



COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

DEXAMETHASONE (Extrapolation to goats)

SUMMARY REPORT (3)

1. Dexamethasone is a synthetic derivative of the glucocorticoid hydroxycortisone. It is used in the treatment of metabolic diseases (e.g. ketosis) in ruminants and inflammatory diseases in a number of animal species. Dexamethasone is included in Annex I of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Dexamethasone	Dexamethasone	Bovine, porcine, <i>Equidae</i>	0.75 µg/kg 2.0 µg/kg 0.75 µg/kg	Muscle Liver Kidney	
		Bovine	0.3 µg/kg	Milk	

2. In reviewing the availability of endo- and ectoparasiticides for sheep and goats, dexamethasone was considered for extrapolation from bovine to caprine species. The considerations and criteria leading to the identification of dexamethasone are described in the Position Paper Regarding Availability of Veterinary Medicines – Extrapolation of MRLs (EMA/CVMP/457/03-FINAL).
3. The scientific justification for this extrapolation was assessed in accordance with the Notes for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMA/CVMP/187/00-FINAL) and on the Establishment of Maximum Residue Limits for Minor Animal Species (EMA/CVMP/153a/97-FINAL).
4. In setting the ADI in the original assessment of dexamethasone, the data summarised in the paragraphs below were considered.
5. Toxicokinetic studies revealed rapid systemic absorption after intramuscular administration with peak plasma levels being attained in 30 minutes and 6 hours in dogs and rats respectively. It is rapidly excreted in urine and faeces. Dexamethasone esters are rapidly hydrolysed in serum. Biotransformation in rats and humans is comparable and mainly involves hydroxylation to 6-hydroxy- and 2-dihydroxydexamethasone.
6. Following repeated administration of dexamethasone to dogs (oral doses of 2 or 8 mg/kg bw per day for 26 weeks; oral doses of 0 or 0.125 mg/kg bw per day for 6 weeks or intramuscular doses of 0, 0.040 or 0.079 mg/kg bw per day for 13 weeks) and rats (subcutaneous doses of 0 or 0.050 mg/kg bw per day for 6 weeks, oral doses of 0, 0.125, 0.25 or 0.4 mg/kg bw per day for 181 to 185 days, subcutaneous doses of 0, 0.040 or 0.079 mg/kg bw per day for 13 weeks, oral doses of 0, 0.0003, 0.001, 0.003, 0.01, 0.03 or 0.1 mg/kg bw per day for 90 days or oral doses of 0.0005, 0.001, 0.0015, 0.002 or 0.004 mg/kg bw per day for 7 days), the target organs were the thymus and adrenal gland.

Corticosteroid levels in plasma and hepatic glycogen were reduced, but lipid levels were increased. In rats dosed orally with up to 0.1 mg/kg bw/day dexamethasone for 90 days, thymus involution and morphological changes occurred in the adrenal gland. The NOEL was 0.003 mg/kg bw/day although a marginal decrease in white blood cells occurred at this dose. When given to rats orally for 7 days with doses of up to 0.004 mg/kg bw/day, corticosterone levels were reduced at the highest dose level, while increases in hepatic tyrosine amino transferase were noted. The NOEL was 0.0015 mg/kg bw/day.

