College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Amphen 200 mg/g granules for use in drinking water for pigs

NL/V/0264/001/DC

Created: March 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0264/001/DC
Name, strength and pharmaceutical form	Amphen 200 mg/ml granules for use in drinking water
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium
Active substance(s)	Florfenicol
ATC Vet code	QJ01BA90
Target species	Pigs
Indication for use	Treatment and metaphylaxis of swine respiratory disease associated with *Actinobacillus Pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol. The presence of the disease must be established in the group before metaphylactic treatment.

Amphen	NL/V/0264/001/DC
Huvepharma NV	DCP
	Publicly available assessment report

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25 September 2019
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FR, HU, IE, IT, LT, LV, PL, PT, RO, SI, SK, UK(NI)

I. SCIENTIFIC OVERVIEW

Amphen is a hybrid application according to Article 13(3) of Directive 2001/82/EC as amended. The reference product is Nuflor drinking water concentrate for swine, for which a marketing authorization was obtained by Intervet Nederland BV with marketing authorisation number REG NL 9949 on 18 April 2002. Amphen has a different strength and a different pharmaceutical form compared to the reference product.

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 florfenicol 200 mg/g granules and the excipients butylhydroxytoluene, disodium edetate, macrogols (4000 and 400), maltodextrin and polysorbate 80.

The container/closure system consists of 500 g and 1 kg block-bottom bags.

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 on three pilot batches have been presented in accordance with the relevant European guidelines. The applicant commits to provide process validation data on the first three full scale batches.

Amphen	NL/V/0264/001/DC
Huvepharma NV	DCP
	Publicly available assessment report

C. Control of Starting Materials

The active substance is florfenicol, an established active substance not 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 ASMF procedure has been followed.

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 when stored under the approved conditions.

The shelf life, in-use shelf life and shelf life of the medicated solutions are based on the studies provided in the dossier.

G. Other Information

Not applicable.

Amphen	NL/V/0264/001/DC
Huvepharma NV	DCP
	Publicly available assessment report

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a hybrid application according to Article 13, and bioequivalence with the reference product has been demonstrated, results of safety, toxicological and residue tests are not required.

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, the environment and consumers.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that Florfenicol is an antibiotic active against bacterial pathogens by inhibition of protein synthesis.
Florfenicol is quickly absorbed, extensively metabolised and rapidly eliminated, mainly in urine.

Toxicological Studies

No results of toxicological studies are required. However, relevant data were summarized derived from the EMA EPMAR of florfenicol, literature on excipients and information from a similar product, which show that:

The toxicity of this product will be determined by its active substance florfenicol. Excipients are of low toxicity. However, hypersensitive reactions cannot be excluded for macrogol and polysorbate 80; and butylhydroxytoluene and disodium edetate may be irritating to the skin or eyes. However, the latter two are present at very low concentrations in the product. Florfenicol is not acute toxic. After repeated exposure effects on haematological parameters and atrophy of testes was observed in rats and increased liver weights in dogs, with an established overall NOEL of 1 mg/kg bw/day. Moreover, florfenicol demonstrated adverse effects on the male reproductive system in a multi-generation study in rats with a NOEL of 1 mg/kg bw/day. Florfenicol shows no potential for embryo- or foetotoxicity. A toxicological ADI of 10 µg/kg bw/day was established by EMA. Florfenicol is not genotoxic and does not present a risk for inducing carcinogenicity. Florfenical has antimicrobial activity, however, for its metabolites the microbiological activity was considered negligible. A microbiological ADI of 3 µg/kg bw/day was established by EMA. Hypersensitivity reactions cannot be excluded for florfenicol. The product may be slightly irritating to the skin and/or eyes.

It is not expected that this product, waxy granules for use in drinking water, will be inhaled as over 99% of the particles are in the range of 125 to 2000 µm in diameter and these particles will settle in the nasopharyngeal region.
However, an acute inhalation study performed with an identical product demonstrated an LC_{50} of > 2.02 mg/L.

Amphen	NL/V/0264/001/DC
Huvepharma NV	DCP
	Publicly available assessment report

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that:

The tasks and situations that would lead to exposure to the product, which will be handled by professionals, are opening the product, transferring the product to a water tank and disposing the empty container or when the product is stored.

