Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, route of administration, applicant in the Member States

Member State (EU/EEA)	Applicant	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Belgium	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Bulgaria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Cyprus	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Czech Republic	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Denmark	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.

Member State (EU/EEA)	Applicant	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Estonia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
France	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Germany	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Greece	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Hungary	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Ireland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.

Member State (EU/EEA)	Applicant	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Latvia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Lithuania	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Luxembourg	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Malta	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
The Netherlands	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.

Member State (EU/EEA)	Applicant	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Portugal	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Romania	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Slovakia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Slovenia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.
Spain	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.

Member State (EU/EEA)	Applicant	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Gutal 1000 g/kg premix for medicated feeding stuff for piglets	Zinc oxide	1000 g/kg	Premix for medicated feeding stuff	Piglet (weaned piglets)	For incorporation into dry feed at the registered mill. Oral use only.

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisation for Gutal 1000 g/kg premix for medicated feeding stuff for piglets

Overall summary of the scientific evaluation of Gutal 1000 g/kg premix for medicated feeding stuff for piglets (*see Annex I*)

1. Introduction

Gutal 1000 g/kg premix for medicated feeding stuff for piglets (thereafter called 'Gutal') contains zinc oxide as an active substance. Studies have shown zinc oxide to be beneficial in piglets at risk of developing mild to moderate diarrhoea. The proposed indication for Gutal is for the prevention of post-weaning diarrhoea in piglets.

The applicant Huvepharma NV submitted a marketing authorisation application, via the decentralised procedure, for Gutal according to Article 13(1) Directive 2001/82/EC, referring to the reference product ZincoTec Zinc Oxide 100% Premix for Medicated Feeding Stuff authorised in the United Kingdom. The marketing authorisation application was submitted to the United Kingdom as reference Member State and Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia and Spain as concerned Member States.

Risks were identified during the decentralised procedure by Belgium, France and the Netherlands who considered that the marketing authorisation of Gutal may present a potential serious risk to the environment and that the risk mitigation measures (RMMs) proposed to control the risk are inadequate to control or prevent continuous zinc accumulation and, in addition, they are not feasible to implement to all pig farms. These issues remained unresolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMD(v)) was started. During the CMD(v) procedure Belgium concluded that a marketing authorisation for Gutal can be granted provided that RMMs are included in the product information. Since the issues raised by France and the Netherlands remained unresolved, the Member States concerned failed to reach an agreement regarding the product and consequently the matter was referred to the CVMP on 30 September 2014 under Article 33(4) of Directive 2001/82/EC.

The CVMP was asked to give its opinion on the concerns raised by France and the Netherlands and to conclude on the benefit-risk balance for Gutal.

2. Assessment of the data submitted

In this procedure, the CVMP was asked to consider if the use of Gutal, a veterinary medicinal product that contains zinc oxide, a metal substance, as an active substance which is classified as very toxic to aquatic organisms, may present a potential serious risk to the environment, and if this is the case, whether risk mitigation measures can be considered relevant to adequately control and/or prevent the environmental risks.

Effect data

The predicted no effect concentrations (PNECs) reported in the European Union Risk Assessment Report (EU RAR) on zinc (2010)[1] are considered reliable and, hence, are suitable for use in the risk characterisation of Gutal. However, since the data search for the EU RAR (2010) was completed more data have become available (e.g. those used in establishing the UK Environmental Quality Standard[2]

[1] European Union Risk Assessment Report (EU RAR) on zinc (2010) - http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/15064/1/lbna24587enn.pdf
[2] Environment Agency. 2010. Proposed EQS for Water Framework Directive Annex VIII substances: zinc (For consultation). Released by the United Kingdom Technical Advisory Group (WFD-UKTAG) 2012. Environment Agency, United Kingdom

for zinc), and were used by the applicant to establish different PNECs for each environmental compartment. The applicant provided the robust summaries of the additional peer-reviewed studies used in the effect assessment that were not included in the EU RAR (2010), including a conclusion on the reliability and validity of each study. Although the endpoint data from one study was not of sufficient quality to be used in calculation of the generic PNEC value from which the site-specific PNECs are derived, it is accepted that the omission of the effects data from this single study would not significantly alter the calculated PNEC. Having considered the above, it can be accepted that the PNECs proposed by the applicant can be used for the characterisation of risks (calculation of risk quotients).

