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productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A
VETERINARY MEDICINAL PRODUCT**

OXIDO DE ZINC CALIER

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V0138/001/MR
Name, strength and pharmaceutical form	OXIDO DE ZINC CALIER premix for medicated feeding stuff for pigs
Applicant	LABORATORIOS CALIER, S.A. Barcelonés, 26 (Pla del Ramassà) 08520-Les Franqueses del Vallés Barcelona (SPAIN)
Active substance(s)	Zinc Oxide
ATC Vet code	QA07XA91
Target species	Pigs (piglets) between 1 week and 11 weeks of age
Indication for use	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 procedure	Day 90: 01/10/2008
Date product first authorised in the Reference Member State (MRP only)	15/11/2004
Concerned Member States for original procedure	IT

I. SCIENTIFIC OVERVIEW

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

This veterinary medicinal product does not contain any excipient. Therefore, the manufacturing process consists simply in the packed into 25 kg bags of this raw material and its labelling under GMP's conditions. The equipment used is mentioned. The product is 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. Semi-extensible Kraft
2. High density polyethylene sheet
3. Semi-extensible Kraft
4. Semi-extensible White

Bags contain a valve, glued, plane, with hexagonal bottom (UNE-EN ISO 8351-1). The quality of the valves is also described in the dossier.

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 manufacturing process consists simply in the packed into 25 kg bags of the raw material and its labelling under GMP's conditions. The equipment used is mentioned.

C. *Control of Starting Materials*

The Zinc Oxide used as active substance in this product complies with specifications of European Pharmacopoeia 2005:1680. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Being supplied by two manufacturers, its quality is documented:

- With a Drug Master File in the case of the manufacturer Ferro Ind. Químicas
- By means of a complete Part II C in the case of the manufacturer Hebei Quingyuan Fine Oxide Plant

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*

The active ingredients used in the manufacture of this product agree with the Directive 81/851/EC, corrected by the Directive 99/104/EC. They are not considered as dangerous according to the guideline EMEA/410/01.

E. *Control on intermediate products*

Not applicable.

F. Control Tests on the Finished Product

The specifications are the same as stated by the active ingredient, being it the only component. Just a control of weight has been included.

As the premix consists entirely of European Pharmacopoeia grade ZnO, the methods used to determine the active substance in the finished product do not vary from those described for the starting material. Quantitative determination of Zinc Oxide in the premix has been validated, and data are presented in the dossier to show its linearity, accuracy and precision.

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. The applicant establishes a re-test period for this active substance of 2 years.

The proposal of a 24-month shelf-life for the product is documented by the Applicant with the submission of long-term stability data of several batches covering all the proposed period, and accelerated stability data up to 6 months.

No stability tests were performed to determine the shelf-life after first opening of the 25-kg bags. Therefore, an instruction of immediate use when open has been included in the texts.

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 (PHARMACOTOXICOLOGICAL)

This application is submitted in accordance with the article 12(3) in Directive 2001/82/EC amended by Directive 2004/28/ as a known active substance.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that the action mechanism of Zinc Oxide is not yet known. Zinc is involved with the activity of several metalloenzims. It also takes part in the metabolism of nucleic acids, proteins, glucides, etc.

Zinc oxide is indicated for the prevention of diarrhoea caused by *E.coli* after the weaning. Its action is because Zinc ions has an inhibitory activity on the breathing chain of *E.coli*, on succinate oxidase and on NADH oxidase.

The proposed administration of Zinc Oxide produces high concentrations of Zinc in plasma, liver and kidney. Zinc is mainly eliminated via faeces and in minor portion via urine. There is a homeostatic regulation mechanism of Zinc in the intestine that allows its reabsorption once it has been excreted into the gut lumen.

Toxicological Studies

The applicant has provided bibliographical data which show that the toxicity of zinc is low and uncommon.

- Single Dose Toxicity

Animal	Administration	LD ₅₀
Rat	Intraperitoneal	240 mg/kg
Rat	Oral	>8437 mg/kg
Rat	Intratracheal	>4979 µg/kg
Mice	Oral	7950 mg/kg
Mice	inhalation	2500 mg/m ³

- Repeated Dose Toxicity

OXIDO DE ZINC CALIER is not expected to cause any kind of toxicity during its long-term oral administration, as the recommended posology and period of administration are far from the chronic toxicity values described in the literature.

- Reproductive Toxicity, including Teratogenicity:

The applicant submits reproductive, embryotoxicity and teratogenicity bibliographic data in rats and pigs which show that Zinc is not teratogenic and generally has no effect on the reproductive performance of treated animals.

The target species of this veterinary drug are piglets, so it should not be used during pregnancy or lactation.

- Mutagenicity and carcinogenicity:

The literature reviewed shows that zinc has no mutagenic and carcinogenic potential. The applicant has not conducted additional studies about genotoxicity and carcinogenicity, but it is not considered necessary taking into account the information included in the dossier.

