ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Suispirin, 1000 mg/g Oral Powder for Pigs

PuAR correct as of 07/06/2018 when RMS was transferred to HU.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0364/001/DC
Name, strength and pharmaceutical form	Suispirin 1000 mg/g Oral Powder for Pigs
Applicant	aniMedica GmbH Im Südfeld 48303 Senden-Bösensell Germany
Active substance(s)	Acetylsalicylic acid
ATC Vetcode	QN02BA01
Target species	Pigs
Indication for use	Supportive treatment for reduction of pyrexia in combination with, appropriate anti-infective therapy, if necessary.

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	Decentralised procedure application in accordance with Article 13 (a) for well-established use, of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28th September 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Portugal, Romania.

I. SCIENTIFIC OVERVIEW

This application was for a well-established use product for use in pigs, containing 1000 mg/g acetylsalicylic acid, for supportive treatment for the reduction of pyrexia in combination with appropriate anti-infective therapy, if necessary. The product is intended for use as a top dressing, for individual pigs, where only a small number of pigs are required to receive treatment. The dose is 30 mg acetylsalicylic acid (30 mg of product) per kg bodyweight, twice daily, for three consecutive days. The minimum bodyweight of pigs to be treated is 11 kg, and the product is mixed with approximately 50 g or 200 g (depending on bodyweight), of the normal dry pelleted feed of the pig, following which, normal feed may be offered. Animals should be isolated from other pigs for treatment. The product is not to be used in a dry hopper or semi-liquid feeder.

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 acetylsalicylic acid. There are no excipients in the product. The container system consists of either 1 x 100 g powder or 10 x 100 g powder filled into sachets consisting of paper/polyethylene/aluminium/polyethylene foil. Polystyrene scoops of 0.4 ml and 3 ml are attached. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence 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. The method of preparation is simply a filling and packaging procedure, and therefore process validation data on the product were not required. In-process controls consist of weighing procedures.

C. Control of Starting Materials

The active substance is acetylsalicylic acid, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice, in accordance with a Certificate of Suitability.

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

Declarations have been provided, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 sites have been provided demonstrating compliance with the specification. Analyses consist of appearance, filling mass and identification, assay, microbial quality, moisture content and purity of the active substance.

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. The active substance re-test period was defined in the Certificate of Suitability.

Stability data for the finished product were provided. Three batches of product were filled into 1 kg and 5 kg containers. Samples were tested against the finished product specifications. 36 months data were available for samples stored at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. No significant changes occurred over the testing periods. A 5 year shelf-life was justified.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 5 years.
Shelf-life after first opening the immediate packaging: 6 months.
Shelf-life after addition to the feed according to directions: 15 hours.

III. SAFETY AND RESIDUES ASSESSMENT

III.A Safety Testing

Pharmacological Studies

The applicant provided data on the pharmacodynamic effects of the active substance, with bibliographical data provided for the pharmacokinetic aspects.

Pharmacodynamics

Salicylic acid is formed after the hydrolysis of the active substance, and the effects of the metabolite arise from the inhibition of cyclo-oxygenase and the synthesis of prostanoids from archidonic acid. The end result of several related actions inhibit platelet aggregation and prolongs bleeding time.

Data from a series of studies provided information on the dose-related effects of acetylsalicylic acid, with 10 mg/person for humans, cited as a pharmacological LOEL.[2]

Common side effects related to the use of acetylsalicylic acid are effects on the gastric mucosa, vomiting nausea and gastric ulceration. For veterinary medicines, overdose symptoms are acid-base abnormalities, seizures, coma and death. As the active substance readily crosses the placenta, use in pregnancy is not permitted. With 80-90% of salicylate being plasma-bound, there is the potential for competitive inhibition, and relevant drug/drug interactions are to be avoided.

Pharmacokinetics

A report was presented citing a single oral administration of a commercial premix containing 50 mg acetylsalicylic acid/kg bodyweight to pigs. The absorption half-life was 0.9 hours, and lag time 0.2 hours. After 3.9 hours, a C_{max}[3] of 64 µg/ml was seen, with an elimination half-life of 4.2 hours. By 24 hours, the concentration was below the limit of detection, (0.08 µg/ml).

A further report described that in humans, there is rapid absorption of salicylates, mainly from the upper intestine. C_{max} is reached in approximately one hour and the plasma half-life is about 15 minutes. Salicylic acid may be absorbed through the skin, with detrimental effect.

