) soil 2.1 % non-extractable residues (NER): 27-39% Mineralisation: 47.6-84.1%	One major transformation product (TP) (>10%, Unk-SD-1) detected in all 4 non-sterile soils over the 120 days incubation has been considered in the DT50 calculation
Transformation in Manure (pig)		DT_{50} for florfenicol residues (including NER and transformation product>10%) **Kinetic** / **K1** / **K2** / **DT50[a] (days)** / **DT50[b] (days)** / **DT50[c] (days)** DFOP / 4.7 / 0.63 / 69.06 / 1052 / 2720 a DT50overall generated by kinetic software (KinGui 2.1) b DT50 modelling (k2) according to FOCUS (2014) c DT50 adjusted from 20°C to 10°C $DT_{50\ pig\ manure,\ rel\ temp\ (adjusted\ to\ 10°C)}$ = 0.36 d (parent only) $Mineralisation_{test\ end\ (119\ d)}$ < 5% (0.02%) Non-extractable residues $_{half\ max\ dst\ (d\ 45,\ pig)}$: 55.78 % Non-extractable residues $_{half\ max\ dst\ (d\ 27,\ weaner)}$: 46.48 % <u>Transformation product(s):</u> UNK-PM-1 (monochloroflorfenicol): max. 55.84%:(d 4)	Temperature (at which study was conducted): 20°C

Environmental fate			
		$DT_{50\ pig\ manure,\ study\ temp\ 20°C}$ =0.96 d UNK-PM-2: max. 11.55%:(d 7) $DT_{50\ pig\ manure,\ study\ temp\ 20°C}$ = 5.58 d	

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks*
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	449	µg/l	m
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC10	36	µg/l	Tier B
Daphnia sp. immobilisation	OECD 202	EC50	>100	mg/l	n
Fish, acute toxicity/*species*	OECD 203	LC50	>100	mg/l	n
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	434	µg/kg	Trigger value: 25% deviation from the control
Fish, early-life stage/*species*	OECD 210	EC10 or NOEC		µg/l	Tier B
Terrestrial Plants, growth test	OECD 208	EC50	286 (*B. vulgaris*)	µg/kg	6 dicot: *Cucumis sativus, Helianthus annuus, Beta vulgaris, Brassica napus, Glycine max, Linum usitatissimum* and *Solanum lycopersicum*) 3 monocot: *Allium cepa*, *Zea mays* and *Triticum aestivum*
Terrestrial Plants, growth test	OECD 208	EC10 or NOEC		µg/kg	Tier B species: (cf above)
Terrestrial Plants, growth test SSD		LLHC5 (EC10)	103 µg/kg		Tier C
Earthworm reproduction	OECD 222	NOEC	5500	µg/kg	
Sediment dwelling organism/species	OECD 218/219	NOEC or EC10		µg/kg	Tier B

*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 (EMEA/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
surface water	3.6 µg/L	14.17 µg/L (weaner pig)	3.94
groundwater	0.45 µg/L	3.85 µg/L (weaner pig)	8.6
	MTCdw= 30 µg/L (drinking water)		0.33
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	No risk
soil	103 µg/kg	164 µg/kg (weaner pig)	1.6

The risk characterisation resulted in risk quotients (RQ) below 1 for the groundwater (drinking water) compartment 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, groundwater (ecosystem) and soil compartments points that a risk for the environment is indicated. Benefit/Risk assessment was included in the evaluation resulting in a positive balance.

The following information on environmental properties needs to be included in the product literature: warning for toxicity to terrestrial plants and cyanobacteria in surface and groundwater and advising for a safe disposal of the unused medicine or waste materials.

Section 3.5 Special precautions for use Other precautions
"The use of the veterinary medicinal product poses a risk to terrestrial organisms (plants) and to aquatic organisms (cyanobacteria), including groundwater organisms.
In order to prevent any adverse effects on terrestrial plants and algae and to prevent possible contamination of groundwater, manure from treated pigs must not be spread onto land without dilution with manure from untreated pigs. Manure from treated pigs must be diluted with at least 5 times the weight of manure from untreated pigs before it can be spread onto arable land or before the manure is traded.".

Section 4.3 Environmental properties:
"Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms".

Section 5.5. Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products:
"Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as florfenicol may be dangerous for aquatic organisms (cyanobacteria), including groundwater organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable for the veterinary medicinal product concerned."

PBT assessment

PBT-assessment

Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	n.a. log Kow < 4 log Kow = 0.3	not B
Persistence	$DT_{50, soil, 12 °C}$	70.8d	not P
Toxicity	NOEC or CMR	$EC10_{algae}$ = 0.036 mg/l	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

B. Residues documentation

Residue tests

No residue depletion studies were conducted on the basis that bioequivalence with the reference product has been demonstrated.

Maximum Residue Limits

FLORFENICOL is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

FLORFENICOL						
Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Sum of florfenicol and its metabolites measured as florfenicol-amine	Bovine, ovine, caprine	200 µg/kg 3 000 µg/kg 300 µg/kg	Muscle Liver Kidney	Not for animals from which milk is produced for human consumption. Not for animals from which eggs are produced for human consumption	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009
	Porcine	300 µg/kg 500 µg/kg 2 000 µg/kg 500 µg/kg	Muscle Skin + Fat Liver Kidney			
	Poultry	100 µg/kg 200 µg/kg 2 500 µg/kg 750 µg/kg	Muscle Skin + Fat Liver Kidney			
	Fin fish	1 000 µg/kg	Muscle and skin in natural proportions			
	All other food producing species	100 µg/kg 200 µg/kg 2 000 µg/kg 300 µg/kg	Muscle Fat Liver Kidney			

Withdrawal Periods

Based on the data provided above, a withdrawal period of 20 days for meat and offal in pigs is justified.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a hybrid application according to Article 19 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been justified, efficacy studies are not required.

The efficacy claims for this VMP are equivalent to those of the reference VMP.

A. Pre-Clinical Studies

No pre-clinical studies were performed.

Pharmacology

An exemption from the need to conduct *in vivo* bioequivalence studies in the target species was accepted in accordance with section 7.1 of the CVMP Guideline on the conduct of bioequivalence studies.

Development of resistance and related risk in animals

The applicant has provided bibliographical information regarding the level of resistance in target pathogens which shows that the prevalence of resistance in target pathogens remains very low across the EU.

Warnings and precautions as listed on the product literature are adequate to ensure prudent and responsible use of the VMP.

Tolerance in the target species of animals

This application has been submitted in accordance with Article 19(1) of Regulation (EU) 2019/6) a so-called Hybrid application. The reference product is NUFLOR® Concentrate for Drinking Water for Pigs.
As bioequivalence is accepted and target animal safety (TAS) has been evaluated for the reference product, the applicant is not required to provide TAS data.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

B. Clinical trials

No clinical trials were performed.

As this is a hybrid application according to Article 19 of Regulation (EC) 2019/6, it is acceptable not to require clinical trials as the bioequivalence with the reference product is justified.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None