Other studies

The applicant has provided bibliographical data which show that immunological effect of zinc is not yet established, however a direct relation between the nutritional state of zinc and immune response capacity seems to exist.

Observations in Humans

The applicant has provided bibliographical information which shows that Zinc is an essential nutrient. Zinc deficiency gives rise to serious health problems in humans. Adverse reactions: Ingestion of zinc as an element can cause lethargy. If large quantities are ingested this can cause stomach cramps, nausea and vomiting. It has also been described that Zinc ingestion could interfere in the use of copper and iron and have an adverse effect on cholesterol levels.

User Safety

The applicant has provided a user safety assessment which shows that the risk of inhalation and dermal exposure for the user of OXIDO DE ZINC CALIER is qualified 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 provided an environmental risk assessment in compliance with the relevant guideline. The assessment concluded that because of Zinc accumulates in the soil and it can, from certain concentrations, affect the flora and fauna, some precautions must be taken in the use of manure coming from treated piglets: biological treatment of the excrement in purifying plants and implementation of risk management measures. 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

A residue depletion study using the final formulation has been conducted in piglets. Samples of muscle, liver, Kidney and fat + skin were taken from animals at several time points (5, 10, 15 and 20 days). Zn levels at 5 days in the tissues were similar to the basal levels of non treated animals.

The zinc oxide content was determined using flame atomic absorption spectrophotometry (air-acetylene). This method was fully validated.

MRLs

Zinc oxide is listed in Annex II of Council Regulation 2377/90. The marker substance is zinc oxide.

Pharmacologically active substances	Animal species
Zinc oxide	All food producing species

Withdrawal Periods

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

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 product under test was administered with the medicated feed at a dose of 85 mg of zinc/kg b.w./day during 14 consecutive days to one of the groups, at a dose 3 times the recommended one to another group (255 mg of zinc/kg b.w./day during 14 consecutive days) and at the recommended dose but with double the time (28 days) to the remaining group.

After studying the safety margin of the specialty for veterinary use ZINC OXIDE in the form of a medicinal premix supplied by Laboratorios Calier, S.A., it has been observed that the administration of the specialty through the feed to recently weaned pigs at a dose of 85 mg/kg b.w./day during 14 days, of 85 mg/kg b.w./day during 28 days and at a dose of 225 mg/kg b.w./day during 14 days, does not provoke any type of alteration in the behaviour or in the general condition of the animals.

Resistance

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 OXIDO ZINC CALIER 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.

Field Trials

-Objective of the study:

Evaluate if the administration of ZINC OXIDE Calier VETERINARY USE at a dose of 2500 ppm of zinc via feed to weaned piglets is capable of reducing diarrhoea.

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.

The morbidity, observed as animals with diarrhoea, was less in the group treated with zinc oxide when compared with the control group. This decrease in the number of cases of post-weaning diarrhoea has been observed in various studies where zinc oxide was administered at a dose of 2500 to 3000 ppm during two weeks after weaning (Holm and Poulsen, 1996; Taylor, 1999; Thomson, 2001; Melin and Wallgren, 2002). Likewise, other authors indicate that the administration of high concentrations of zinc in the diet in the form of zinc oxide decreases the incidence of non-specific diarrhoea at post-weaning (Poulsen, 1995).

The improvement in the registers of faecal consistency has also been demonstrated in other studies (Mc Cully et al 1995) when the pigs were treated with 3000 ppm of zinc oxide.

The colour of the faeces was an index where a higher score was observed (diarrhoeic faeces) in the pigs of the control group. These results coincide with another study where the colour of the faeces was evaluated; observing that the group treated with zinc oxide had better faecal colour parameters than the control group (Hill HM et al 2000).

With regard to the consumption of feed, these results coincide with other studies (Smith et al, 1997) where no differences were observed in the ingestion of food of the control group and the group treated with zinc oxide from day 0 to day 14 of the study. In spite of the fact that, in our case, the animals of the untreated group were heavier than the treated group at the beginning of the study, there were no differences at the end of the study either, which was due to the fact that the animals of the untreated group consumed less food because of the severity of the digestive pathology observed in the animals.

It has not been possible to demonstrate a significant increase in the weight gains of the animals treated with zinc oxide during the first week post-weaning, although some authors (Mc Cully et al, 1995) have observed that the dose of 3000 ppm in the form of zinc oxide significantly stimulates the growth of the treated piglets.

In a study carried out (Hahn and Baker, 1993) no differences of food conversion between the control group and the group medicated with zinc oxide were observed.

The results of our study revealed that the E. coli count diminished in all the study pigs at a level of 10^6 , although the difference observed was not significant. This coincides with other studies where they did not find significant differences in the number of faecal coliforms between the control group and the group treated with zinc oxide (Jensen-Waern et al, 1998; Katouli et al, 1999), although they did observe that zinc oxide had a prophylactic effect on the development of post-weaning diarrhoea.



The results obtained in this study demonstrate that the premix ZINC OXIDE CALIER VETERINARY USE 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