Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Amphen, 200 mg/g Granules for Use in Drinking Water for Pigs
(Belgium, Bulgaria, Czech Republic, Estonia, France, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Slovakia, Slovenia, UK)

Colfen SP
(Denmark)

Colfen 200, 200 mg/g granules for use in drinking water for pigs
(Spain)

PuAR correct as of 26/02/2019 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0456/001/DC
Name, strength and pharmaceutical form	Amphen, 200 mg/g Granules for Use in Drinking Water for Pigs
Applicant	Huvepharma NV, Uitbreidingstraat 80, 2600 Antwerp, Belgium
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Pigs
Indication for use	For the treatment of swine respiratory disease associated with *Pasteurella multocida* susceptible to florfenicol.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	29th May 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Slovakia, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

Amphen 200 mg/g granules for use in drinking water for pigs contain florfenicol as the active substance. The application was submitted in accordance with Article 12.3 of Directive 2001/82/EC, as amended, for a full marketing authorisation.

The product is indicated for use in pigs to treat swine respiratory disease caused by bacteria susceptible to florfenicol, such as *Pasteurella multocida*. Amphen should only be used when the presence of the disease has been established and should be administered at a dose of 10 mg florfenicol/ kg bodyweight for 5 days. The product is contraindicated for use in boars intended for breeding and piglets less than 6 weeks old.

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[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 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

II. QUALITY ASPECTS

A. Composition

The product contains florfenicol as active substance and butylhydroxytoluene (E321), disodium edetate, macrogols (4000 and 400), maltodextrin and polysorbate 80 as excipients.

The container/closure system consists of 0.5 kg, 1 kg or 5 kg of granules packaged into polyester/ aluminium/ polyethylene laminate bags. 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. The product is manufactured by firstly weighing and mixing the solid materials and separately mixing the liquid materials. The solid and liquid materials are then mixed together to form the granules and, following a holding period, are packed into the bags.

C. Control of Starting Materials

The active substance is florfenicol, an established active substance not described in the European Pharmacopoeia (Ph. Eur). Data on the active substance is supplied in the form of an active substance master file (ASMF). 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.

All excipients comply with their respective Ph. Eur monographs. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

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

Not applicable.

F. 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. Tests include identification and assay of the active substance, assay of impurities, appearance and microbial purity.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites 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. A retest period of 3 years has been established.

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. A shelf life of 4 years for the finished product as packaged for sale is supported.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale: 4 years.
- Shelf life after first opening the immediate packaging: 3 months.
- Shelf life after dilution or reconstitution according to directions: 24 hours.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics
Florfenicol is an analogue of thiamphenicol and chloramphenicol which has potent wide spectrum antibacterial properties. Florfenicol inhibits microbial protein synthesis by binding to the 50S ribosomal subunit and preventing the

formation of peptide bonds between amino acids thus disrupting translation of bacterial mRNA.

Florfenicol has a bactericidal mode of action and is very active against Gram-negative bacteria and many anaerobic bacteria, demonstrated by MICs[2] of ≤ 1 µg/ml. Moderate activity has been observed against most Gram-positive bacteria, with MICs of 2 – 8 µg/ml. For *P. multocida* in swine respiratory disease MICs for florfenicol were determined as; susceptible: ≤ 2 µg/ml, intermediate: 4 µg/ml and resistant: ≥ 8 µg/ml.

Pharmacokinetics
Following oral administration to pigs, florfenicol is completely absorbed and extensively distributed. During administration of florfenicol for 5 consecutive days the mean plasma concentration was determined as 0.5 µg/ml and the mean terminal half life was 5.6 hours, whilst the mean AUC_{0-24}[3] was 44.7 µg·h/mL. The maximum plasma concentration was 3.92 µg/ml and occurred approximately 4 hours after administration. Florfenicol is mainly excreted, along with its metabolites, via the urine.

Toxicological Studies

The florfenicol toxicology database has been reviewed by the CVMP which established MRLs and studied toxicology data, deeming florfenicol to be a suitable substance to use in animals with an acceptable toxicity profile. On this basis, and as florfenicol is a well established substance, it is acceptable for the applicant not to submit toxicological studies.

