

Agencia Española de Medicamentos y Productos Sanitarios

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Edificio 8
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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

APSAMIX ZINC 1000 mg/g

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0128/001/MR
Name, strength and pharmaceutical form	APSAMIX ZINC 1000 mg/g medicated premix for pigs
Applicant	ANDRÉS PINTALUBA S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana, nº 5 43206 Reus (Tarragona) SPAIN
Active substance(s)	Zinc Oxide
ATC Vet code	QA07XA91
Target species	Pigs (piglets)
Indication for use	Piglets: Prevention of the 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 procedure	Day 90: 28/05/2008
Date product first authorised in the Reference Member State (MRP only)	28/03/2005
Concerned Member States for original procedure	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. The Applicant justifies this decision in the basis of the Directive 2004/28/CE and the Queries from Industry VRMF/121/99-FINAL.

The product is packaged in bags of 25 Kg with the following layers:

1. White calendered kraft paper outer sheet
2. Intermediate kraft paper sheet
3. Inner sheet of kraft paper
4. Neutral coloured low-density polyethylene bag 150 µm thick.

The containers are closed first by heat-sealing and then sewn and bordered along the top. The particulars of the containers and controls performed are provided and conform to the regulation.

Part II.A.4 demonstrates the suitability of the product when mixed with feed at the proposed rate. Several studies have been performed by the applicant according to the EMEA/CVMP/080/95 Guideline "Additional Quality Requirements for Product Intended for Incorporation into Animal Feeding Stuffs".

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.

C. Control of Starting Materials

The active substance is Zinc Oxide, 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 quality of the active ingredient is documented via Drug Master File

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 (pharmaceuticals)

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 36-months shelf life when stored under the approved conditions.

Stability test were performed to justify the 4-week shelf-life after first opening of the 25-kg bags.

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

H. Genetically Modified Organisms

Not applicable

J. Other Information

Not applicable

III. SAFETY AND RESIDUES ASSESSMENT

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that zinc active acts by stabilization intestinal microflora maintaining the diversity of coliforms and minimizing the growth of “opportunistic” pathogen microorganisms.

The applicant has also provided bibliographical data which show that zinc oxide seems to present low absorption in the gastrointestinal tract in swine. It is principally absorbed in the small intestine. It is transported in the blood circulation bound to plasmatic proteins, principally the albumin (approximately 80%). It is distributed in the tissues. The liver is the main organ involved in its metabolism. Due to the bioavailability of zinc oxide, a high percentage of the zinc given is not absorbed and is excreted in faeces.

Toxicological Studies

The applicant has provided bibliographical data which show that the toxicity of zinc is low and uncommon. The acute toxicity of orally administered zinc depends on the salt form in which it is found.

There are no data showing that zinc oxide has either mutagenic or carcinogenic potential. Neither have effects on the reproductive function or teratogenic effects been described

- Single Dose Toxicity
DL50 (oral, mice)= 7950 mg/kg
DL50 (oral, rats)> 5000 mg/kg
- Repeated Dose Toxicity
Lowest published toxic dose= 17431 mg/kg in rats for 90 consecutive days after oral administration. Effects: motor activity disorders.
- Reproductive Toxicity, including Teratogenicity:
Lowest published toxic dose= 6846 mg/kg/oral in rats, from day 1-22 of pregnancy → specific development abnormalities (homeostasis), death of neonates, disorders on growth parameters of neonates. Zinc and its salts are not teratogenic in laboratory animals and have no effect on reproductive parameters.
- Mutagenicity
Zinc is not mutagenic according to the results of different tests performed on bacterial and mammal cells.
- Carcinogenicity (if necessary):
There is no convincing evidence that an excess of zinc plays an aetiological role in carcinogenesis in humans. Zinc is neither genotoxic nor teratogenic.

Other Studies (if relevant – or delete)

The applicant has provided bibliographical data which show that zinc has a positive effect on both the immune response to pathogens and on the prevention of disease and that zinc oxide is not classified as sensitising to the skin.

Observations in Humans

The applicant has provided bibliographical data which show that zinc is an essential nutrient. It is necessary for the growth and it is related to different physiological functions. Zinc deficiency gives rise to serious health problems in humans.

Microbiological Studies (if relevant – or delete)

The treatment with zinc oxide, which acts in the digestive tract thanks to its low bioavailability, helps to maintain the stability of the intestinal flora of weaned pigs and thus protects the flora which could otherwise be lost on weaning. It also maintains a great diversity of coliform bacteria which can compete for colonisation with pathogenic strains which produce diarrhoea.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk of inhalation and dermal exposure for the user of APSAMIX ZINC 1000 mg/g, qualifies as a globally acceptable. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant carried out an environmental risk assessment according to the current guidelines. The Phase I Assessment showed that PEC_{soil} is $>100 \mu g/kg$, Therefore, a Phase II assessment was conducted.

The environmental risk evaluation assessment allows to conclude that all the evaluated tolerances are fulfilled (with the exception of the previsibly long permanence on zinc oxide in the soil due to its high stability and its very low aqueous solubility). Consequently, it is inferred that there is no necessity of carrying on with the corresponding environmental risk evaluation.

Due the fact that the zinc may tend to accumulate in the ground, a monitoring assessment was required by the “Spanish Agency of medicinal products”, to study the environmental impact derived from soil application of manure of from animals treated with medicated feeds based on zinc oxide. The study will last for 5 years. The study shows that zinc content in soils is completely normal. In principle, zinc content in groundwater can also be seen as normal.

