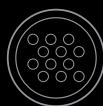
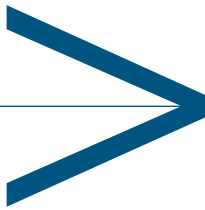




Gutal®

1000 MG ZINC OXIDE/G PREMIX





Indications for use

For the prevention of post-weaning diarrhoea in weaned piglets

Origin of the molecule

Zinc oxide is an inorganic compound. Zinc oxide is a white powder that is insoluble in water. There are two methods to produce zinc oxide:

1. Indirect process
2. Direct process

Gutal[®] is produced with the first, indirect method:

- To guarantee Pharma quality
- Ensure purity of the zinc oxide
- No contaminants like lead (Pb) and/or dioxines

Product categorization and use

Gutal[®] is **not classified as an antimicrobial agent**, but as an anti-diarrhoeal, intestinal anti-inflammatory product.

(ATC Vet Code QA07XA91)

Environment

Zinc is an essential element, occurs naturally and is ubiquitous in all environmental matrices.

A big part of the zinc in soil forms complexes or is bound to organic compounds and not bioavailable. The bioavailability of zinc, and therefore the environmental risk, varies between soil types and environmental conditions (e.g. dissolved organic carbon, calcium and pH).

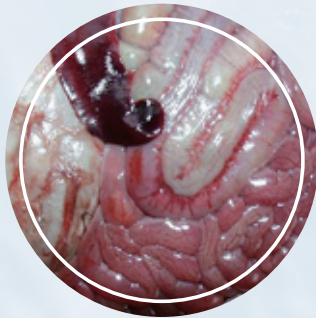
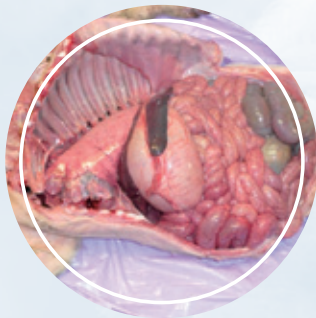
The possible impact of Gutal[®] on the environment was intensively investigated by Huvepharma[®] and the potential risks were identified. Local codes of good manure management mitigate the risk for the environment and are also taken up in the special precautions for use. (see SPC)



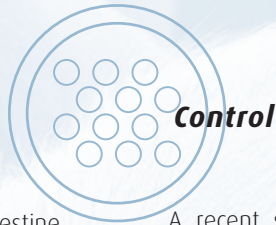
Post weaning diarrhoea

Etiology

The bacterium *E. coli* is a common inhabitant of the intestine of the pig. There are two types, non-haemolytic and haemolytic, which describe whether or not the organism breaks down blood (haemolysis) on a culture plate. In some countries, haemolytic types invariably cause disease due to the toxins that they produce but in others non-haemolytic strains predominate. At weaning time, the loss of sows milk and IgA allow the *E. coli* to attach to the villi of the small intestines, the toxins cause acute enteritis and diarrhoea. Post-weaning diarrhoea is a common cause of mortality and morbidity.



Picture 1. Post weaning diarrhoea, appearance of intestine at necropsy (source: Dialab)



A recent study (Callens et al., 2012) indicated 55% of all antimicrobial substances prescribed in pigs are used to control post- weaning diarrhoea. Colistin (polymyxine) is by far the most commonly used product in countries without a registered zinc oxide on the market; it represents 76% of all antibiotics used for this indication.¹

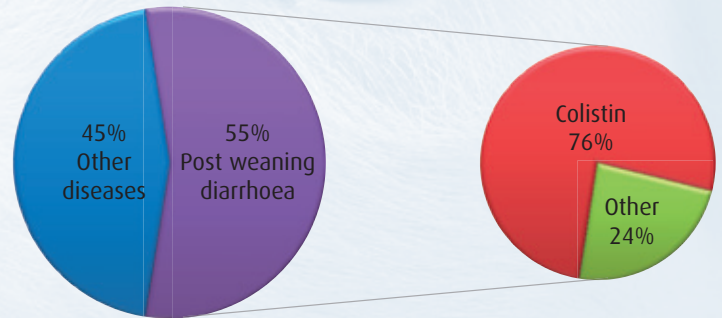


Figure 1. Percentage of antibiotics used for post weaning diarrhoea and the percentage of colistin used for this indication

Efficacy of Gutal® to control post-weaning diarrhoea

Identify whether Gutal® supplementation has an effect on:

1. Health
2. Production parameters
3. Reduction in the use of antibiotics

In comparison with:

- Colistin supplemented
- Negative control group

Animals, material and methods

- Three commercial pig herds with two successive weaning rounds.
- Each round, four treatment groups of 60 weaners each
 - one group received colistin in the feed (14d) = Colistin Feed.
 - another group colistin in the drinking water (14d) days =Colistin Water.
 - a third group Gutal®, 2500 ppm (14d).
 - negative control group.
- During the entire nursery period:
 - the backhand of the piglet was scored every week.
 - feed intake.
 - antimicrobial usage.
- On day 7 and 14:
 - Faeces samples for total and hemolytic *E. coli*.
- Day 14 and at the end:
 - Individually weighing.