Other Studies

The applicant has conducted additional studies looking at florfenicol as a skin sensitizer, dermal and ocular irritant as well as inhalation toxicity. Skin sensitization studies were performed on mice to measure the irritant potential of florfenicol. Significant lymphoproliferation was noted which validated the study; whilst no mortality, clinical signs or cutaneous reactions were observed thus the conclusion that florfenicol is not a skin sensitizer was formed.

Dermal and ocular irritation studies were performed on rabbits. A slight erythema was noted in all rabbits but had disappeared by day 4 at the latest and it was concluded florfenicol should not be classed as a skin irritant. The ocular irritant study involved administration of 100 mg florfenicol to the conjunctival sac of the left eye, whilst the untreated right eye served as control. The reactions observed included chemosis, slight reddening of the conjunctiva and clear discharge. The study concluded that florfenicol administered directly to the eye was slightly irritating but determined it could not be classed as an eye irritant.

The inhalation toxicity study exposed rats to an aerosol atmosphere produced from a formulation of florfenicol and distilled water. No mortality was observed and the adverse effects included laboured respiration, increased respiratory rate

[2] MIC – Minimum inhibitory concentration
[3] AUC – Area under the curve

and hunched posture but all the effects had disappeared within an hour after exposure. It was concluded that florfenicol is not toxic when inhaled.

Microbiological Studies

The applicant has not provided any data but refers to the CVMP MRL summary report.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which identified the main routes of exposure as dermal and ocular from handling the product and accidental splashes whilst mixing with drinking water and when cleaning water troughs after use. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- People with known hypersensitivity to florfenicol or any of the excipients should avoid contact with the veterinary medicinal product.
- Contact of the product or medicated drinking water with skin or eyes should be avoided.
- Personal protective equipment consisting of homologated protective gloves, coverall and safety glasses should be worn when handling and mixing the veterinary medicinal product.
- In case of accidental spillage onto eyes, wash them immediately with water. In case of contact with skin, wash immediately the affected area and take the contaminated clothes off.
- 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.
- Do not smoke, eat or drink when handling the product or mixing the medicated drinking water.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required, as the $PEC_{soil\ initial}$ is above the trigger value of 100µg/ kg. The Phase II assessment concluded that florfenicol, which will be introduced to the environment by the spreading of manure, is not expected to pose a risk to non-target organisms except certain plants. The calculated PEC values were acceptable and the product is unlikely to pose a risk to the environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed:

- Florfenicol degrades in pig manure and in soil and as such will not persist in the environment.

III.B Residues documentation

Residue Studies

Residue depletion studies using the final formulation have been conducted in pigs. Samples of tissues, kidneys, liver, loin muscle and abdominal skin and fat, were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period.

The analytical method used samples that had been minced and homogenised, filtering and liquid extraction were then performed and once dry the samples were re-dissolved in acid. Acid hydrolysis was necessary to convert florfenicol to florfenicol amine the marker residue. The method was fully validated.

MRLs

MRLs are listed below and the marker substance is the sum of florfenicol and its metabolites measured as florfenicol-amine.

Tissue	**MRL**
Muscle	300 µg/kg
Liver	2000 µg/kg
Kidney	500 µg/kg
Fat / skin	500 µg/kg

Withdrawal Periods

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

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
Florfenicol is an analogue of thiamphenicol and chloramphenicol which has potent wide spectrum antibacterial properties. Florfenicol inhibits microbial protein synthesis by binding to the 50S ribosomal subunit and preventing the formation of peptide bonds between amino acids thus disrupting translation of bacterial mRNA.

Florfenicol has a bactericidal mode of action and is very active against Gram-negative bacteria and many anaerobic bacteria, demonstrated by MICs[4] of ≤ 1

[4] MIC – Minimum inhibitory concentration

µg/ml. Moderate activity has been observed against most Gram-positive bacteria, with MICs of 2 – 8 µg/ml. For *P. multocida* in swine respiratory disease MICs for florfenicol were determined as; susceptible: ≤ 2 µg/ml, intermediate: 4 µg/ml and resistant: ≥ 8 µg/ml.

