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

EMEA/MRL/393/98-FINAL
April 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ALUMINIUM DISTEARATE, ALUMINIUM HYDROXIDE ACETATE, ALUMINIUM PHOSPHATE AND ALUMINIUM TRISTEARATE

SUMMARY REPORT

1. Aluminium is an ubiquitous element in the environment. It is present in varying concentrations in living organisms and in foods. Aluminium compounds are widely used in veterinary and human medicine. Other uses are as an analytical reagent, food additives (e.g. sodium aluminium phosphate as anticaking agent) and in cosmetic preparations (aluminium chloride).

   Aluminium distearate is used for thickening lubricating oils. Aluminium hydroxide acetate and phosphate are antacids with common indications in veterinary medicine: gastric hyperacidity, peptic ulcer, gastritis and reflux esophagitis. A major use of antacids in veterinary medicine is in treatment and prevention of ruminal acidosis from grain overload, adsorbent and antidiarrheal. The dosage of aluminium hydroxide is 30 g/animal in cattle and 2 g/animal in calves and foals. Gel preparations contain approximately 4% aluminium hydroxide. Aluminium potassium sulphate is used topically as a antiseptic, astringent (i.e. washes, powders, and 'leg tighteners' for horses (30 to 60 g/animal) and antimycotic (1% solution for dipping or spraying sheeps with dermatophilus mycotic dermatitis). In cattle it is occasionally used for stomatitis and vaginal and intrauterine therapy at doses of 30 to 500 g/animal.

   In human medicine, aluminium hydroxide-based preparations have a widespread use in gastroenterology as antacids (doses of about 1 g/person orally) and as phosphate binders (doses of about 0.8 g/person orally) in patients an impairment of renal function. It is also a component of skin protective pastes.

2. Magnesium aluminium silicate has already been scientifically assessed by the CVMP and an entry into Annex II of Council Regulation (EEC) 2377/90 has been recommended.

   Aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522) and aluminium ammonium sulphate (E 523) are permitted food additives under European Parliament and Council Directive 95/21/EC. Aluminium (E 173) is permitted as a food colour under European Parliament and Council Directive 94/36/EC.

3. The aluminium powder is an highly potent adsorbent. It mixes well with the intestinal content and renders the gastro-intestinal toxins innocuous. Aluminium acts as co-agent in controlling bacterially induced gastro-intestinal affections. Owing to the astringent action, the colloidal structure of the upper tissue layers is solidified.

   The mechanism of action of antacid products is generally accepted to be chemical neutralisation of the hydrogen chloride present in gastric fluid. However, inactivation of pepsin is of importance, especially as far as peptic ulcers are concerned. Since pepsin activity for peptic digestion is optimal at pH 2 to 3, antacids should be able to raise the pH of gastric fluids to at least 3 or 4 without causing systemic alkalosis. It is important to realise that neutralisation of acid in the stomach antrum removes negative feedback control of gastrin release, which in turn will lead to elevated gastrin levels and enhanced hydrogen chloride secretion, with increased tone of the lower oesophageal sphincter.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

The action of antacids is usually transient and lasts only 1 to 2 hours. One gram of these antacid compounds will generally neutralise 20 to 35 mEq of acid *in vitro*. Additionally aluminium hydroxide forms a gel which protects the intestinal wall from irritations

4. Several studies on the pharmacokinetics of aluminium in mammalian species are available. The average fraction of absorbed aluminium is usually below 1% (close to 0.1 to 0.5%), depending on whether extra aluminium was given and in which form. However the absorption of some water soluble chelates such as aluminium citrate show a higher degree of absorption after oral administration to laboratory animals and man. The mechanism of absorption are fairly complex and not yet fully understood. This is partly due to chemical properties of aluminium, particularly great variability of solubility at different pH values, amphoteric character and formation of various chemical forms depending on pH, the ionic strength and presence of complexing agents. Although some studies on isolated everted gut sacs indicate that aluminium is taken up by an energy dependent process there are several studies suggesting energy independent mechanisms also occurring via paracellular pathways. A few studies report elevated uptake of aluminium in humans with low ferritin levels and an uptake mechanism employing the iron pathway in studies on rats.

   The aluminium hydroxide after oral administration is absorbed to a very small degree and will be almost completely excreted via the kidney.

   In dogs, the mean plasma half-life of aluminium after intravenous administration is approximately 4.5 hours. Only a small fraction is excreted in faeces, the main excretory pathway being via the kidney into urine. Current data indicate that biliary excretion is the major route of excretion, but renal elimination (through glomeruli) appears more important after large aluminium loads. There are no reliable data supporting dermal absorption from aluminium compounds.

5. Human studies have shown a low degree of oral bioavailability of aluminium hydroxide taken as an antacid with no apparent accumulation in the tissues in individuals with normal renal function.

