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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

FORCYL SWINE 160 MG/ML SOLUTION FOR INJECTION FOR PIGS

Date: 08/01/2013

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0220/002/DC
Name, strength and pharmaceutical form	FORCYL SWINE 160 MG/ML SOLUTION FOR INJECTION FOR PIGS
Applicant	VETOQUINOL SA MAGNY VERNOIS F-70200 LURE
Active substance(s)	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Pigs: fattening pigs and weaned piglets
Indication for use	In fattening pigs: Treatment of respiratory tract infections caused by susceptible strains of *Pasteurella multocida*. In weaned piglets: Treatment of intestinal infections caused by susceptible strains of *E. coli*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

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	27/06/2012
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, EE, EL, ES, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK

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.

II. QUALITY ASPECTS

A. Composition

The product contains 160 mg/ml marbofloxacin as the active substance and the excipients benzyl alcohol, glucono-delta-lactone and water for injection.

The container/closure system is a glass vial (50, 100 or 250 ml) with rubber closure. 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 marbofloxacin, an established 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

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.

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.

An in-use shelf-life of the finished product as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided MICs of marbofloxacin against target pathogens isolated in Europe.
Bacterial kinetics (static and dynamic models) against *P. multocida, and E. coli* were provided showing that marbofloxacin has a bactericidal concentration dependant activity against these pathogens.

The applicant has provided three pharmacokinetic studies in the target species after the administration of the product at the recommended dosage. The first one aimed at selecting one of the two 16 % formulations for further development and two subsequent studies with the final formulation respectively in growing pigs and weaned piglets.

The applicant has used two *in vitro* PK/PD models for digestive and respiratory infections respectively which reproduce marbofloxacin concentration pharmacokinetic profile after administration of the product in pigs at the recommended dosage in order to determine an optimal dosing regimen for efficacy and for limiting the development of resistance in target pathogens.

Toxicological Studies

The toxicological profile of marbofloxacin was assessed during the MRL regulation (the applicant was already Vetoquinol). It is included into table I of the MRL regulation for bovine and porcine.

Acute toxicity of marbofloxacin after oral and subcutaneous administration is low in rat and mouse. The mouse is the most sensitive laboratory species, and females appeared to be more sensitive to marbofloxacin than males.

The lowest NOEL from repeated dose toxicity studies is 4 mg/kg (from a 13-week study in rats and a 13-weeks study in dogs).

In dogs, effects of fluoroquinolone on articular cartilage were shown in young animals from 10 mg/kg. On rats, such lesions appeared at very high doses.

From a 2-generation study in rats, a NOEL for effect on the fertility of 10 mg/kg was retained. Lowest NOEL for maternoxic and foetotoxic NOEL were 10 and 30 mg/kg, respectively (from embryo/foetotoxicity study in rabbits). No teratogenic effects were reported from studies conducted in laboratory animals (rats and rabbits).

In cutaneous and ocular irritation studies conducted in rabbits, marbofloxacin appeared to be slightly irritant for intact and abraded skin and moderately irritant for eyes.

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 has provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

The product is not expected to pose a risk for the environment when used as recommended.

III.B Residues documentation

Residue Studies

The applicant has provided 2 studies performed after the administration of the tested product in the target species (fattening pigs and weaned piglets respectively).

The analytical method was fully validated.

MRLs

a. active substances

The active substance, marbofloxacin, is included in table 1 of the MRL regulation 470/2009, as follows:

Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
MARBOFLOXACIN		Bovine, porcine	150 µg/kg 50 µg/kg 150 µg/kg 150 µg/kg	Muscle Fat Liver Kidney	For porcine the fat MRL relates to "skin and fat in natural proportions	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009
		Bovine	75 µg/kg	Milk			

b. excipients

The MRL status of excipients of the product is indicated in the following table.