Pharmacokinetics

Following oral administration to pigs, florfenicol is completely absorbed and extensively distributed. During administration of florfenicol for 5 consecutive days the mean plasma concentration was determined as 0.5 µg/ml and the mean terminal half life was 5.6 hours, whilst the mean $AUC_{0\text{-}24}$[5] was 44.7 µg·h/mL. The maximum plasma concentration was 3.92 µg/ml and occurred approximately 4 hours after administration. Florfenicol is mainly excreted, along with its metabolites, via the urine.

Tolerance in the Target Species of Animals

The applicant has presented a controlled target animal tolerance study using multiples of the recommended dose in the target species. Water was used as a control. All doses were administered daily by oral gavage for two weeks.
Parameters evaluated were general health and clinical signs, including body condition, faecal consistency and behaviour. In addition blood and urine samples were analysed with gross pathology and histology performed on necropsy.

Minimal adverse effects were seen following doses up to five times the recommended dose. The most common side effect observed was diarrhoea whist some animals receiving five times the recommended dose had reduced food intake and exhibited depression towards the end of the treatment period.

Resistance

The information provided notes that florfenicol is a phenicol and only intended for use in veterinary medicine. Although not to be used in human medicines it is thought florfenicol could select for cross resistance to chloramphenicol. Several mechanisms of resistance have been identified for phenicols. These mechanisms include enzymes and florfenicol resistant genes. However despite the use of phenicols in animal medicine the resistance in the target pathogens is very low and there is no evidence to suggest there would be any increase in the rate of transfer of resistance between bacteria.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted dose determination and confirmation studies in the target species, pigs. An initial dose titration study compared the efficacy of 3 different doses of florfenicol in pigs which were challenged with *Pasteurella*

[5] AUC – Area under the curve

multocida. The results showed the higher doses of 10 mg/kg bodyweight and 15 mg/kg bodyweight administered once daily for five days were both effective in treatment of swine respiratory disease when compared with a 5 mg/kg bodyweight dose and a control group receiving no treatment. Dose confirmation and field studies using a dose of 10 mg/kg bodyweight were then performed and non-inferiority analysis was used to compare the test product to other products authorised with the same indication.

Dose confirmation studies:

Study title	**Dose Confirmation Study to evaluate the efficacy of a water soluble formulation of ALO230 at a dosage of 10.0 and 15.0 mg Florfenicol/kg BW in swine showing clinical signs of swine respiratory disease caused by bacterial pathogens including *Pasteurella multocida* in Europe.**
Objectives	To evaluate the efficacy of two different dose rates of florfenicol to treat naturally occurring swine respiratory disease.
Test site(s)	Multi-centre, commercial pig farms, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Group 1: Florfenicol was given at a dose rate of 10.0 mg/kg BW per day for five consecutive days. Group 2: Florfenicol was given at a dose rate of 15.0 mg/kg BW per day for five consecutive days.
Control product/placebo	A positive control group received Tilmicosin at a dose rate of 20 mg/kg BW per day for five consecutive days.
Animals	Female and castrated male commercial cross bred swine aged 8-14 weeks, weighing 6.7 – 73.5 kg and displaying signs of swine respiratory disease (SRD). Group 1: 171 animals Group 2: 192 animals Control: 172 animals
Outcomes/endpoints	The primary endpoint was defined as the percentage of animals that completed the study on day 14. The secondary endpoint was based on clinical signs.
Randomisation	Randomised.
Blinding	Blinded.
Method	On day 0 animals a number of animals displaying signs of acute pneumonia were euthanased for gross pathology, histology and bacteriology from each site to