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

Residue Studies

The applicant has conducted a residue depletion study using the final formulation which show that there is an increase in zinc concentrations during the treatment phase, largely in the kidney and liver, whereas the concentrations in muscle and skin+fat remain at levels close to those of the control animals. In the liver, the concentrations were 4-6 times higher than those found in the kidney.

The analytical method was inductively coupled plasma atomic emission spectrometry (ICP-AES). The method was fully validated.

MRLs

Zinc oxide is listed in Annex II of Council Regulation 2377/90.

Withdrawal Periods

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

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The mechanism of action of zinc oxide is poorly understood; several authors suggest the possibility of a stabilization action on the intestinal flora by maintaining the diversity of coliform bacteria and indirectly improving feed digestion (Ref. 23).

On the basis of expert's experience, the most valid theories on zinc oxide's mechanism of action would be those that propose that the decrease in diarrhoea is caused by the substance's action on the enterocyte membrane. In some way, zinc oxide must prevent contact between bacteria and intestinal epithelial cells, as we have seen that the bacteria are excreted in exactly the same way even though the animal does not suffer any digestive pathology

Tolerance in the Target Species of Animals

The applicant has performed an experimental study of the general tolerance of APSAMIX ZINC 1000 mg/g medicated premix, in order to assess the possible adverse reactions and determine the safety margin of the product.

This study was performed in accordance with GLP.

The purpose of this study was to analyse the possible adverse reactions of this active substance by studying the performance and the health of the animals. Administration of the premix at 6200 ppm for 28 days (twice the dose and twice the administration period) in group 3 led to significant differences in the animals regarding production and health parameters, with abnormal results in the analyses.

It is concluded from the study that treatment 2 with a dose of 3100 ppm of the 100% zinc oxide premix for 14 or 28 days did not have any statistically significant adverse effects on the production parameters, state of health or blood and urine parameters.

Resistance

On the basis of the experience, there are no known cases of bacterial resistance to zinc oxide. In a study performed by Danish researchers (Holm et al. in 1996) in commercial conditions, zinc oxide was shown to be effective after 10 years of use in the field at high doses (Ref. 1).

It can be inferred from this article and the experience acquired in Spain that zinc oxide does not cause bacterial resistance. It is considered that zinc oxide, when given at the dose proposed, may provide an alternative to antibiotics (when accompanied by improved hygiene and biosafety) and, by extension, a solution for the phenomenon of bacterial resistance.

IV.B Clinical Studies

Laboratory Trials

The efficacy part of the registration dossier for APSAMIX ZINC 1000 mg/g summarises a series of efficacy studies performed by several authors that show the positive effects on the growth, feed intake and incidence of digestive disorders in weaned piglets. We consider that the literature available provides sufficient proof of the product's efficacy.

The geographical location is a problem in these cases because there are no efficacy studies performed in Spain in the literature. The availability of such studies would be very helpful.

Field Trials

The study was carried out at the farm run by Ganado Porcino de Selección in Urda (Toledo). 600 healthy, 21-day-old piglets were chosen randomly and randomized into two groups taking into account the weight. These groups were a Control (C) group and a Treatment (Z) group which received 3100 ppm of 100% zinc oxide in the diet (ZINCOTEC ZINC OXIDE, registered product in the United Kingdom, Vm authorisation no. 03941/4000, and holder of an exceptional marketing authorisation in Spain from 1 August 2003 to December 2004).

The feeds used were manufactured by Nutral S.A. in Colmenar Viejo. The animals had access to water and feed *ad libitum*. The following parameters were monitored during the study: live weight at baseline and after 14 days, overall feed consumption during the growth stage and daily incidence of diarrhoea in the pens.

The study shows very clear, statistically significant differences between the zinc oxide group and the control group. The differences between the two treatments are clear and substantial. All of the differences are greater than 20% for production parameters and the proportion of animals with diarrhoea at the end of the study is 42% for the Control group and less than 1% in the Zincotec group.

Therefore, it can be concluded that the product Zincotec, at the dose of 3100 mg ZnO/kg live weight, is effective in preventing post-weaning diarrhoea in piglets aged between 21 and 35 days

A further study was carried out: **“Evaluation of the efficacy of APSAMIX ZINC (Zinc Oxide) administered orally in the feed for the prevention of post-weaning diarrhoea in piglets”**. Its main objective was to evaluate the efficacy evaluation of APSAMIX ZINC (Zinc Oxide) administered at 100 mg of Zinc Oxide/kg bodyweight per day, during 14 days in the feed, compared to ZINCOTRAX administered at 100 mg of Zinc Oxide/kg bodyweight per day, during 14 days to prevent post-weaning diarrhoea in piglets.

The study was designed according to the Guideline 81/852/EEC (modified by the guideline 199/104/EC) and the Good Clinical Practices approved by the CVMP.

The trial was unicentered and randomized field, in order to demonstrate the “NON INFERIORITY” of the experimental product in the control group.

Three weeks old weaned piglets were used for the study. The initial bodyweight was 6 kg, approximately. The feed was distributed *ad libitum*, like drinking water. The study included 100 animals by treatment (at least 4 pens), a total of 200 (at least 8 pens).

The primary endpoints comprised the variables: faeces consistency, appearance and weight loss.

The non-inferiority (equivalence in the success proportion on day 14) of the experimental product (APSAMIX ZINC 1000 mg/g) versus the control product (ZINCOTRAX) was demonstrated as a preventive treatment of diarrhoea in weaned piglets

No significant differences between groups were detected in the secondary endpoints (weight, consumption and conversion rate). Only a slight difference ($p < 0.05$) in the daily mean gain was detected.

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).