The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BENZOCAINE

SUMMARY REPORT (1)

1. Benzocaine (4-aminobenzoic acid ethyl ester) (synonym: ethyl aminobenzoate), is a local anaesthetic of the ester type with a poor solubility in water. It is used in cattle, sheep, swine and horses for local and prolonged low epidural anaesthesia. Standard therapeutic doses of benzocaine ranged from 150 to 750 mg per animal. Benzocaine is also currently used as surface anaesthetic as ointments (0.5% benzocaine) for wounds and ulcerated surfaces in horses, cattle and sheep applied twice a day until healing.

2. Benzocaine acts on the central nervous system, cardiovascular system, neuromuscular junctions and ganglion synapse. Its mechanism of action is to prevent the generation and conduction of the nerve impulse. Local anaesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that is produced by a slight depolarisation. This action of local anaesthetics is due to their direct interaction with voltage-sensitive Na^+ channels.

   Benzocaine is mainly hydroxylated in the metabolite para-aminobenzoic acid (PABA) that inhibits the action of sulphonamides.

3. Benzocaine is distributed in the body, crosses the placenta and is metabolised in the liver and in the plasma by non-specific cholinesterases. Benzocaine and its main metabolite (para-aminobenzoic acid) are excreted into urine.

4. Benzocaine appears as a moderately toxic compound after single administration. The acute intraperitoneal LD_{50} value was 216 mg/kg bw in mice. Benzocaine may induce methemoglobinemia in several species such as sheep, cats and dogs.

5. While no studies on repeated dose toxicity, reproductive toxicity including embryotoxicity/ foetotoxicity, mutagenicity, carcinogenicity and tolerance in target species were presented, submission of such studies was not considered necessary as benzocaine has a long history of safe use in human and veterinary medicine and is rapidly eliminated.

6. Literature on observations in human was available. The pharmacodynamic properties presented contained insufficient data to derive a pharmacological NOEL. The common signs or accidents seen after administration of benzocaine in human beings include: nervous, respiratory and cardiovascular alterations and foetal deaths. Allergic reactions have been described associated with benzocaine and PABA appears as responsible for these clinical manifestations. Benzocaine elicits positive reactions in the cutaneous sensitisation test in 3.3-5.9% of the patients. Benzocaine may also induce methemoglobinemia in humans. Information on the oral bioavailability in man is also unavailable.

7. While no residue depletion studies were available these studies were not considered necessary as pharmacokinetic data indicate rapid elimination of benzocaine.

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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:

- the substance is used in individual animals on an infrequent basis,
- treated animals are unlikely to be send for slaughter after treatment,
- the substance is rapidly eliminated;

the Committee concludes that there is no need to establish an MRL for benzocaine when used as a local anaesthetic 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
Benzocaine	All food-producing species	For use as local anaesthetic only