	confirm the presence of respiratory disease. Animals included in the study received clinical observations once daily on day 1-13.
Statistical method	Primary efficacy criteria, including the number of animals completing the study, underwent non-inferiority statistical analysis. The results were analysed as a binary variable (1= completed, 0= did not complete) and 95% confidence interval constructed. Superiority analysis of the product to the control product was also performed on this data with a significance value of 5%. Secondary criteria were also measured and analysed using non-inferiority testing.
RESULTS	
Outcomes for endpoints	Per protocol non-inferiority analysis compared Groups 1 and 2 to the control group for the primary criteria. The results for both doses produced a critical value of 70.11 which was outside the 95% confidence limit thus showing non-inferiority of the test product compared to the control. Superiority analysis was also performed (p value = 0.0899) and no difference was shown. Per protocol testing for SRD relapse was also preformed. Non-inferiority analysis compared Group 1 and Group 2 with the control and in both cases the critical value was above the upper limit of 95% confidence interval. No mortalities as a result of SRD were observed during the study. No significant difference was seen in weight gain between the groups. Repeated measures analysis was performed on the daily body temperature data. Pairwise comparisons showed a statistically significant difference between Group 2 and the control ($p = 0.0014$) and between Group 2 and Group 1 ($p = 0.0030$). The treatment by time interaction showed a significant difference ($p<0.0001$) when Group 1 and Group 2 were compared with the control.
DISCUSSION	The study demonstrated the non-inferiority of the test product compared to the control product. The difference between the two dose rates of the test product was not found to be statistically significant. Based on this study it was concluded that a dose of 10 mg florfenicol/ kg bodyweight administered for five consecutive days is appropriate for treatment of swine respiratory disease.

Field Trials

Study title	**Evaluation of efficacy and safety of a water soluble formulation of ALO230 at a dosage of 10 mg Florfenicol/kg BW in swine showing clinical signs of swine respiratory disease caused by bacterial pathogens including *Pasteurella multocida* in Europe.**
Objectives	The aim of this study was to evaluate the efficacy and the safety of the test product for the treatment of pigs naturally infected with swine respiratory disease kept in commercial housing conditions in Europe.
Test site(s)	Multi-centre, commercial pig farms in EU countries.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Florfenicol administered via the drinking water at 10 mg/kg BW per day for 5 consecutive days.
Control product/placebo	Positive control: Tilmicosin administered via the drinking water at 20 mg/kg BW per day for 5 consecutive days.
Animals	Female and castrated male commercial cross bred swine, 5-11 weeks of age and weighing 4.5 – 42.8 kg. Displaying signs of swine respiratory disease (SRD). Test group: 180 animals Control group: 171 animals
Outcomes/endpoints	The primary endpoint was defined as the percentage of animals that completed the study on day 14. The secondary endpoint was based on clinical signs.
Randomisation	Randomised.
Blinding	Blinded.
Method	On day 0 animals a number of animals displaying signs of acute pneumonia were euthanased for gross pathology, histology and bacteriology from each site to confirm the presence of respiratory disease. Animals included in the study received clinical observations once daily on day 1-13.
Statistical method	Primary efficacy criteria, including the number of animals completing the study, underwent non-inferiority statistical analysis. The results were analysed as a binary variable (1= completed, 0= did not complete) and 95% confidence interval constructed. Secondary criteria were also measured and analysed using non-inferiority testing.
RESULTS	
Participant flow	177 pigs were randomly assigned to the test group and received the intended treatment. In this group 170 pigs completed the study. The control group was comprised of 167 randomly assigned pigs, each receiving the intended treatment, and 164 pigs completed the study.

	All animals that completed the study were included in analysis. During the study 11 animals were excluded after receiving concomitant treatments and 2 animals were excluded from the analysis of efficacy as their suitability for inclusion was not recorded.
Duration of follow-up	The animals were observed daily for 14 days. Treatment was administered for 5 consecutive days (D0-D4) and observations continued until D14.
Outcomes for endpoints	Per protocol non-inferiority analysis compared the test and control group. The critical value of 78.2 was found to be less than the lower confidence interval of 91.92, demonstrating non-inferiority of the test product. Analysis on the secondary criteria was also performed. The number of animals cured by day 5 was compared between the groups using non-inferiority analysis and the critical value (18.32) fell below the lower limit of the 95% confidence interval (59.96). A cure rate was determined and a t-test showed the test group had a cure rate significantly better than the control group ($p<0.0001$). Mortality due to bronchopneumonia occurred in one animal, from the test product group, and relapse occurred in one animal.
Adverse events	Data on adverse events were collected during the study. More adverse events were seen in the test group and than in the control group. The Fisher's exact test was performed and this difference was shown to be statistically significant ($p = 0.0086$). Diarrhoea was observed in all animals.
DISCUSSION	The study demonstrated non-inferiority of the test product compared to the control product, containing tilmicosin. A greater number of adverse events occurred in the test product group but the product was shown to reduce the clinical signs of swine respiratory disease.

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 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 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)