The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ZINC SALTS

SUMMARY REPORT

Name of substances

Zinc salts : zinc acetate, zinc chloride, zinc gluconate, zinc oleate and zinc stearate.

Indications for use

Zinc is indicated for the prevention and correction of nutritional deficiencies of zinc. It also constitutes an active ingredient in medicinal products intended for topical application. Zinc sulphate is used in ophthalmic solutions at concentrations of 0.20-0.25%; it is also an active ingredient (concentration of 4%) in lotions intended for treatment of various chronic skin diseases. Zinc chloride and zinc acetate are incorporated as astringents in various solutions, usually at concentrations of 0.2-2%, but occasionally at considerably higher concentrations. Zinc oxide exerts mild astringent and antiseptic effects; it is an active ingredient of various lotions, ointments, powders, and plasters in concentrations varying from less than 10% (lotions) to almost 100% (powders). Zinc oxide is commonly incorporated in the diet of weaning piglets at a concentration of 1000-2500 ppm i.e. in amounts far higher than the recommended concentration of 30-45 ppm in the diet, as a preservative against post-weaning diarrhoea.

Zinc stearate and zinc oleate have actions similar to those of the zinc oxide.

Zinc is present in virtually all plant and animal tissues. The average daily intake per capita in the US has been estimated at 12-15 mg, mostly from food. Daily dietary allowances of zinc recommended for humans by the US Food and Nutritional Board vary from 2 mg for infants 0-0.5 years to 15 mg for adults.

Pharmacological activity

Zinc is an essential element in the nutrition of animals and man. It acts as a cofactor of numerous enzymes, e.g. alcohol dehydrogenase, carbonic anhydrase, carboxypeptidase. Zinc plays a role in protein synthesis and cell division. It also exerts crucial influence on the maintenance of cell membrane stability and in the function of the immune system. The connection between the known physiological functions of zinc and the various manifestations of zinc deficiency (e.g. anaemia, short stature, hypogonadism, impaired wound healing, geophagia and poor skin conditions, alopecia and lesions of the hooves) remain largely unexplained. The mechanism behind the beneficial effect of zinc oxide as a prophylatic against weaning diarrhoea is unknown; however the effect is coincident with an increase alkaline phosphataese activity in serum. Zinc interacts with several metallic ions. Copper, calcium and phytate (a constituent of cereals) reduce zinc absorption; cadmium and zinc compete with each other.

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Toxicological profile

The acute toxicity of orally administered zinc depends on the salt; it is relatively low for the salts used for veterinary medicinal purposes. The oral LD_{50} for zinc chloride (high water solubility) was 350 mg/kg for rats and mice, 200-250 mg/kg in the rabbit. The oral LD_{50} for zinc sulphate (moderate solubility) was 2200 mg/kg in the rat and 2100mg/kg in the rabbit.

No evidence of significant pathological effects were observed in rats following daily oral administration of zinc (as zinc oxid, zinc acetate, zinc citrate or zinc maleate) in doses up to 34 mg/kg for 35 to 53 weeks. In a 6-month study in rats oral administration of 600 mg zinc chloride/day gave rise to gastrointestinal erosions. Human subjects tolerated 660 mg zinc sulphate per day for 10 weeks without any evidence of haematologic, hepatic or renal toxicity.

Zinc was not teratogenic in laboratory animals and had no effect on the reproductive performance. Zinc was not mutagenic in a number of bacterial and mammalian systems. A 45-week study in mice provided no evidence of carcinogenic potential; however, the available long-term studies are insufficient to assess carcinogenicity.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated zinc in 1982 and set a provisional maximum tolerable daily intake for man of 0.3-1.0 mg/kg.

Pharmacokinetics

Absorption of orally administered zinc depends on the salt (water soluble salts are more easily absorbed than water insoluble salts), the concentration of zinc in the diet (absorption decreases with increasing levels) and the concentration of interfering substances such as iron and calcium and phytate. Absorption rates for dietary zinc of 20-30% are quoted for humans. The human adult body contains about 2.3 g zinc, 65% of it in muscle, 20% in bone, 6% in plasma, 2.8% in the erythrocytes, and about 3% in the liver.

The normal concentrations in tissues and milk are 54 mg/kg in muscle, 60 mg/kg in liver, 55 mg/kg in kidney and 3.9 mg/kg in cows' milk. The intracellular concentration is several times higher than the extracellular concentration. Excretion of absorbed zinc takes place mainly via the bile (80%) and less via urine and sweat. Enterohepatic circulation takes place. Zinc does not accumulate in the body following continued [excessive] exposure.

Risk assessment

Zinc is a normal constituent of the diet. It is an essential trace element for humans and hence in the diet. Daily requirements in human adults are about 15 mg/day;

If an animal (e.g. a 500 kg cow) was administered a 600 mg zinc (the highest prescribed) dose, this would only result in an increase in the concentration of zinc in edible tissues which is biologically insignificant for the consumer.

It appears unlikely that the use of zinc oxide, zinc chloride, zinc sulphate, zinc gluconate, zinc stearate and zinc oleate, when used for veterinary purposes under the conditions specified, represents any significant risk to the consumer due to ingestion of residues in foodstuffs of animal origin.

Recommendations and conclusion

The Committee considers that there is no need to establish an MRL for zinc acetate, zinc chloride, zinc gluconate, zinc stearate and zinc oleate and recommends their inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substances(s)	Animal species	Other provisions
Zinc acetate Zinc chloride Zinc gluconate Zinc oleate Zinc stearate	All food producing species	