Post-absorbtion, salicylates are distributed throughout the majority of tissues and fluids. The majority of bound salicylate drops as plasma concentrations increase. A portion of acetylsalicylic acid enters the systemic circulation as salicylic acid.

Qualitative metabolism is similar in all mammalian species and involves the hydrolysis of the parent compound in particular in liver and plasma to salicylic acid, which is then converted to further metabolites. Salicylates are excreted in the urine.

A pharmacokinetic study was conducted in a suitable number of pigs, using the final formula of Suisprin 1000 mg/g Oral Powder for Pigs. The dose was 30 mg/kg acetylsalicylic acid twice daily, for a period of three days. Blood samples were taken at various time points. No significant accumulation of the active substance was observed.

Toxicological Studies

The applicant has provided bibliographical data which show that the product is safe for use in the target species when used as directed.

- Single Dose Toxicity

[2] LOEL – Lowest observed effect level.
[3] C_{max} – Maximum plasma concentration of the active substance.

In one report, the LD_{50} values in mice and rats for acetylsalicylic acid DL-lysine ranged from 2200 to 2600 mg/kg via the oral route. Clinical symptoms of toxicity were non-specific.

A further report described an acute toxicity study in rats, in which doses from 0 to 2 g/kg of the active substance were administered. A number of adverse clinical signs were noted, and the LD_{50}[4] value of acetylsalicylic acid, as given in this case was 0.92 ± 0.045 g/kg bodyweight.

- Repeated Dose Toxicity

In a repeated dose toxicity study in dogs, acetylsalicylic acid DL-lysine and sodium acetylsalicylate were administered at doses between 0 and 500 mg/kg/bodyweight/day. Adverse effects and mortality were noted, particularly at the higher dose levels. A similar study was conducted in rats, and adverse clinical effects seen at the higher dose levels. No NOEL was established for these studies.

- Reproductive Toxicity, including Teratogenicity

Inhibition of ovulation was observed in rabbits in two studies. In a third study in a variety of species, high levels of acetylsylacylic acid gave rise to stillborns in dogs and resorption in rats and mice, with acetylsylacylic acid at a concentration of 500 to 1200 mg/kg bodyweight. A further study in rhesus monkeys given 40 mg/kg bodyweight produced no ill effects.

In a further study delay of onset of labour and duration of labour were noted in rats. The NOEL was noted as being 80 mg/kg/day. Further studies supported the occurrence of abnormal effects in rabbits and rats with regard to maternotoxicity/foetotoxicity/teratogenicity, with, in one study the NOEL for rats and dogs being accepted as 30 mg sodium salicylate/kg/ for teratogenicity.

- Mutagenicity

Positive results were only reported for one assay out of several, (bibliographic reference), for an *in vitro* metaphase analysis in rat bone marrow. There was no evidence of chromosomal damage in humans given the active substance for one month.

- Carcinogenicity

Studies provided for this section generally reported a lowering of the effects of carcinogenesis when acetylsalicylic acid were given to rats. However, one study showed that 0.5% acetylsalicylate given for 12 weeks in the diet after initiation with a bladder cancer cause an increase in bladder carcinomas.

[4] LD_{50} – The median lethal dose.

Other Studies

The applicant has provided bibliographical data which discussed the possible effects of the active substance with regard to the gastro-intestinal tract, eye irritation, and use in pregnancy and sensitisation. The SPC carries suitable warnings.

Observations in Humans

The applicant has provided bibliographical data which describe the known effects of exposure to acetylsalicylic acid in humans.

Gastrointestinal

Clinical symptoms related to the adverse effects of salicylate in humans are: vomiting, abdominal pain, and occasional haematemesis. A series of separate, controlled studies, with the active substance taken at 75 mg and/or 300 mg were presented, outlining the effect of the active substance in humans. Common symptoms were peptic ulcer and gastric bleeding. It was concluded that taking 75 mg per day carried only a small, measurable risk.

Liver

Hepatic damage due to acetylsalicylic acid in humans is related to blood concentration and dose, with patients having rheumatic disease appearing more vulnerable. Children have a higher incidence of acetylsalicylic acid-related events. Although there may be a risk of severe hepatic injury, these occurrences are rare. Symptoms of acetylsalicylic acid effects are normally reversible after cessation of drug administration.