Exposure: accumulation, bioavailability and model calculation of zinc concentrations in the environment

It is acknowledged that due to the physico-chemical properties of zinc (non-volatile and non-degradable), continual application of manure from treated animals to land under practices of intensive pig breeding will cause a gradual increase in the topsoil zinc concentration, followed by an increase in other relevant compartments, over time. Therefore, it will only be a matter of time before any PNECs are exceeded in these compartments.

A critical consideration in relation to assessing environmental risk of metals is determining their bioavailability. For each compartment (soil, water and sediment), zinc bioavailability is dependent on various biotic and abiotic factors. In the aquatic compartment, zinc bioavailability in water has been predicted using the Metal Bioavailability Assessment Tool (United Kingdom Environment Agency)[3], a user-friendly version of the Biotic Ligand Model, a model that is used to predict the bioavailable metals for different aquatic species (algae, Daphnia and fish) and has been used and well reported in a large number of peer-reviewed studies for zinc, and the data used in the EU RAR for zinc (2010). The Metal Bioavailability Assessment Tool requires fewer data inputs to predict zinc bioavailability in water than the Biotic Ligand Model, and can be used to calculate site-specific PNECs. The Metal Bioavailability Assessment Tool is based on the outputs from the zinc Biotic Ligand Models and the dataset used in the derivation of the Environmental Quality Standard for zinc, and only requires input data for water pH, dissolved organic carbon and dissolved calcium concentration, but does not take into account the presence of other ions that could affect zinc speciation and, hence, bioavailability.

In soil, properties such as pH, organic carbon content, cation exchange capacity, and clay content determine bioavailability in the terrestrial compartment. The bioavailable fraction of zinc in soils is small (<1%). The most important factors in determining bioavailability (and, hence, ecotoxicity) in soils are soil type and the time between the addition of zinc to soil and toxicity testing ('ageing'). For instance, soils contaminated over an extended period of time show reduced toxicity compared to freshly spiked soils. Consequently an 'ageing' factor of 3 has been established and is used in calculating site-specific PNECs. The calculation of site-specific PNECs for Gutal was carried out using an Excel tool soil PNEC calculator (developed by Arche Consulting)[4] which incorporates parameters relevant to determine soil zinc bioavailability, such as pH, organic and clay content, and the cation exchanged capacity.

For sediment systems, since the sediment predicted environmental concentration (PEC) was derived (EU RAR, 2010) there have been significant changes in the way sediment concentrations are determined. It is believed that bioavailability of metals in sediment can be predicted by measuring the acid volatile sulphide (AVS) and the simultaneously extracted metal (SEM) contents of sediments. Other parameters affecting (lowering) zinc bioavailability in sediments are the presence of precipitated

[3] Metal bioavailability assessment tool (M-BAT) - http://www.wfduk.org/resources/category/environmental-standard-methods-203/tags/bioavailability-assessment-tool-205/tags/metals-181
[4] Arche Consulting Soil PNEC calculator - http://www.arche-consulting.be/metal-csa-toolbox/soil-pnec-calculator/

mineral phases, e.g. iron (oxy)hydroxides and manganese oxides, as well as the organic matter content in sediments.

Zinc binds strongly to AVS and becomes non-bioavailable, which would allow for making a correction on the exposure assessment for bioavailability of metals in sediment systems (ECHA 2014)[5]. AVS is produced by bacteria in anoxic sediments. At the time of the zinc EU RAR (2010) there were too few effects or exposure data to be able to account for the effect of these two parameters (AVS/SEM) on zinc bioavailability in sediments. Consequently, bioavailability was not considered for exposure calculations (establishing the PECs), thus leading to a risk assessment that did not account for the bioavailable fraction of zinc but rather for the total zinc concentrations (bioavailable and non-bioavailable). Hence, where an excess of AVS exists and zinc sulfides are formed, the PNEC may be exceeded considerably before any adverse effects are observed. At a site-specific level, PNEC bioavailability corrections in sediment as a result of AVS/SEM content in sediment, can be made if the necessary data are available; however, such data are scarce. Therefore, while soils and surface waters can both be corrected for bioavailability, a correction has not been possible for the calculation of the sediment PECs in this environmental risk assessment.

Given that the VICH and CVMP guidelines on the Phase II environmental risk assessment of veterinary medicinal products are not primarily developed for inorganic molecules, many of the assumptions and exposure models described in the guidelines are unsuitable for a substance such as zinc. Thus, a model used by EFSA for estimating the environmental exposure from the use of zinc oxide as feed additive, the Intermediate Dynamic Model for Metal (IDMM) by Monteiro et al. (2010)[6], and was used to refine the risk assessment for Gutal as it is considered appropriate as it can be used for inorganic substances.

