Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Gutal 1000 mg/g Premix for Medicated Feeding Stuff for Piglets

Date Created: February 2016

PuAR correct as of 20/12/2018 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0501/001/DC
Name, strength and pharmaceutical form	Gutal 1000 mg/g Premix for Medicated Feeding Stuff for Piglets
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Anwerp Belgium
Active substance(s)	Zinc oxide
ATC Vetcode	QA07XA91
Target species	Weaned piglets
Indication for use	For the prevention of post-weaning diarrhoea.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	27 October 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

Gutal 1000 mg/g Premix has been developed as a generic of ZincoTec – Zinc Oxide 100% Premix for Medicated Feeding Stuff. The reference product was first authorised in the UK in July 1990. A biowaiver was granted in accordance with Section 7.1d) of the guideline EMA/CVMP/016/00-Rev.2. Due to the essential similarity of the product with the reference product exemption from *in vivo* studies was permitted and bioequivalence could be assumed. The product is authorised for incorporation into dry feed at a registered feed mill and indicated for the treatment and control of diarrhoea in weaned piglets.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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 [2] 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.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITIATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains zinc oxide as active substance and no excipients. The container/closure system consists of 5 kg and 20 kg multi-ply paper bags with an internal polyethylene bag. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of filling the bags with either 5 kg or 20 kg of the active substance. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is zinc oxide an established active substance described in the European Pharmacopoeia (Ph. Eur.). Data on the active substance have been presented in an Active Substance Master File (ASMF). 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.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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. Control tests on the finished product include those for identification and

assay of the active substance, identification of impurities, appearance, solubility and alkalinity.

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.

II.F. 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. A retest period of 4 years has been established,

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. Data were provided for batches stored at 25ºC/60%RH and 30ºC/65%RH for 24 months, and for batches stored at 40°C/75%RH for 6 months.

In-use stability studies have also been performed. Data were provided for opened bags stored at 25°C/60%RH for 6 months. Data were also provided following in-feed mixing. Following mixing, samples of feed were stored at 25°C/60%RH for 3 months and at 40°C/75%RH for 4 weeks.

G. Other Information

Shelf life
Shelf life of the finished product as packaged for sale is 2 years.
Shelf life after first opening the immediate packaging is 6 months.
Shelf life after incorporation into meal or pelleted feed is 3 months.

Special precautions for storage
The veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of pharmacological studies are not required. Exemption from *in vivo* studies has been granted as the product is identical to the reference product, therefore bioequivalence can be assumed.

Toxicological Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of toxicological studies are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which identified the main routes of exposure as dermal exposure, inhalation or accidental ingestion of the premix or of medicated feed. The risk to the user is low as the premix will only be handled at feed mills by professionals, and on farm the product will be in a diluted form. As the product is essentially similar to the reference product the risk to the end user is considered the same. The same warnings and precautions as listed on the reference product are on the product literature and are adequate to ensure safety to users of the product.

- Use in a well ventilated area. Avoid inhalation of the product while preparing the medicated feed. Wear either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143 when mixing or handling the feed.
- Avoid contact with the eyes by wearing protective goggles or safety glasses. In case of accidental eye contact, irrigate thoroughly with large quantities of water.
- Avoid contact with the skin by wearing protective clothing including impermeable gloves. In case of accidental skin contact wash the exposed skin with soap and water.
- Contaminated clothing should be removed and washed before being reused.
- In case of accidental ingestion, drink plenty of water and seek medical attention.
- Wash hands after use.

Environmental Safety

An Environmental Risk Assessment (ERA) consisting of both a Phase I and Phase II assessment has been provided. The assessment was performed in accordance with VICH and CVMP guidelines. The compound is an inorganic molecule and outside the scope of the VICH and CVMP guidelines, which have been designed primarily for assessing the risks from organic compounds. Therefore, an alternative method was used for the Phase II assessment based on models developed for European assessments, such as a recent EFSA[3] study.

[3] EFSA – European Food Safety Authority

Phase I:
The product will be used to treat groups of piglets and the main route of exposure to the environment will be the spreading of manure from treated animals onto agricultural land. The initial predicted environmental concentration (PEC) in soil was calculated to be 6690 µg/kg. As this is greater than 100 µg/kg a Phase II ERA was required.

Phase II Tier A:
A Phase II tier A data set was established using the Intermediate Dynamic Model for Metals (IDMM). The model has been developed to allow calculation of long term metal accumulation in, and leaching from, topsoil. Metal behaviour and fate in the environment is very complex and there are some uncertainties associated with the use of the IDMM; such as the potential effects of hydrology, dissolved organic carbon and metal aging. Despite the uncertainties, the information provided in support of the validation of IDMM is sufficient to give confidence that the model can be used to achieve a pragmatic assessment of the risk to the environment. Furthermore, the IDMM has been taken into consideration for the EFSA assessment for zinc.

Zinc is an inorganic molecule making it non-volatile and non-degradable. Continual application of manure from treated pigs to land will result in the accumulation of zinc in environmental compartments over time.

PEC values for soil, surface water and sediment were calculated using the IDMM for a number of different FOCUS and VetCalc model scenarios. The dose and duration of treatment were taken from the proposed SPC of the product and considered manure application rates of up to 8.2 kg zinc ha^{-1} y^{-1}; based on implementation, or not, of legal manure application rates and risk mitigation measures.

