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agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ZINTESTIN 1000 mg/g Premix for medicated feeding stuff for pigs

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0191/001/MR
Name, strength and pharmaceutical form	ZINTESTIN 1000 mg/g Premix for medicated feeding stuff for pigs
Applicant	Vetpharma Animal Health, S.L. C/ Les Corts, 23 08028 Barcelona Spain
Active substance(s)	Zinc Oxide
ATC Vet code	ATC Vet Code : QA07XA91
Target species	Pigs (piglets)
Indication for use	<u>Piglets</u> : Prevention of post weaning diarrhoea.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition	Day 90: 25-07-2012
Date product first authorised in the Reference Member State (MRP only)	15-11-2004
Concerned Member States for original procedure	IT, PT

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range:

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 zinc oxide as unique component. No excipients have been added to the formulation. It was considered suitable due to the nature of the active substance.

The medicinal product is packaged into bags of 25 kg with paper valve and the following four layers:

- Semi-extensible Kraft paper (inner layer)
- High-density polyethylene sheet (intermediate layer)
- Semi-extensible Kraft paper (intermediate layer)
- Semi-extensible white Kraft paper (outer layer)

The particulars of the containers and controls performed are provided and conform to the regulation.

The suitability of the medicinal product for the proposed use has been satisfactorily proven according to the *Note for Guidance on Additional Quality Requirements for Products Intended for Incorporation into Animal Feedingstuffs (Medicated Premixes)* EMEA/CVMP/080/95-FINAL.

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 manufacturing process consists simply on the weighting and packing of the raw material into 25 kg bags and its labelling under GMP conditions. A flow chart of the process is included and the equipment used is mentioned.

C. Control of Starting Materials

The zinc oxide used as active substance in this product fulfils the requirements of the current monograph of the Ph. Eur. (0252). The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

The zinc oxide is supplied by one manufacturer and its quality is documented by means of ASMF.

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 specifications and methods employed to control the finished product are the same than those stated for the active substance (single component), except by the addition of a weight test.

Once demonstrated in Part 2.C that the only component of the product fully complies with the requirements of Ph. Eur. and being the manufacture merely a packaging process, the specifications fixed for the finished product have been deemed enough to adequately control the quality of the product. The absence of additional tests has been justified by experimental results.

A validation study of the assay method has been included in this section.

Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specifications.

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 (2 years) when stored under the approved conditions.

No in-use stability studies have been carried out and the advertence of “immediate use” has been stated in section 6.3 of the SPC.

Stability of the medicated feed in normal use up to 3 months has been documented in Part 2.A.4.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

This application is submitted in accordance with Article 12(3) of Directive 2001/82 and amendments as a known active substance.

The veterinary medicinal product ZINTESTIN is a premix for medicated feeding stuff with zinc oxide as active substance and with no excipients added to the formulation.

The product is indicated for the prevention of post weaning diarrhoea in piglets.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that the mechanism of action of zinc oxide in diarrhoea prevention is not precisely known. Several theories could explain this effect of zinc oxide. Zinc may act on the stability of the intestinal microflora, maintaining the diversity of coliform organisms and preventing the proliferation of opportunistic pathogenic microorganisms without having a clear antibacterial effect.

The applicant has also provided bibliographical data which show that the administration of zinc oxide produces high concentrations of zinc in plasma, liver and kidneys. Zinc is excreted mainly in faeces and in less proportion in urine. There is a homeostatic regulatory mechanism of zinc in the intestine that allows the re-absorption of the zinc excreted to the lumen.

Toxicological Studies

The applicant has provided bibliographical data which show that zinc oxide has low toxicity when administered orally, it is not teratogenic and it has no mutagenic or carcinogenic potential.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product poses an acceptable risk for users.

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 product in the target specie as recommended in the SPC will not 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 indicated.

III.B Residues documentation

Residue Studies

A residue depletion study using the final formulation has been conducted in the target specie. Samples of muscle, liver, kidney and skin plus fat were taken from animals at several time points.

The analytical method used was an atomic absorption method. The method was fully validated.

