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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BENZALKONIUM CHLORIDE

SUMMARY REPORT

1. Benzalkonium chloride is a quaternary ammonium antiseptic and surfactant. It consists of a mixture of alkyldimethylammonium chlorides, the alkyl chains having chain lengths of C_8 to C_{18}. The European Pharmacopoeia requires that benzalkonium chloride should contain not less than 95 % and not more than 104 % of alkyldimethylammonium chlorides, calculated as $C_{22}H_{40}NCl$.

2. In veterinary medicine, benzalkonium chloride is used as an excipient in an injectable glycocorticoid formulation intended for use in cattle, pigs, horses, sheep, goats and pigs. When used as excipient, the concentration in the formulation is less than 0.05%, resulting in a dose approximately of 0.006 and 0.009 mg/kg bw. This application is restricted to its use as excipient in an injectable formulation.

   It may also be used as eye lotion or as dermal spray. It has also been approved for the cleansing and disinfecting of stablings and animal transport in 0.04% concentration.

   In human medicine, benzalkonium chloride is used primarily as a skin disinfectant at concentrations of 0.1 to 0.2 % and as preservative at concentrations of 0.01% for eye drops. It is also the active ingredient of vaginal spermicide ovules (0.35 mg/kg bw/application).

3. Benzalkonium chloride possesses depolarising muscle relaxant properties, and hypotensive effects. It has no other known pharmacological effects. No information on the pharmacokinetics and on the metabolism of benzalkonium chloride was provided. However, benzalkonium chloride belongs to the family of the quaternary ammonium compounds known to be poorly absorbed from the gastrointestinal tract after oral administration.

4. In mice and rats the LD_{50} values were 350-400 mg/kg bw after oral administration.

5. The oral administration of 300 mg/kg bw/day of benzalkonium in the diet for 4-5 week did not induce overt effects in rats (no more experimental details were provided).

   In rabbits, oral administrations of 50 mg/kg bw/day for 2 weeks provoked accumulation of blood and fibrous deposits in the lungs, yellow patches on the liver but no changes in the blood cellular parameters in the two rabbits who died (no more experimental details were provided).

   Repeated dermal applications of benzalkonium chloride or C_{14}-C_{16} benzalkonium at doses of 10 mg/kg bw or more 5 times/weeks for 3 months to rats caused changes in blood cellular parameters, liver and kidney damage (no more informations were provided), increased body temperature and increased weights of adrenals, kidney and testes (no more experimental details were provided).

   In rabbits, dermal applications of C_{18} benzalkonium at doses of 2 mg/kg bw/5 days/week for 4 weeks showed no adverse effects (no more experimental details were provided).

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6. In an oral reproduction study, mice received benzalkonium chloride by gavage at doses of 0.001, 0.05, 0.1, 3, 10 and 30 mg/kg bw/day from the day 0 to the day 6 of pregnancy. At 3 mg/kg bw/day and above, significant dose-related decreases in the rate of pregnancy and in the number of implantations and in the number of foetuses were reported. No adverse effects were noted up to 0.1 mg/kg bw.

   The oral administrations of benzalkonium chloride at doses of 0.001 and 0.05 mg/kg bw/day from the day 0 to the day 18 of pregnancy did not induce adverse effects.

   In non-oral embryotoxicity study, Wistar female rats received 0, 25, 50, 100 and 200 mg/kg bw of benzalkonium chloride in an aqueous solution, by instillation into the vagina 24 hours post-conception. In the 100 and 200 mg/kg bw dose groups, clinical signs (decrease in the bodyweight, watery discharge from the vagina) related to vaginal inflammation were reported. At 100 mg/kg bw or more, abnormal bone development, increases in resorptions, reduced foetal growth were seen. At 50 mg/kg bw and above, a significant dose-related decrease in the number of live foetuses per litter and in litter size and weights was noted. No adverse effects were noted at the dose of 25 mg/kg bw/day, neither in females nor in foetuses. In this study, NOELs of 50 mg/kg bw/day and of 25 mg/kg bw/day were retained for maternotoxicity and embryotoxicity.

7. Benzalkonium chloride gave negative results *in vitro* in the Ames test, in chromosomal aberrations tests in Chinese hamster ovary cells. Benzalkonium chloride caused DNA damage in *Escherichia coli* and gave equivocal results in *Bacillus subtilis* in rec assay. No evidence of chromosomal damage was seen in the *in vivo* micronucleus tests carried out after intra-peritoneal injections of 20 mg/kg bw of benzalkonium. However as only brief summary reports were provided, no conclusion on the mutagenicity of this compound can be reached.

8. Carcinogenicity studies conducted on rats (up to about 250 mg/kg bw/day in the diet for 2 years) and on guinea pigs (up to 25 mg/kg bw/day for 1 year) did not reveal evidence of carcinogenicity.

   Twice-weekly uncovered dermal applications of up to about 85 mg/kg bw onto mice and up to 1.7 mg/kg bw onto rabbits gave no evidence of tumors in the major organs (no more details were provided).

   The studies described in this session involved only limited examination of the tissues. However, further data were not considered necessary due to the lack of mutagenic and carcinogenic potential of the quaternary compounds.

9. In humans, if ingested, benzalkonium chloride causes nausea and vomiting. Topical preparations are associated with an extremely low incidence of adverse reactions; there have been occasional reports of skin irritation and some patients become hypersensitive after repeated applications.

10. Repeated dermal or intradermal applications of 0.01-3 % water solution of benzalkonium induced senzitization, eye irritation and skin irritations in several laboratory animals (rabbits, guinea pigs, mice).

11. No residues depletion studies have been carried out.

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 2277/90 and in particular that:

- benzalkonium chloride belongs to the group of quartenary ammonium compounds which are known to be of low toxicity and are poorly absorbed from the gastrointestinal tract,
- the total dose administered to animals is low (less than 0.009 mg/kg bw),
- benzalkonium chloride has a long history of safe use in human medicinal products,
- the use of benzalkonium chloride should not result in residues in food of animal origin at concentrations which are toxicologically relevant for the safety of the consumer;

the Committee considers that there is no need to establish MRLs for benzalkonium chloride and recommends its 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**
Benzalkonium chloride	All food producing species	For use as an excipient at concentrations up to 0.05% only