To assess the risk to each compartment, PECs for zinc in soil, surface water and sediment were compared to associated PNECs for each FOCUS and VetCalc scenario. It was assumed manure from treated animals was applied continually (up until 2020, 2040 and 2060) at four different application rates (Table 1):

- Hypothetical worst case level, not considering legal manure restrictions, of 8.2 kg zinc ha^{-1} y^{-1}
- Practical worst case level of 7.2 kg zinc ha^{-1} y^{-1}
- Actual worst case level considering an application of 170 kg N ha^{-1} y^{-1} and taking into account actual farming practices of 3.3 kg zinc ha^{-1} y^{-1}
- Actual worst case level considering application of 150 kg N ha^{-1} $y^{-1}$and taking into account actual farming practices of 2.8 kg zinc ha^{-1} y^{-1}

Time point		2020				2040				2060			
Zn application rate (kg ha^{-1} y^{-1})		**2.8**	**3.3**	**7.2**	**8.2**	**2.8**	**3.3**	**7.2**	**8.2**	**2.8**	**3.3**	**7.2**	**8.2**
Environmental compartment	**Soil (n=19) Range (RQs >1)**	0.19 – 0.69 (0)	0.22 – 0.74 (0)	0.36 – 1.13 (1)	0.39 – 1.23 (1)	0.19 – 0.70 (0)	0.23 – 0.77 (0)	0.48 – 1.33 (1)	0.51 – 1.47 (3)	0.25 – 0.87 (0)	0.28 – 0.94 (0)	0.55 – 1.51 (4)	0.61 – 1.66 (5)
	Surface water (n=15) Range (RQs >1)	0.11 – 1.87 (2)	0.11 – 2.19 (2)	0.12 – 4.76 (2)	0.13 – 5.42 (3)	0.12 – 2.16 (2)	0.12 – 2.51 (2)	0.13 – 5.32 (5)	0.14 – 5.86 (5)	0.13 – 3.4 (2)	0.13 – 3.76 (2)	0.14 – 6.54 (5)	0.14 – 7.25 (5)
	Sediment (n=15) Range (RQs >1)	1.10 – 5.79 (15)	1.21 – 6.00 (15)	2.10 – 7.63 (15)	2.32 – 8.05 (15)	1.37 – 5.97 (15)	1.51 – 6.23 (15)	2.62 – 8.29 (15)	2.90 – 8.81 (15)	1.64 – 6.16 (15)	1.81 – 6.48 (15)	3.14 – 8.94 (15)	3.48 – 9.57 (15)

Table 1. Extrapolated RQs for soils, surface waters and sediments for VetCalc and FOCUS scenarios; with range (min. to max.) of RQs and number of scenarios with RQ >1(bracketed).

The assessment concluded that, following continual application of manure from treated pigs to land, zinc will accumulate in all environmental compartments either immediately (sediment) or delayed (soil, ground-, and surface waters). Zinc is persistent in soils and may accumulate in sediments; therefore it will only be a matter of time for PNECs to be exceeded. The greatest risks were identified to free draining, acidic (pH ≤6), sandy soils and aquatic organisms. Zinc is toxic to aquatic organisms, but may also affect the growth, survival and reproduction in aquatic and terrestrial plants and animals.

Risk mitigation measures (RMMs) have been implemented to reduce the risk to the environment through using this product. The following RMMs are included on the SPC and product literature:

- When spreading manure from treated animals, the maximum total zinc load as defined in national or local regulations has to be strictly respected. Undiluted manure from treated piglets should not be applied to land. Dilution with manure from treated animals or sows is required so that the total amount of treated piglet manure is as low as possible and is never exceeding 40%, the ratio when manure of weaned piglets and sows is stored together. The product should not be used on farms where mixing of manure from treated animals with manure of non-treated animals is not possible.
- The bioavailability of zinc, and therefore the environmental risk, varies between soil types. Manure from treated piglets should not be spread on vulnerable soil types, which have been identified as freely draining, acidic (pH ≤6), sandy soils.
- Manure containing zinc should not be spread on the same area of land in successive years to avoid accumulation of zinc which may cause adverse effects in the environment.

- When spreading manure from treated animals, the minimum distance to surface water as defined in the national or local regulations has to be strictly respected, and at least a minimum buffer zone of 3m applied, because the manure contains zinc which may cause adverse effects in the aquatic environment.

III.B.2 Residues documentation

Residue Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of residues studies are not required.

MRLs

Zinc oxide is listed in Table 1 of Regulation 37/2010 with the statement that the active substance is approved for all food producing species with no MRL required.

Withdrawal Periods

The withdrawal period is the same as for the reference product.
Meat and offal: 28 days

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of pharmacological studies are not required. Exemption from in vivo studies has been granted as the product is identical to the reference product, therefore bioequivalence can be assumed.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of tolerance studies are not required.

Resistance

Information was provided on bacterial resistance to zinc. The information showed that resistance to zinc is conferred by bacterial cation efflux channel-tunnels. There is evidence that zinc resistance genes can be located on the

same mobile elements as antibiotic resistance genes and this could contribute to the emergence of resistance strains. Adequate warnings and precautions appear on the product literature, as well information on the resistance mechanism.

IV.II. Clinical Documentation

As this is a generic application according to Article 13 (1) of Directive 2001/81/EC as amended, and bioequivalence with a reference product has been established the results of clinical studies are not required.

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 of the product(s) is favourable

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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 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)