MINISTERIO DE SANIDAD
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)

DECENTRALISED PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PIRETAMOL 300 mg/ml Oral Solution

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0126/001/DC
Name, strength and pharmaceutical form	PIRETAMOL, 300 mg/ml, oral solution
Applicant	GLOBAL VET HEALTH S.L. C/Capçanes, nº12 bajos Polígono Agro – Reus Reus 43206, ESPAÑA
Active substance(s)	Paracetamol
ATC Vet code	QN02BE01
Target species	Porcine (fattening pigs)
Indication for use	Symptomatic treatment of fever in fattening pigs

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MODULE 2

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23/03/2011
Date product first authorised in the Reference Member State (MRP only)	
Concerned Member States for original procedure	BE, BG, DE, DK, EL,FR, HU, IT, NL, PL, PT, RO, 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 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 300 mg/ml paracetamol as active substance and benzyl alcohol (E-

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1519), azorubine (E-122), macrogol 300, dimethylacetamide, saccharin sodium and purified water as excipients.

The container/closure system is an opaque and white high density polyethylene 5 litres barrel, sealed by induction and green high density polyethylene screw-on cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are 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 paracetamol, an established active 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.

The suitability of the Ph.Eur monograph for controlling this active substance is confirmed with a copy of the current CEP.

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

The tests performed during production are described and the results of 3 consecutive runs,

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conforming to the specifications, are provided.

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.

The claim of three months stability after opening the container is based on the demonstration of stability for a batch opened and stored 3 months at in-use storage conditions.

The claim of 24 hours stability after incorporation into drinking water is based on the demonstration of stability in accordance with applicable European guidelines.

H. Genetically Modified Organisms

No applicable.

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

The marketing authorisation application of a veterinary medicine use is submitted in accordance with the article 12(3) of Directive 2001/82/EC (amended by article 12(3) of Directive 2004/28/EC) by means a decentralised procedure. Paracetamol is considered a known active substance with a recognized effectiveness and an acceptable level of safety for the proposed indications in the target species (growings pigs) using the proposed route of administration (oral administered via drinking water) and dosage regimen (30 mg/kg/d).

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III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that Paracetamol or acetaminophen acts by inhibition of endogen pyrogen agents in pigs in the hypothalamic centers of temperature regulation. It is a weak inhibitor of COX-1 synthesis; therefore it has not side effects at gastrointestinal level, neither on platelet aggregation.

The applicant has provided data which show that bioavailability was 81% reaching a maximum concentration (C_{max}) of 10,41 mg/l at 2 hours (T_{max}) later. Paracetamol is extensively and rapidly metabolized. It is rapidly excreted ($t_{1/2}$: 2,23 h).

Toxicological Studies

The applicant has provided bibliographical data which show relevant acute and chronic toxicity, reproductive, mutagenicity and carcinogenicity.

- Single Dose Toxicity:

Route / Specie	DL_{50}	Effect
Oral / mouse	400 to 900 mg/kg bw	Hepatotoxicity and nephrotoxicity
Oral / rat, rabbit, guinea pig	>2000 mg/kg bw	Hepatotoxicity and nephrotoxicity
Oral / dog	500 mg/kg bw	Methaemoglobinaemia
Oral / cat	50 mg/kg bw	Methaemoglobinaemia

- Repeated Dose Toxicity
  NOEL: 400 mg/kg bw/day (males mice) and 800 mg/kg bw/day (females rats), for 13 weeks, oral route.

- Reproductive Toxicity, including Teratogenicity: In mice, reductions in fertility were seen in the F0 generation and foetal survival was significantly reduced at all tested dose levels.

- Mutagenicity: Paracetamol and its metabolite did not cause gene mutations in bacteria in a series of Salmonella microsomal assay.

- Carcinogenicity (if necessary): recent studies in the rat and mouse found no evidence of carcinogenicity.

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Other Studies

The applicant has provided bibliographical data which show that effects on the renal function, inhibition of the production of antibodies, ocular effects, cytotoxic effects, autoprotection in paracetamol intoxication, and protection against paracetamol hepatotoxicity.

Observations in Humans

The applicant has provided bibliographical data which show that paracetamol is widely used in human medicine, paracetamol is usually well tolerated, paracetamol increases the action of antidiuretic hormone and paracetamol is indicated for use during pregnancy.

Studies on Metabolites, Impurities, Other Substances and Formulation.

The applicant has provided bibliographical data regarding metabolite which shows that the iminoquinone metabolite of acetaminophen, N-acetyl-p-benzoquinoneimine (NAPQI), inhibits both the isomerase and the biological activities of MIF (cytokine macrophage migration inhibitory factor).

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline on User Safety for Pharmaceutical Veterinary Medical Products EMEA/CVMP/543/03-FINAL.

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

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that the use of the medicinal product Piretamol as recommended in the SPC will not pose a risk to the environment. No warnings are therefore required.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because the referenced residue study from the EMEA Summary Report has been conducted in accordance with Volume VI of the Rules governing Medicinal Products in the European Community in order to be evaluated by the CVMP and use it as reference in the Summary Report, and that the test article used for the study is representative of the commercial formulation based on a set of premises.

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MRLs

Paracetamol is listed in Council Regulation 470/2010 and in accordance with Comission Regulation (EU) No 37/2010 Paracetamol is not required MRL as showed below:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions According to article 14(7) of regulation (EC) No 470/2009	Therapeutic classification
Paracetamol	Not applicable	Porcine	No MRL required	Not applicable	For oral use only	Not entry

Withdrawal Periods

Based on the data provided above, a withdrawal period of 1 day for meat in porcine is justified.

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IV. CLINICAL ASSESSMENT (EFFICACY)

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IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology

The applicant has provided bibliographical data to show that Paracetamol or acetaminophen is only a weak inhibitor of cyclooxygenase which implies the low antiinflamatory effects, has antipyretic effects and analgesic properties which differ from the nonsteroidal anti-inflammatory drugs and acetaminophen protects the gastric mucous membrane increasing the synthesis of prostaglandin of the mucous.

Tolerance in the Target Species of Animals

The applicant has conducted two controlled target animal tolerance studies in compliance with the relevant guideline.

Parameters evaluated were initial and final weight, water intake, feed intake, daily weight gain, animals general state and behaviour, digestive disturbance, blood biochemistry, haematology and histopathological study of the liver, kidneys, the stomach and duodenum.

No adverse effects were seen following the tested doses and treatment regimes. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Field Trials

The applicant has conducted a field study which shows that Piretamol can be considered as effective for the symptomatic treatment of fever in growing pigs.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance

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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.

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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

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