Results:

1. Daily weight gain

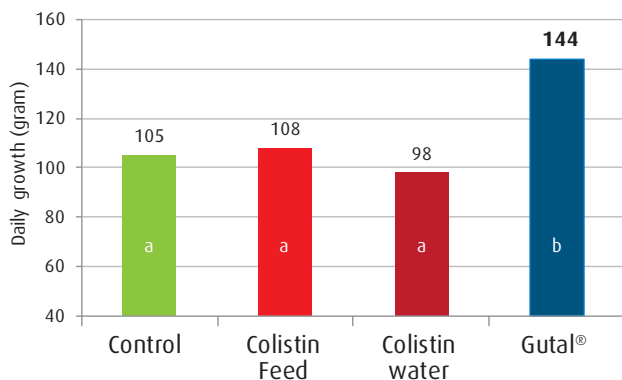


Figure 2. Daily weight gain in grams per day during first 14 days.

2. Diarrhoea

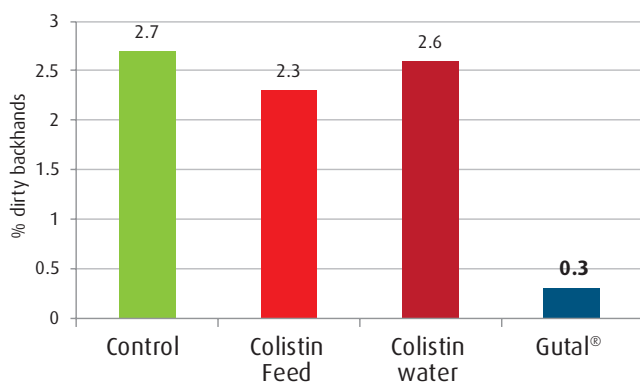


Figure 3. Backhand scoring: % dirty backhands.

3. Antibiotic usage

Dependent variables	Control group	Colistin Feed	Colistin Water	Gutral®
% hemolytic <i>E. coli</i>	73.50%	45.80%	45.70%	34.30%
Antibiotic usage	4	459	466	2

Figure 4. Antibiotic usage (treatment incidence per 1000 pig days) and % positive samples for hemolytic *E. coli* of the faeces samples.

Conclusion:

Gutral® has a positive effect on:

1. Health
2. Production parameters (as a result of better health)
3. Antibiotic usage

¹¹Bénédicte Callens et al., 2012.

Contraindications

None.

Special warnings for each target species

Studies have shown zinc oxide to be beneficial in piglets at risk of developing mild to moderate diarrhoea. However, there are no studies available in piglets at risk of developing severe/haemorrhagic forms of diarrhoea.

Special precautions for use

Special precautions for use in animals

The product should only be administered to animals at risk of diarrhoea, for example if the piglets are from sows with a history of regularly occurring cases of post-weaning diarrhoea.

Feeding of high zinc concentrations may stimulate the occurrence of resistance to zinc in the pig gut microflora and may play a role in the co-selection of MRSA and in increasing the proportion of multiresistant *E. coli*.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

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.

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 a minimum buffer zone of at least 3 m applied, because the manure contains zinc which may cause adverse effects in the aquatic environment.

Adverse reactions (frequency and seriousness)

The administration of the medicated premix may lead to a white-yellowish colouring in faeces, which stops following the withdrawal of treatment.

With prolonged use, copper deficiency is possible, associated with hypochromic anemia. Furthermore, growth depression, decreased food consumption and joint pain are described.

The administration of the medicated premix may alter certain biological parameters (alkaline phosphatase, α -amylase activity) which reverts following withdrawal of the treatment.

Use during pregnancy, lactation or lay

Not applicable.

Interaction with other medicinal products and other forms of interaction

Factors affecting the oral bioavailability of zinc include the presence of minerals in the diet that compete for transport (Fe, Cu) and interfering substances that may bind zinc (phytate-Ca). High zinc dosages may also affect the availability of minerals such as Fe and Cu.

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).

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.