The main route of exposure will be dermal exposure. However, some ocular contact may also occur due to splashing or hand-to-eye contact. Oral ingestion due to hand-to-mouth contact is not expected if personal hygiene measures are maintained by the user. However, a sentence with respect to washing hands and not to eat, drink or smoke during handling the product is considered to be a helpful warning and safety measure. Inhalation is not expected due to the size of the particles in the product.

Oral ingestion by children is not expected as this product will be used in a professional setting. It is not expected that this product, waxy granules for use in drinking water, or its final application, dissolved in water, will be inhaled.

It is not expected that this product will easily penetrate the skin and result in significant systemic levels. Therefore, after dermal exposure, no systemic exposure is expected resulting in significant levels that would have adverse effects. In addition, the user is already recommended to wear gloves, which would mitigate the risk of dermal exposure.

The product may give hypersensitivity reactions due to presence of florfenicol, polysorbate 80 and polyethylene glycol. The product may be slightly irritating to the skin and/or eyes. Therefore, warnings should be in place and the user is recommended to wear personal protective equipment, especially gloves.

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

"This product may cause hypersensitivity reactions. If you have known hypersensitivity to florfenicol, polysorbate 80 or polyethylene glycol, avoid skin contact with this product. Wear protective gloves and clothing when handling and mixing this product. If you develop symptoms following exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician.

This product may be slightly irritating to the eyes and/or skin. Avoid contact with the skin and eyes, including hand-to-eye-contact. Wear safety glasses. In case of accidental spillage onto eyes, wash them immediately with water. In case of contact with the skin, wash immediately the affected area and take the contaminated clothes off.

This product may be harmful after ingestion. Do not smoke, eat or drink when handling the product or mixing the medicated drinking water."

Environmental Risk Assessment

The applicant provided a phase I environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required.

Amphen	NL/V/0264/001/DC
Huvepharma NV	DCP
	Publicly available assessment report

The assessment concluded that the prescribed use of florfenicol does not pose a risk to surface water and groundwater. A risk to the soil compartment, in particular to terrestrial plants, is indicated, and should be considered in the risk/benefit analysis.

Warnings regarding toxicity to soil are therefore required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Substance (common name): Florfenicol			
CAS-number: 73231-34-2			
Phase II, Tier A Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	960 mg/L	20°C
pKa	OECD 112	8.3	
UV-Visible Absorption Spectrum	OECD 101	225 nm	pH 1.1, 6.8 and 13
Melting Point/Melting Range	OECD 102	154-156 °C	
Vapour Pressure	OECD 104	1.6 x 10^{-9} Pa	20°C
n-Octanol/Water Partition Coefficient	OECD 107	0.5	pH 4
		0.4	pH 7
		0.3	pH 9.5
Soil Adsorption/Desorption	OECD 106	K_{oc} = 24.6	clay, pH 7.2, Corg 1.75%
		K_{oc} = 32.1	clay, pH 5.7, Corg 3.27%
		K_{oc} = 15.3	loam, pH 5.5, Corg 3.01%
		K_{oc} = 16.3	loamy sand, pH 3.1, Corg 5.96%
Soil Biodegradation	OECD 307	DT_{50} = 8.46 d dissipation half-live Transformation products > 10 %: florfenicol amine 47% Mineralisation 16% NER	sand, pH 5.1, Corg 0.81%
Manure Degradation		DT_{50} = <30 d including metabolites >10% and NER Transformation products > 10 %: detected but not identified 0% Mineralisation 22.1% NER	