7. In teratology studies with mice (using subcutaneous doses of 6 mg/kg bw per day), rats (subcutaneous doses of 0, 0.02, 0.04 or 0.079 mg/kg bw per day, subcutaneous doses of 0.25, 1 or 4 mg/kg bw per day, subcutaneous doses of 0, 0.04 or 0.079 mg/kg bw per day, subcutaneous doses of 0, 0.002, 0.004 or 0.008 mg/kg bw per day, oral doses of 0, 0.01, 0.05, 0.25 or 1.25 mg/kg bw per day or oral doses of 0, 0.02, 0.2 or 1 mg/kg bw per day) and rabbits (intramuscular doses in the range 0.025 to 1 mg/kg bw per day or subcutaneous doses of 0, 0.04 or 0.079 mg/kg bw per day), increases in pre- and post-implantation losses occurred along with reductions in foetal weight. In these studies, a number of malformations were seen but only at maternally toxic doses. The overall NOEL for developmental toxicity was derived from a rat study and was based on embryotoxicity (0.01 mg/kg bw/day).
8. Dexamethasone has been tested for gene mutations in bacteria and in mammalian cells *in vitro* and gave negative results. Negative results were also obtained in the mouse micronucleus test *in vivo*. No carcinogenicity studies have been conducted with dexamethasone but in view of the negative results in mutagenicity studies, and the lack of structural similarity with known carcinogens, these are not required.
9. Using a safety factor of 100 and the NOEL of 0.0015 mg/kg bw/day for the induction of tyrosine transaminase in the rat, an ADI of 0.000015 mg/kg bw/day is calculated.
10. For the extension to include caprine species in Annex I the information summarised in the paragraphs below was taken into account.
11. Residue studies indicate that different ester preparations lead to different dexamethasone depletion rates. However, studies in cattle indicate that dexamethasone residues are quickly eliminated from muscle and the milk of cows. Residues do not occur in the free form in fat and the depletion rate in liver is the slowest. Hence, this is identified as the target tissue.
12. The major metabolic excretion route for dexamethasone in all species involves hydroxylation at 6-position of the steroid ring. Conjugates are also formed and these metabolic pathways lead to rapid and extensive loss of corticosteroid activity. Consequently, parent dexamethasone is proposed as the marker residue.
13. Following intramuscular administration of 0.06 mg/kg bw dexamethasone (as the phosphate ester) to 8 dairy cows, mean residues in the milk declined from 7.03 µg/kg at the first milking after treatment, to 1.25 µg/kg at the 3rd milking after treatment and were below the limit of quantification (0.25 µg/kg) at the 5th milking. Following treatment of heifers and young bulls with 60 µg/kg dexamethasone, the mean residues in liver declined from 127 µg/kg 1 day after treatment to 16 µg/kg, 2 days after treatment to below 2.6 µg/kg 4 days after treatment. Over the same time period, mean residues in kidney and muscle declined from 78 µg/kg to 13 µg/kg to less than 0.9 µg/kg and 3.3 µg/kg to 0.75 µg/kg to below the limit of quantification (0.5 µg/kg) respectively. Residues were undetectable in fat. Four days after treatment, residues were undetectable in most samples except for the residues at the injection site; these declined from a mean of 8 µg/kg, one day after treatment, to 3.7 µg/kg, 2 days after treatment, to 2.2 µg/kg, 4 days after treatment.
14. Following intramuscular administration of 0.06 mg/kg dexamethasone (as the phosphate ester) to pigs, residues in all tissue samples taken 1, 2 and 4 days after treatment were below the limit of quantification (2.5 µg/kg for liver and 0.5 µg/kg for other tissues).

15. The analytical method for the determination of residues of dexamethasone was based on HPLC with mass spectrometric detection *via* thermospray interface with positive filament ionisation. The method was validated in accordance with Volume VI¹ of the Rules Governing Medicinal Products in the European Community. The limits of quantification were 0.25 µg/kg for bovine milk, 0.5 µg/kg for bovine liver, 1.0 µg/kg for porcine and equine liver, and 0.5 µg/kg for bovine, porcine and equine muscle and kidney. The limits of detection were 0.1 µg/kg for milk and 0.25 µg/kg for tissues. Because dexamethasone esters are rapidly hydrolysed upon entering the peripheral circulation, the method did not include a hydrolysis step. However for the analysis of injection site tissue, an enzymatic hydrolysis step has to be included after homogenisation. Although the limit of quantification for milk was more than 50% of the proposed MRL, the values for accuracy and precision suggested that this was acceptable. The analytical method was satisfactorily described in the ISO 78/2 format. This method should be applicable to caprine species and therefore from this aspect extrapolation to the tissues and caprine milk is possible.
16. Because residues of dexamethasone are not detectable in fat, no MRL is required.
17. The MRLs proposed by the CVMP are slightly different from those proposed by the WHO/FAO Joint Expert Committee on Food Additives (JECFA). It was decided not to adopt the JECFA values because the limits of quantification of the assay for muscle and kidney are the same as the JECFA MRLs.
18. Ruminant species such as bovine and caprine share a similar gastro-intestinal physiology. The available pharmacokinetic and residues depletion data indicate that dexamethasone metabolites show extensively less corticosteroid activity than the parent substance and residues are quickly eliminated from muscle and milk in cows. It was considered that goats were unlikely to show any significant differences in these parameters. Therefore, it was considered appropriate to recommend the extension of the MRLs so that that the same MRL values would apply to caprine species, including milk.

Conclusions and recommendation

Having considered that:

- an ADI of 0.000015 mg/kg bw/day (i.e. 0.9 µg/person) was previously established for dexamethasone,
- MRLs were previously established in bovine species; these MRLs would apply to goats,
- an analytical method for the monitoring of residues in tissues and milk of caprine species was available;

the Committee for Veterinary Medicinal Products recommends the inclusion of dexamethasone in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Dexamethasone	Dexamethasone	Caprine	0.75 µg/kg 2.0 µg/kg 0.75 µg/kg 0.3 µg/kg	Muscle Liver Kidney Milk	

On the basis of these MRLs, the theoretical estimated consumer intake of dexamethasone in the food package was 0.0009125 mg/day. This exceeded the ADI of 0.0009 mg/day by a small amount. However it was considered that this would not represent a risk to human health because the substance was used only occasionally in individual animals.

¹ Now Volume 8 following revision on September 2001 and June 2003