The level of accumulation and time dependency for the different environmental compartments were evaluated. The IDMM predicts the long-term mass balance of metals, with defined inputs (e.g. veterinary medicinal products usage) and outputs (e.g. crop off-take, ageing), and concludes that zinc will accumulate in soil following continual application of treated manure with acidic sandy soils being most vulnerable as these soils have a tendency to accumulate zinc more rapidly than other type of soils and will also have a higher drainage and run-off of zinc to surface water.

Supporting field studies on zinc accumulation in soils are scarce, and the available data may be considered equivocal or of limited reliability because, for example, they may not reflect the pattern of application of manure expected following the use of zinc oxide in pig breeding or soil types representative of the whole of Europe.

However, in contrast to the CVMP/VICH approach, the IDMM predicts the fate and behaviour of zinc in soil, differentiates sites on zinc sensitivity, accommodates aged zinc, considers environmental sources of potential toxicants, and accommodates for ambient levels of naturally occurring substances. The IDMM also considers several soil compartments and the fluxes between these and aquatic compartments.

There are a number of uncertainties associated with use of the IDMM for predicting the environmental exposure of zinc from use in veterinary medicinal products, such as the effects of hydrology, dissolved organic carbon and metal aging. Additionally, as the model was not made available to the CVMP, the relevance of the default input parameters could not be assessed and the model could not be run using data on specific application rates for zinc. Therefore, exposure on application rates that are considered relevant from the use of zinc containing veterinary medicinal products are calculated from the pre-defined loading rates of the IDMM. Yet, for higher application rates than those reported using the

[5] ECHA, 2014. Guidance on information requirements and chemical safety assessment. Chapter R.7b:Endpoint specific guidance

[6] Monteiro SC, Lofts S, Boxall ABA. 2010. Pre-Assessment of Environmental Impact of Zinc and Copper Used in Animal Nutrition. Report to the European Food Safety Authority - http://www.efsa.europa.eu/en/supporting/pub/74e.htm

IDMM (EFSA, 2012)[7] extrapolation is required, and the relationship between the zinc loading rate and the PEC values calculated by the IDMM is not linear, which could question the validity of the extrapolated PECs at the highest zinc application rates. Despite these uncertainties, and in the absence of a better alternative, it is considered that the IDMM can be used to gain a reasonable assessment of the risk to the environment posed by the use of Gutal. Moreover, validation of the IDMM has been performed by the comparison of model predictions against published monitoring data for zinc applications. Although limited data were available, results show zinc concentrations are predicted accurately in soils but less so in surface waters and sediment. A pragmatic approach should be taken when considering the validation of environmental mechanistic models (e.g. IDMM and FOCUS[8]), where validation is concerned with substantiating claims on the applicability of predictions with reference to the intended use or purpose. By their nature, models are an incomplete representation of the system under investigation but that is not to say that they cannot be very useful and widely implemented. Though limited, the validation data for the IDMM is sufficient to give confidence that the model can be used to achieve an ample, pragmatic assessment of the exposure of zinc to the environment. Additionally, as the IDMM has been taken into consideration for the EFSA assessment of zinc exposure, it may also be considered relevant for the assessment of veterinary medicinal products in terms of environmental exposure assessment.

Risk assessment

To assess the risk for each compartment following extended application of manure to land, PECs and PNEC values for each FOCUS scenario were compared at three time points (years: 2020, 2040, 2060), using two application rates: a worst case application rate (7 kg zinc ha^{-1} a^{-1}) and a lower application rate (4 kg zinc ha^{-1} a^{-1}). In the terrestrial and aquatic compartments a risk (RQ >1) was found at 4 out of 19 scenarios and at 5 of out 15 scenarios from 2060 onwards, for the worst case and lower application rate, respectively. For two of the FOCUS scenarios (acidic, sandy soils) the risk quotients (RQs) are >1 for both loading rates at all time points. A risk was identified for all FOCUS sediment scenarios, at both loading rates and at each time point. The results of the environmental risk assessment for Gutal reflect the conclusion from EFSA on zinc i.e. there is a potential environmental concern related to the aquatic compartment (including sediment), with acidic, sandy, well-drained soils being most vulnerable to these processes.