Reye's Syndrome

Reye's syndrome has been observed, normally in children suffering from viral infections. The effects are linked to concentration of the active substance. The occurrence of Reye's syndrome is unlikely to be caused by the minute amounts that may be present in food residues, or following the handling of the product.

Cancer

There is no data suggesting that tumour promotion will be instigated when the product is used as directed.

Pregnancy and breastfeeding

Some effects have been noted when the active substance is administered during pregnancy and breast-feeding in humans.

Hearing

Gradually increasing doses of the active substance in volunteer patients with rheumatoid arthritis produced tinnitus which lasted for approximately five minutes.

Hypoglycaemia

Overdose with salicylates in children have caused hypoglycaemic deaths, and daily use of the active substance in a rheumatoid arthritis patient caused hypoglycaemia.

User Safety

The applicant concluded that the most likely routes of accidental self-administration are via the oral and dermal routes. Hypersensitivity to the product is also a possibility, the SPC therefore carries the following warnings:-

- Do not eat, drink or smoke whilst using this product.
- Contact via the skin or mucous membranes of the user must be avoided due to the risk of sensitisation.
- If you know that you are allergic to aspirin, avoid contact with this product.
- Use suitable protective clothing when using this product, such as gloves and a face mask.
- Wash hands and all exposed skin after use.

Ecotoxicity

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

III.B Residues documentation

The applicant conducted a residue depletion study in accordance with good laboratory practice standards. Rapid elimination and no bioaccumulation of the active substance were demonstrated, including a study using the product. High levels of analytes were demonstrated after administration, but these fell one day later. Therefore, the withdrawal period was set at one day for meat and offal.

Withdrawal Periods

Based on the data provided above, a withdrawal period of one day for meat and offal was justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Acetylsalicylic acid acts via the non-selective inhibition of cyclooxygenases. The therapeutic effects are antipyrexia, anti-inflammatory, analgesia and anti-haemostasis. An additional therapeutic effect is the prolongation of bleeding time The modification of prostaglandin production provides treatment for hypersensitivity reactions and protection in a number of species against anaphylactic shock caused by endotoxins. Interactions with other active substances are cited in the SPC.

A GLP[5]-compliant dose determination study was provided, examining the therapeutic effect of three doses of Suispirin 1000 mg/g Oral Powder for Pigs in endotoxin-challenged pigs, in addition to data from published literature. For the randomised, placebo-controlled study, a suitable number of pigs were divided into four groups, given a single dose of 0, 6, 18 or 54 mg/kg of Suispirin 1000 mg/g Oral Powder for Pigs, and then given 6 ug/kg endotoxin via injection into an ear vein, two hours later. Clinical examinations took place at various time points. Efficacy was demonstrated, and all three doses were well-tolerated. No adverse events attributable to the use of the product were seen.

Pharamcokinetics

A non-blinded GLP-compliant study was conducted which investigated the use of Suispirin 1000 mg/g Oral Powder for Pigs after repeated oral administration via feed or drinking water. A suitable number of pigs were divided into groups, and given either medicated feed or water at 30 mg/kg over twelve hours. Clinical examinations were made at various time points. It was concluded that the product was more efficacious when given in feed as opposed to drinking water.

Tolerance in the Target Species of Animals

A randomised, blinded, placebo-controlled GLP-compliant study analysed the use of Suispirin 1000 mg/g Oral Powder for Pigs acid as given to pigs after repeated administration via water or feed, with regard to target animal safety. A suitable number of animals were divided into four groups. Three treatment groups received Suispirin 1000 mg/g Oral Powder for Pigs at 30 mg/kg in water or feed for three days, over twelve hours or every twelve hours or 90 mg/kg every twelve hours, in feed for three days. No adverse effects due to treatment were observed.

[5] GLP – Good Laboratory Practice.

IV.B Clinical Studies

The applicant conducted a GCP[6]-compliant, blinded, randomised study to analyse the clinical efficacy of Suispirin 1000 mg/g Oral Powder for Pigs when administered via feed, in order to assess the efficacy of the product under field conditions. A large number of animals, diagnosed as suffering from a febrile condition, were divided into two groups. They received either Suispirin 1000 mg/g Oral Powder for Pigs, or a placebo. The dose was 30 mg product, every twelve hours for three days. Clinical examinations were performed at various time points. Animals were provided with antibiotic therapy when this was deemed necessary. No adverse effects due to treatment were seen.

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.

[6] GCP – Good Clinical Practice.

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)