Phase II, Tier A Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	EC50	6.71	mg/L	*Anabaena flos-aquae,*
Daphnia sp. imobilization	OECD 202	EC50	>800	mg/L	*Daphnia magna*
Fish,acute toxicity	OECD 203	LC50	>960	mg/L	*Onchorhynchus mykiss*
Nitrogen Transformation	OECD 216	>25% effect	1	mg/kg	after 28 days
Terrestrial plants	OECD 208	EC50, fresh weight	0.75	mg/kg	*Allium cepa*
	OECD 208	EC50, multiple endpoints	>5.00	mg/kg	*Avena sativa*
	OECD 208	EC50, fresh weight	0.25	mg/kg	*Brassica napus*
	OECD 208	EC50, fresh weight	1.87	mg/kg	*Cucumis sativus*
	OECD 208	EC50, dry weight	3.0	mg/kg	*Glycine max*
	OECD 208	EC50, fresh weight	13.81	mg/kg	*Helianthus annuus*
	OECD 208	EC50, dry weight	8.5	mg/kg	*Lollium perenne*
	OECD 208	EC50, fresh weight	2.59	mg/kg	*Phaseolus vulgaris*
	OECD 208	EC50, dry weight	8.5	mg/kg	*Raphanus sativus*
	OECD 208	EC50, fresh weight	0.32	mg/kg	*Sinapis alba*
	OECD 208	EC50, fresh weight	0.76	mg/kg	*Solanum lycopersicum*
	OECD 208	EC50, fresh weight	1.10	mg/kg	*Triticum aestivum*
	OECD 208	EC50, dry weight	8.4	mg/kg	*Zea mays*
Earthworm sub-acute/reproduction	OECD 220	NOEC	5.5	mg/kg	*Eisenia fetida*
Phase II, Tier B studies					
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	<25% effect	1	mg/kg	after 55 days
Terrestrial Plants, Growth Test	OECD 208	EC10, fresh weight	0.06	mg/kg	*Allium cepa*
	OECD 208	EC10, emergence	0.34	mg/kg	*Avena sativa*
	OECD 208	EC10, emergence	0.01	mg/kg	*Brassica napus*
	OECD 208	NOEC, fresh weight	0.37	mg/kg	*Cucumis sativus*
	OECD 208	NOEC, phytotoxicity	0.37	mg/kg	*Glycine max*
	OECD 208	EC10, fresh weight	0.73	mg/kg	*Helianthus annuus*
	OECD 208	NOEC , dry weight	3.3	mg/kg	*Lollium perenne*
	OECD 208	EC10, emergence	0.57	mg/kg	*Phaseolus vulgaris*
	OECD 208	NOEC, phytotoxicity	1.1	mg/kg	*Raphanus sativus*
	OECD 208	EC10, fresh weight	0.07	mg/kg	*Sinapis alba*
	OECD 208	EC10, growth	0.25	mg/kg	*Solanum lycopersicum*
	OECD 208	NOEC, fresh weight	0.12	mg/kg	*Triticum aestivum*
	OECD 208	NOEC, dry weight and phytotoxicity	1.1	mg/kg	*Zea mays*

Amphen	NL/V/0264/001/DC
Huvepharma NV	DCP
	Publicly available assessment report

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this is a hybrid application according to Article 13(3) of Directive 2001/82/EC as amended.

MRLs

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

	Porcine
Muscle	300 microgram/kg
Liver	2000 microgram/kg
Kidney	500 microgram/kg
Fat / skin	500 microgram/kg

Withdrawal Periods

Based on the bioequivalence with the reference product, a withdrawal period of 20 days for meat in pigs is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a hybrid 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, taking into account the Opinions regarding referral procedures for florfenicol containing products, excluding the use of florfenicol in preventative herd treatments.

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 Heads of Veterinary Medicines 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.

Summary of change	**Section updated**	**Approval date**
NL/V/0264/001/IB/001 Change of the product name from Huveflor to Amphen for several CMSs	SPC, labelling, package leaflet	23 April 2020
NL/V/0264/001/IB/002 Extension of the shelf life of the finished product as packaged for sale (supported by real time data)	SPC	30 March 2021
NL/V/0264/001/IB/003 Minor change to the restricted part of an Active Substance Master File	NA	22 October 2020
NL/V/0264/001/IB/004 Change of the product name from Huveflor to Amphen for all remaining CMSs	SPC, labelling, package leaflet	21 May 2021
NL/V/0264/001/IA/005 Change(s) in the Summary of Product Characteristics and Package Leaflet to implement the outcome of a procedure concerning PSUR	SPC, Package Leaflet	2 December 2021