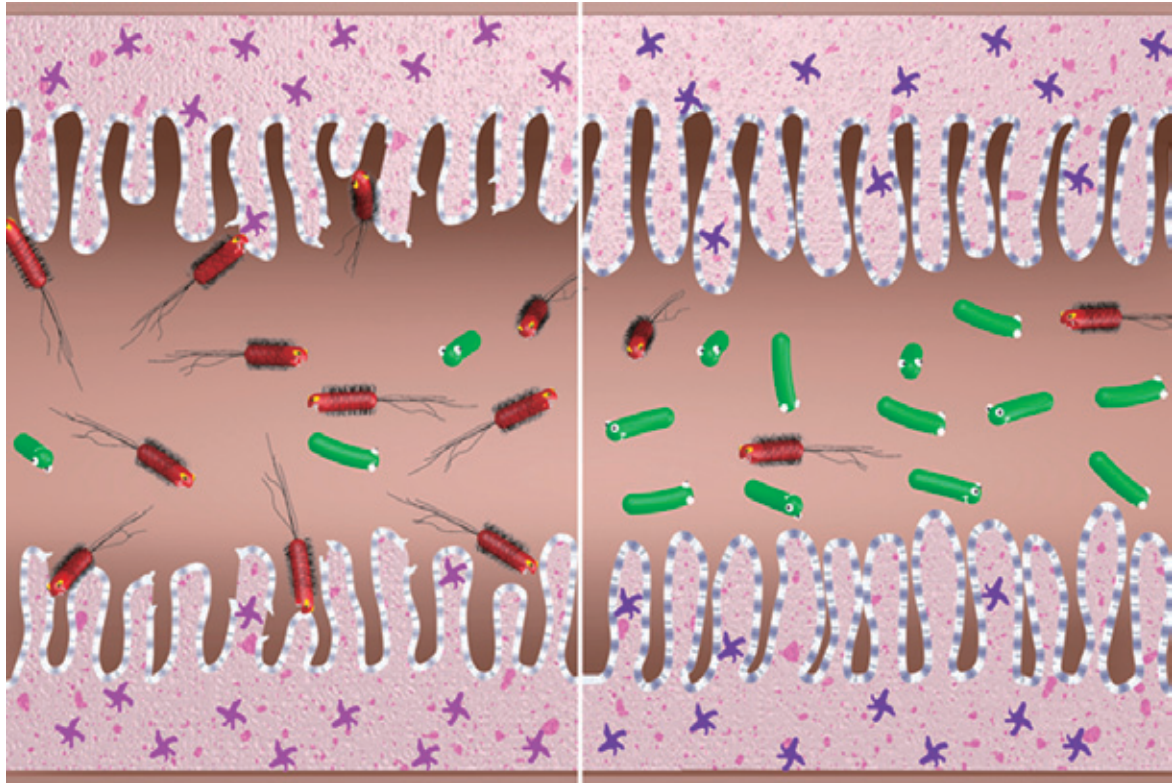
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Pharmacokinetics

Gutal[®], at therapeutic levels, is poorly absorbed and is believed to be voided unchanged in the faeces.

Pharmacodynamics

The mode of action of zinc oxide in the prevention of diarrhoea has not been fully established, but following has been suggested:



Unhealthy intestine

Gutal[®]

1. Microflora stabilization¹

2. Strengthening tight junctions²

3. Reduction of adhesion of *E. coli*³

4. Stimulation of local and systemic immunity^{4,5}

¹Katouli et al. (1999).

²Zhang, B. et Guo, Y., (2009).

³Crane, J.K., Byrd, I.W. et Boedeker, E.C., (2011).

⁴Roselli, M., Finamore, A., Garaguso, I., Britti, M.S. et Mengheri, E., (2003).

⁵Martinez-Montemayor, M.M., Hill, G.M., Raney, N.E., Rilington, V.D., Tempelman, R.J., Link, J.E., Wilkinson, C.P., Ramos, A.M. et Ernst, C.W., (2008).

Keypoints

1. Is the first EU-multinational registered zincoxide = Pharma quality

2. Gutal[®] is not classified as an antimicrobial

3. Environment: [Local codes of good manure management mitigate the risk](#)

Practical dosing and administration

Oral use only.

For incorporation into feed as medicated premix.

A mostly used practical dosing:

Add 3 kg of Gutral® per 1000 kg of feed for 14 days after weaning to prevent diarrhoea.

However:

Administer 2900-3100 mg of the product per kg of dry feed (which provides 2320-2489 mg/kg elemental zinc) so that the amount of zinc already present in the feed (naturally occurring zinc plus added nutritional zinc) is taken account of to ensure that the final feed contains 2500 mg/kg of elemental zinc.

To ensure adequate distribution of the product in the final feed it is recommended that it be premixed with a suitable quantity of feed ingredients before blending into the final feed. Medicated feed may be pelleted using a pre-conditioning step for 5 minutes at a temperature not exceeding 85°C.

The final feed should be fed as the only feed for 14 days from weaning.

Withdrawal period(s)

Meat and offal: 28 days

Overdose

Not known.

Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

Shelf and storage

This veterinary medicinal product does not require any special storage conditions.

- Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
- Shelf-life after first opening of the immediate packaging: 6 months.
- Shelf life of the veterinary medicinal product after incorporation into meal or pelleted feed: 3 month

Packaging

5 kg and 20 kg multi-ply paper bags with internal polyethylene bag.
Not all pack sizes may be marketed.



* Use references can be obtained upon demand.
** Please consult the local label and veterinary surgeon for exact indications and posology.
*** Use medicines responsibly.
**** POM-V Vm number 80282/4021.