In order to better indicate the risks posed at application rates considered particularly relevant by the use of Gutal of 8.2 kg zinc ha^{-1} y^{-1}, 7.2 kg zinc ha^{-1} a^{-1}, 3.3 kg zinc ha^{-1} a^{-1} and 2.8 kg zinc ha^{-1} a^{-1}, RQs have been extrapolated (linearly) from application rates of 4 and 7 kg zinc ha^{-1} a^{-1}. This linear extrapolation is questionable, since the processes involved are not linear. The information provided indicates that there are errors and these are more pronounced for the sediment compartment and at low loadings. Despite these uncertainties, considering the nature of the active substance, as an inorganic molecule, and the difficulties identified throughout the application procedure in terms of assessing the environmental risk for a compound 'outside' of current CVMP/VICH guidance, it may be accepted that the estimated PEC values extrapolated from the IDMM outputs offer an reasonable reflection of the environmental exposure for use in the risk characterisation for Gutal.

Although the PEC values for each compartment cannot be verified because the IDMM is not provided, overall they appear fairly conservative since a reasonable worst case exposure scenario is considered, i.e. continual application of undiluted manure until 2060. Concerning sediment PECs particularly, accumulation factors are not considered (e.g. deposition, re-suspension, and burial of zinc), it is assumed that suspended sediments are representative of the deposited sediment, and no account is made for acid volatile sulfide levels. The latter can reduce zinc bioavailability and, although levels are

[7] EFSA Scientific Opinion on safety and efficacy of zinc compounds (E6) as feed additive for all animal species: Zinc oxide, based on a dossier submitted by Grillo Zinkoxid GmbH/EMFEMA - http://www.efsa.europa.eu/en/search/doc/2970.pdf
[8] Forum for Co-ordination of Pesticide Fate Models and their Use (FOCUS) - http://focus.jrc.ec.europa.eu/

variable, where zinc sulfides are formed PNECs may be greatly exceeded before adverse effects are observed.

The combination of a conservative PNEC (not accounting for bioavailability) and PEC may result in an overestimate of the risk due to zinc in sediments. The greatest certainty in the IDMM PECs is for the soil compartment, with a lower certainty for surface waters and, then sediments. However, it is apparent that, for all compartments, RQs will be exceeded either immediately (sediment) or eventually (soil, ground-, and surface waters), and these risks must be addressed. As zinc is a metal, general assumptions that are usually made about degradation are not applicable, therefore, once critical concentrations are exceeded, the risk will be difficult to remediate.

Overall, it is apparent that the long-term, continual use of zinc-containing veterinary medicinal products will result in a gradual net input of zinc to the environment. No matter which model and application rates are used, a risk to the environment is calculated with only the time needed to arrive at this risk varying.

Risk mitigation measures

The applicant has generated RQ values for alternative application rates via linear extrapolation of the IDMM results for application rates of 4 and 7 kg zinc ha^{-1} a^{-1} for a better consideration of relevant RMMs. Although there are uncertainties with the linear extrapolation of the IDMM results, the PEC values extrapolated from the IDMM outputs are considered to offer a reasonable reflection of the environmental exposure for use in the risk characterisation for Gutal. At present it is uncertain as to what represents a reasonable worst case exposure scenario for the manure application rate. Nonetheless, for each compartment, risks have been identified for some scenarios at each application rate investigated.

In terms of RMMs and in view of the necessity to prevent the accumulation of zinc in environmental compartments above PNEC levels, it has been proposed that undiluted manure from treated piglets should not be applied to land and manure from treated animals be diluted with manure from untreated animals, so that the treated manure comprises 40% or less of the total mixture. In major pig breeding regions stringent rules and controls on manure application are in place, although it is realised that this advice is followed on a voluntary basis and Good Agricultural Practice may vary throughout the Member States. However, this measure would slow down the accumulation of zinc and, hence, reduce the risk for each environmental compartment. Usually piglets and sows are kept on the same farm allowing treated piglet manure to be diluted. Even where manure storage is combined, piglet manure would account for 40% or less of the mixture. The product should not be used on farms where dilution of manure is not possible. Although this RMM would most likely reduce the risk for all compartments, a risk for surface water and, particularly, sediment may remain.