No MRLs neither ADI for zinc oxide have been published. The withdrawal period is calculated by means of the calculation of the daily intake that is compared to the human zinc requirements.

Withdrawal Periods

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

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology

The applicant has provided bibliographical data to show that:

It is known that, Piglet weaning has always been one of the most difficult stages of pig production because the post weaning scours and decrease in feed uptake. This environment and diet changes are stressful factors for piglets that may cause an instability and diversity decrease of the enteric microflora causing subsequently scours caused by *E.coli* strains.

ZnO feed supplementation reduces *E.coli* proliferation and dissemination from the small intestine, suggesting the possibility of a stabilizing action on the intestinal flora by maintaining the diversity of coliform bacteria and indirectly improving feed digestion. *The action is exerted on the enterocyte membrane.*

In some way, zinc oxide should prevent contact between bacteria and intestinal epithelial cells, due it has be seen that bacteria are excreted in exactly the same way even though the animal does not suffer any digestive pathology.

Zinc bioavailability depends on the administration source. In pigs, zinc bioavailability in the ZnO form is low, around 20%.

Zinc intestinal absorption is reduced when there is some metallic ions in the feed, such as Copper, calcium and Cadmiun.

Tolerance in the Target Species of Animals

Oral Tolerance to high doses of Zinc (around 1000 ppm and above) has been tested in other Zinc compounds, as lactate, sulphate or carbonate, exhibiting a higher toxicity than ZnO compound.

Although there are numerous literature references showing the absence of adverse effects administrating the recommended dose, the applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species according to VICH 43 guideline. A placebo was administrated as a control group. The tested product administered with the medicated feed at dose of 85 mg of zinc/kg b.w./day during 14 consecutive days to one group (1X), at a dose 3 times the recommended one to another group (3X) (255 mg of zinc/kg b.w./day during 14 consecutive days) and at the recommended dose level but with double the time (28 days) to the remaining group. The study was carried out in piglets, the target specie of the veterinary medicinal product.

Clinical, haematological, biochemical parameters were evaluated, as well as necropsies were carried out.

Results shows that no clinical, biochemical or necropsy findings were found with respect to controls at any level of dose. Only was found slight adverse effects consisting of a white-yellowish colour of faeces that subsides when treatment is withdrawn, and this issue is advised in SPC.

Product literature accurately reflects type and incidence of adverse effects which might be expected.

Resistance

Not applicable.

IV.B Clinical Studies

Field Trials

The applicant has provided bibliographical data which support that the inclusion of ZnO at a rate of 2500 ppm in feed

As appropriate, include brief description of specific studies including date and location, whether multicentre, blinded, controlled, inclusion criteria, no. of animals, pivotal criteria, degree of significance, outcome, conclusions

Several studies support that the inclusion of ZnO at a rate of 2500 ppm in feed, reduced de incidence in post weaning diarrhoea and improved growth performance, having a beneficial effect on the stability of intestinal flora and on the composition of coliforms.

A proprietary field study is submitted which Objective was to Evaluate if the administration of ZINC OXIDE PREMIX (ZINTESTIN) at a dose of 2500 ppm of zinc via feed to weaned piglets was effective in reducing diarrhoea.

A double-blind, randomised, controlled clinical proprietary field study was carried out in parallel design to assess the efficacy in postweaning scours using a placebo group -feed without treatment- (Treatment Group 1) and a treated group (Treatment Group 2).

The Criteria for efficacy assessment were morbidity, faecal consistency and colour of the faeces scores. E coli identification and cuantification was carried out,

Results

The statistical analysis of the data obtained in the study demonstrated the efficacy of the product in reducing the number of piglets affected by diarrhoea, based on morbidity, faecal consistency and colour of the faeces scores.

The results obtained in this study demonstrate that the premix ZINC OXIDE PREMIX (ZINTESTIN) administered at a pharmacological dose of 2500 ppm during 14 days to recently weaned piglets is capable of controlling and treating diarrhoea in piglets at weaning.

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 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