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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DEXAMETHASONE

SUMMARY REPORT (1)

1. Dexamethasone is a synthetic analogue of the glucocorticoid hydroxycortisone which has been used for many years in human and veterinary medicine. It is available as the free alcohol or in the form of esters, and it is used in the treatment of metabolic diseases (e.g. ketosis) in ruminants and inflammatory diseases in a number of animal species.

2. 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-dihydroxdexamethasone.

3. Following repeated oral administration of dexamethasone to dogs and rats in short-term toxicity studies, 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 100 µg/kg bw/day dexamethasone for 90 days, thymus involution and morphological changes occurred in the adrenal gland. The NOEL was 3 µg/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 4 µg/kg bw/day, corticosterone levels were reduced at the highest dose level, while increases in hepatic tyrosine amino transferase were noted. The NOEL was 1.5 µg/kg bw/day.

4. In teratology studies with mice, rats and rabbits, 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 embrotoxicity (10 µg/kg bw/day).

5. 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 carcinogeniticy studies have been conducted with dexamethasone but in view of the negative results in mutagenicity studies, and the lack of structural similarity with know carcinogens, these are not required.

6. Using a safety factor of 100 and the NOEL of 1.5 µg/kg bw/day for the induction of tyrosine transaminase in the rat, an ADI of 0-0.015 µg/kg bw/day is calculated.

7. Residues studies indicate that different ester preparations lead to different dexamethasone depletion rates. However, studies in cattle and pigs 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 that the depletion rate in liver is the slowest. Hence, this is identified as the target tissue.

8. 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. Enzymatic treatment of extracts is required to ensure that all conjugates are converted to parent drug for the purposes of residues analysis.

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9. Based on the ADI of 0-0.015 µg/kg bw/day the permitted daily intake of parent dnig is 0.9 µg/day. From this and the residues depletion data, the following MRLs can be elaborated for cattle, horses and pigs.

muscle	0.5 µg/kg
liver	2.5 µg/kg
kidney	0.5 µg/kg
milk	0.3 µg/kg

There is inadequate information for fat but as residues of the free drug do not occur in this tissue, no MRL is required. On the basis of these MRLs, the amount of dexamethasone residues present in the food package would not exceed the ADI.

10. The limit of quantitation of the assay is the same as the maximum residue limits. Consequently, the MRLs proposed are provisional until a fully validated routine analytical method, which takes account of these MRL values in accordance with the requirements of Volume VI, is available. These provisional MRLs expire on 1.1.1997. The required information, as mentioned below, shall be submitted before 1.1.1996.

LIST OF QUESTIONS

Residues File

1. The MRLs are set at the limit of quantitation of the analytical method. The applicant shall provide a suitable method for residues surveillance which has a limit of quantitation below the MRLs for each tissue, in accordance with the requirements of Volume VI.