   In an investigation using ^{26}Al-citrate exposure *in vivo*, the following distribution in plasma was observed at 6 hours: 80% (transferrin), 10% (albumin), 5 % (other proteins) and 5% (ultrafiltrable) (species not stated). Aluminium is distributed to soft tissues and it has been suggested that it is taken up by a transferrin receptor mediated mechanism. The brain appears to be one of the most important targets for aluminium toxicity. However, the blood brain barrier is normally permeable only to small molecules or actively transported proteins.

   The reference value of aluminium in human blood is in general in the range of 1 to 3 µg/l. The level of aluminium in plasma does not appear to reflect the intake of aluminium unless this is extremely high or combined with compromised kidney function. In contrast to aluminium in serum the excretion in urine correlates more closely over time with current aluminium exposure in exposed workers.. The aluminium excretion in healthy individuals is around 2.7 to 8.1 µg/l urine, or about 12 to 36 µg/day. Assessments of half-life for excretion following cessation of exposure indicate a relatively rapid phase with a half-life of 8 to 14 hours and a slow release phase with half lives of one or several months.

   Reported concentrations of aluminium in human tissues are virtually limited to bone, liver and brain. Values of 2.6 µg/g dry weight and 2.2 µg/g ash weight have been reported for bone and liver respectively of elderly Norwegians dying from causes other than renal failure. In renal failure much higher values in bone have been reported. The reported background level of aluminium in the brain is in the range of 1 to 3 µg/g dry weight. The mean level of aluminium in the frontal and temporal cortices of 14 and 11 deceased elderly persons with no brain pathology were 1.7 and 1.5 µg/g dry weight, respectively. Values ranging from 0.35 to 5.3 µg/g dry weight in deciduous teeth have been measured.

6. Nearly no information is available regarding toxicity of aluminium hydroxide in experimental or domestic animals. In general aluminium preparations tend to cause constipation.

7. While no studies on acute and repeated dose toxicity, reproductive toxicity including embryotoxicity/ foetotoxicity and tolerance in target species were available, submission of such studies was not considered necessary as aluminium and its salts have a long history of safe use in human and veterinary medicine and are not absorbed after administration (topical and oral).

8. In humans an increased exposure to aluminium via dialysis water (aluminium sulphate) is a known ethiological factor in several pathological conditions in patients on haemodialysis. Clinical manifestations of aluminium toxicity include hypercalcemia, anaemia, vitamin D refractory osteodystrophy, and a dialysis encephalopathy. Bone pain, pathological fractures, and proximal myopathy can occur. Aluminium has also been implicated in aetiology of various neurodegenerative diseases such as Alzheimer senile and pre-senile dementia and amyotrophic sclerosis. However, the most recent epidemiological investigations have failed to corroborate this hypothesis. A study in man has confirmed the possible deleterious interaction of aluminium salts in phosphorous metabolism, especially long-term ingestion of aluminium containing antacids.

9. The general population is principally exposed to aluminium from foods and beverages including drinking water. Aluminium intake from foods, particularly those containing aluminium compounds used as food additives (the sodium aluminium phosphate is a primary source of dietary aluminium intake), represent the major route of aluminium exposure with exception of persons who regularly ingest aluminium-containing drugs.

10. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) Committee in 1989 outlined that even at high levels of consumption, only a small amount of aluminium is absorbed. Aluminium which is absorbed is located primarily in the heart, spleen, and bone but its presence in these sites was without histopathologic lesions. JECFA estimated a provisional tolerable weekly intake of aluminium of 7 mg/kg bw (which includes intake of aluminium from the use as a food additive). Current estimates of aluminium intakes from food, based on newer methods of analysis, range about 2 to 6 mg/day for children and 6 to 14 mg/day for teenagers and adults.

11. No residue depletion studies in the target species after topical and oral administrations are available. Nevertheless, it is learned that aluminium levels of 24 to 68 µg aluminium/kg and 27 to 86 µg aluminium/kg can be reached in meat and fish respectively. The conceivable total intake of aluminium from unprocessed foods was by use of the food balance sheet calculated to about 600 µg/person/day.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No. 2377/90 and in particular that:

- aluminium compounds are mainly used as co-active substance in individual animals which are unlikely to be sent for slaughter immediately after treatment,
- aluminium compounds used in veterinary medicine have only a limited systemic availability and no toxicologically significant residues in the slaughtered animal are expected,
- the data available indicate that the bioavailability of the aluminium ingested in foods is low, presumably due to the presence of aluminium complexes of low solubility,
- aluminium compounds are used as food additive (anticaking, leavening, and stabilisers agents as well as food colorants);

the Committee concludes that there is no need to establish an MRL for aluminium distearate, aluminium hydroxide acetate, aluminium phosphate and aluminium tristearate and recommends their inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Aluminium distearate	All food producing species	
Aluminium hydroxide acetate	All food producing species	
Aluminium phosphate	All food producing species	
Aluminium tristearate	All food producing species	