In order to limit nutrient loss and eutrophication, Good Agricultural Practice recommends manure should not be spread on vulnerable soils (acidic, freely draining, sandy soils). Although Good Agricultural Practice varies amongst Member States and is followed on a voluntary basis, a similar RMM for Gutal may be practical and appropriate. Additionally, advice to avoid the spreading of manure on the same area of land in successive years in order to slow down the accumulation of zinc would seem a suitable RMM.

The final RMM proposed is to apply local or national rules for the minimum distance from open water at which manure should be spread. Similar regulations concerning the control of open watercourses from exposure to nutrients are adhered to in line with Good Agricultural Practice. Currently, data specific to zinc are not available, however, the ability of buffer strips to reduce suspended sediment loads, which are the predominant route of transport of zinc to local water courses, may be used as an indicator. This supportive data suggests a buffer zone of 3 m or more could reduce the run-off by 3 to 5-fold.

Despite the data gap, it may be accepted that such a measure would, most likely, reduce run-off of zinc to watercourses.

The proposed RMMs fulfil the criteria laid out in the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6[9] and GL 38[10](EMEA/CVMP/ERA/418282/2005)[11], as indicated in the CVMP reflection paper on RMMs related to the environmental risk assessment of veterinary medicinal products[12], except in instances where they may not be line with common agricultural practice in a particular Member State, for example, in Member States where manure trading is common and, hence, the farmer may not be the person spreading the manure, or in instances where the effect of the RMM has not been definitively demonstrated (e.g. buffer zones). Nonetheless, although it is recognised that the proposed RMMs have deficiencies, and the extent to which they reduce the environmental risk cannot be fully quantified, they can be anticipated to slow down the accumulation of zinc in the environment.

3. Benefit-risk assessment

Benefit assessment

The proposed indication for Gutal is for the prevention of post-weaning diarrhoea in piglets. Since the marketing authorisation application was submitted in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence was accepted, the therapeutic benefits for Gutal are considered to be the same as those for the reference product, ZincoTec - Zinc Oxide 100% Premix for Medicated Feeding Stuff and have not been re-evaluated as part of this procedure.

Risk assessment

Quality, target animal safety, user safety impact on antimicrobial resistance development and residues were not assessed in this referral procedure, as no concern was notified by the reference Member State.

Risks to the environment

Due to the intrinsic nature of zinc (non-volatile and non-degradable) the potential for PNECs to be eventually surpassed as a result of continual application of manure from treated animals to land over an extended period is a significant environmental concern, particularly with regard to the most vulnerable soil types (acidic, freely draining, sandy soils) and organisms of the aquatic compartments. Following continual application of manure from treated animals, by 2060 an environmental risk (defined by RQ values >1) is seen in 4 of 19 soil scenarios, 5 of 15 surface water scenarios and each of the 15 sediment scenarios. A risk was identified from 2020 for two of 15 surface water scenarios (acidic, sandy soils) and for all 15 sediment scenarios. However, it is noted that the level of uncertainty in the risk characterisation for sediment is considerably greater than for soil or surface water.

[9] VICH GL6: Guideline on Environmental Impact Assessment (EIAS) for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98) – http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004394.pdf

[10] VICH GL38: Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II (CVMP/VICH/790/03) – http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004393.pdf

[11] CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005) – http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004386.pdf

[12] CVMP reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products (EMA/CVMP/ERAWP/409328/2010) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500124187.pdf

Risk management or mitigation measures

In order to reduce the risk from the accumulation of zinc in environmental compartments, a number of RMMs are proposed to be included in the product information. Firstly, that undiluted manure from treated piglets should be diluted before being applied to land (so that the treated manure comprises 40% or less of the total mixture). The product should not be used on farms where appropriate dilution of manure is not possible. Secondly, as the bioavailability of zinc varies between soil types, manure from treated piglets should not be spread on the soil types which have been identified as most vulnerable, i.e. freely draining, acidic (pH ≤6), sandy soils. Thirdly, in order to reduce the accumulation of zinc, manure from treated animals should not be spread on the same area of land in successive years. Finally, the SPC advises compliance with measures taken by local/national authorities to prevent manure entering waters and excessive leakage of minerals with the implementation of a buffer zone. Although it is recognised that the proposed RMMs have deficiencies, and the extent to which they reduce the environmental risk cannot be fully quantified, they can be anticipated to slow down the accumulation of zinc in the environment.

Evaluation of the benefit-risk balance

Since the marketing authorisation application was submitted in accordance with Article 13(1) of Directive 2001/82/EC, the therapeutic benefits for Gutal are considered to be the same as those for the reference product, ZincoTec - Zinc Oxide 100% Premix for Medicated Feeding Stuff and are not re-evaluated under this procedure.

