



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ALFAPROSTOL (extension to rabbits)

SUMMARY REPORT (2)

1. Alfaprostol is a synthetic analogue of prostaglandin F₂α. Its activity is similar to that of the endogenous PFG₂α, causing luteolysis. It is used as a single intramuscular injection in cows (0.015 mg/kg bw), sows (2.0 mg/animal) and mares (3.0 mg/animal).

An ADI of 1 µg/kg bw (i.e. 60 µg/person), based on a NOEL of 0.1 mg/kg bw/day observed in a 13-week rat study has been previously established.

Currently, alfaprostol is included in Annex II to Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
Alfaprostol	Bovine, porcine, equidae	

An application for the extension of the current entry to include rabbits has now been submitted. In rabbits alfaprostol is indicated for routine grouping of parturition and oestrus synchronisation at the recommended dose of 0.2 mg/animal in a single subcutaneous injection. A second injection may be given after 7 days if required.

2. Alfaprostol is rapidly absorbed following administration by either subcutaneous or intravaginal route in rabbits. Peak levels are achieved by 4 hours following subcutaneous administration and by 0.5 hours following intravaginal administration. Elimination is rapid with a total of 70% and 50% of the dose eliminated in the urine and faeces within 24 hours after subcutaneous injection.
3. Following administration of alfaprostol at a dose rate of 8.47 mg/kg bw by the subcutaneous route and 6.54 mg/kg bw by the intravaginal route, plasma levels in rabbits show a rapid decline over 120 hours, C_{max} was reached in 4 hours, t_{1/2} was calculated as 16 hours and a plasma level of 60 ng/ml was measured at 10 days, the levels in liver at this time was 39 µg/kg while kidney had levels of 54 µg/kg.
4. There is no information on metabolism in rabbits but it will be assumed that this will follow a similar pattern to metabolism in cattle, pigs and horses-pharmacokinetic parameters show similar characteristics in all species mentioned.
5. Tissue levels in liver and kidney of rabbits following either subcutaneous or intravaginal administration were determined at 10 days after treatment in two groups of three animals each; there were no values for alfaprostol in muscle and fat. Extrapolation from residue levels observed in muscle and fat of cows, pigs or horses is not possible due to the discrepancy in the dosage tested in rabbits and in slaughter times (rabbits: 10 days after treatment; cattle, horses and pigs: 24 hours after treatment).

From these studies it is evident that the pharmacokinetic profile of alfaprostol is similar in all species and that rapid absorption and elimination occurs.

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, also the criteria outlined for Establishment of Maximum Residue Limits for Minor Animal Species-EMEA/CVMP/153a/97 and in particular that:

- alfaprostol is rapidly excreted from treated animals,
- treated animals are unlikely to be sent for slaughter immediately after treatment,
- residues in animals treated at the recommended doses are not orally active;

the Committee considers that there is no need to establish an MRL for alfaprostol for treatment of rabbits 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
Alfaprostol	Rabbits	