Excipient	MRL status	ADI
gluconolactone	Table 1, no MRL required	-
Benzyl alcohol	Table 1, no MRL required	5 mg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 9 days for meat in pigs is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant provided two specific tolerance studies, one in fattening pigs and the other in weaned piglets. From these studies, it can be concluded that the tolerance of the tested product after intramuscular administration at the recommended dose is good.
Local reactions at injection sites were observed and were reported in the section 4.6 of the SPC. Joint lesions were observed after a three days treatment at 24 mg/kg (three times the dose for three times the duration) and were reported in the section 4.10 of the SPC.

Resistance

Marbofloxacin resistance was well documented, in compliance with VICH topic GL27.
No significant evolution of the susceptibility pattern of target bacteria and food-borne bacteria to marbofloxacin was observed in Europe, except for *Campylobacter spp*.

Neither selection nor development of resistant pathogenic strains were induced in PK/PD testing or dynamic tests. During field studies, the bacterial ecosystem exposed to the antibiotic selective pressure were much more complex, including commensal as well as pathogenic bacteria, and emergence of marbofloxacin resistant *E. coli* and multi resistant strains of *P. multocida* were observed (possible dates of a return to original susceptibility were not fully investigated).

The usual warning as regards to resistance were stated in section 4.5i) of the SPC. Furthermore, the use of the product is contra-indicated as prophylaxis or metaphylaxis to prevent diarrhoea at weaning.

IV.B Clinical Studies

Laboratory Trials

Respiratory claim

The dynamic PK/PD testing with field bacteria corresponding to the MIC_{90} and plasmatic marbofloxacin concentrations in regards to the efficacy of the product and resistance of target pathogens following the use of the product has validated the therapeutic scheme for *P. multocida*.

Digestive claim

To select the final dose for the digestive claim, the applicant presented PK/PD studies and a dose determination study.
The PK/PD studies proposed by the applicant was questionable since surrogate values usually used in PK/PD analysis (AUIC (AUC/MIC) >125 or 250h and QI (Cmax/MIC) >8 or 10) are based on studies run with plasmatic data. Note that no PK/PD surrogate endpoints are validated for treatment of digestive infections with antibiotics.
The dose determination study demonstrated the efficacy of the treatment on the clinical endpoint “mortality rate”. Significant difference in total *E. coli* counts were observed in favour of one shot treatment regimen of 8 and 10 mg/kg compared to 4 mg/kg once and 4 mg for two consecutive days. All data were obtained on clinically affected animals, and thus the claim is limited to these animals only.

Field Trials

Respiratory claim

One multicentric comparative clinical study (versus NUFLOR) demonstrated the efficacy of the product in the treatment of respiratory tract infections due to *Pasteurella multocida* in fattening pigs.
The clinical trial was performed in compliance with all current regulations, guidance and guidelines. The study protocol was appropriately designed as regards the randomisation, blinding, number of cases, statistical analysis and endpoints (clinical and/or bacteriological). The test groups were comparable at inclusion.
The main efficacy criterion was the cure rate on D7. A pig was considered as cured if its rectal temperature was ≤ 39.5°C and if its global clinical score was null (or 1 only if sneezing or slight coughing), and if no alternative antibiotic treatment was administered before D7.
The percentage of cured animals on D7 was 68.4% in the tested product group and 72.1% in the comparator group. The non equivalence hypothesis H0 was rejected and the two products were considered as significantly ($p = 0.014$) equivalent in terms of cure rate.
An insufficient number of other porcine respiratory disease complex bacteria such as *Actinobacillus pleuropneumoniae* and *Haemophilus parasuis* were identified from the cases of this field trial for the product to be indicated for these pathogens.

Digestive claim

One multicentric comparative clinical study (versus ADVOCINE) demonstrated the efficacy of the product in the treatment intestinal infections due to *E. coli* in weaned piglets.
The clinical trial was performed in compliance with all current regulations, guidance and guidelines. The study protocol was appropriately designed as regards the randomisation, blinding, number of cases, statistical analysis and endpoints (clinical and/or bacteriological).
The percentage of clinical cure was 66.7 % in the tested group versus 62.8 % in the comparator group. The test groups were comparable at inclusion. The non equivalence hypothesis H0 was rejected and the two products were considered as significantly equivalent in terms of cure rate ($p<0.025$).

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.