Quality, target animal safety, user safety, impact on antimicrobial resistance development and residues and efficacy were not assessed in this referral procedure, as no concern was notified by the reference Member State.

This referral was raised due to concerns regarding the environmental risk assessment. A risk to the environment has been identified due to accumulation of zinc, particularly to the aquatic compartment. There is some uncertainty associated with the scale of this risk. Various RMMs are proposed which are anticipated to reduce the accumulation of zinc.

Conclusion on the benefit-risk balance

Gutal contains zinc oxide as an active substance. Zinc oxide is included in veterinary medicinal products currently authorised in several EU Member States for use in pigs.

Since the marketing authorisation application was submitted in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence was accepted, the benefit-risk for Gutal is considered to be equivalent to that of the reference product, ZincoTec - Zinc Oxide 100% Premix for Medicated Feeding Stuff.

A risk to the environment has been identified due to accumulation of zinc, particularly to the aquatic compartment.

In general terms, as for the benefits, other risks are expected to be the same as for the reference product and have not been evaluated by the CVMP.

The CVMP concluded that the concerns expressed by France and the Netherlands should not prevent the granting of a marketing authorisations provided that the recommended risk mitigation measures, which are anticipated to reduce the accumulation of zinc, are added to the product information.

Grounds for the granting of the marketing authorisations for Gutal 1000 g/kg premix for medicated feeding stuff for piglets

Having considered all data submitted the CVMP concluded that:

- This referral was raised due to concerns regarding the environmental risk assessment. A risk to the environment has been identified due to accumulation of zinc, particularly to the aquatic compartment.
- Since the marketing authorisation application was submitted in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence was accepted, the benefit-risk for Gutal is considered to be equivalent to that of the reference product, ZincoTec - Zinc Oxide 100% Premix for Medicated Feeding Stuff.
- However, it is deemed appropriate that having addressed the environmental concerns of the use of Gutal and having identified an environmental risk from the use of zinc containing veterinary medicinal products, that further risk management measures are taken to reduce the accumulation of zinc in soil, water and sediment compartments.

Therefore, the CVMP recommended the granting of the marketing authorisations for the veterinary medicinal products referred to in Annex I with amendments to the Summary of Product Characteristics and package leaflet of the reference Member State. The amended Summary of Product Characteristics and package leaflet of the reference Member State are set out in Annex III.

Annex III

Amendments in the relevant sections of the Summary of Product Characteristics and package leaflet

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination Group procedure with the following amendments:

Add the following text in the relevant sections of the product information:

Summary of Product Characteristics

4.5 Special precautions for use

Other precautions regarding impact on the environment

Zinc is very toxic to aquatic organisms, but can affect growth, survival and reproduction in both aquatic and terrestrial plants and animals. Zinc is persistent in soils and may accumulate in sediments. Toxicity will depend on environmental conditions and habitat types. The risk to the environment can be reduced by adhering to the following measures.

When spreading manure from treated animals, the maximum total zinc load as defined in the national or local regulations has to be strictly respected. Undiluted manure from treated piglets should not be applied to land. Dilution with manure of untreated 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 3 m applied, because the manure contains zinc which may cause adverse effects in the aquatic environment.

5.3 Environmental properties

Zinc is very toxic to aquatic organisms and is persistent in soils and sediments.

Zinc may accumulate in soil following continual application of manure from treated animals; with acidic sandy soils being most vulnerable.

The bioavailability of zinc, and therefore the environmental risk, varies between soil types and environmental conditions (e.g. dissolved organic carbon, calcium and pH).

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used containers.

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

Package leaflet:

12. SPECIAL WARNINGS

Other precautions regarding impact on the environment

Zinc is very toxic to aquatic organisms, but can affect growth, survival and reproduction in both aquatic and terrestrial plants and animals. Zinc is persistent in soils and may accumulate in sediments. Toxicity will depend on environmental conditions and habitat types. The risk to the environment can be reduced by adhering to the following measures.

When spreading manure from treated animals, the maximum total zinc load as defined in the national or local regulations has to be strictly respected. Undiluted manure from treated piglets should not be applied to land. Dilution with manure of untreated 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 3 m applied, because the manure contains zinc which may cause adverse effects in the aquatic environment.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCT OR WASTE MATERIALS, IF ANY

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used containers.

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.