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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HYDROCORTISONE

SUMMARY REPORT

1. Hydrocortisone is a naturally occurring corticosteroid which is produced by the adrenal cortex. It is used in veterinary medicine in topical preparations for ocular administration. A range of preparations is used in human medicine.

2. Hydrocortisone influences carbohydrate, protein and lipid metabolism but its mineralcorticoid action is weak. Its gluconeogenic potency is approximately 2.5% of that of dexamethasone. There were no data to establish a pharmacological NOEL.

3. In humans the oral bioavailability of hydrocortisone was shown to range from 45 to 80% and was dose-dependent. In fasted adult males, a C_{max} value of 199 ng/ml was attained 1 hour after an oral dose of 10 mg. In the same individuals, a C_{max} value of 419 ng/ml was attained 1.7 hours after an oral dose of 50 mg. The half-life for plasma elimination was reported to be in the range 80 to 120 minutes. Plasma clearance was dose-dependent and ranged from 300 to 500 ml/min over the dose range 5 to 50 mg. At normal physiological concentrations (400 nmol/l) hydrocortisone was extensively bound to plasma proteins, 89.5% to transcortin and 6.6% to albumin. Endogenous plasma hydrocortisone concentrations showed diurnal variation and plasma clearance was significantly higher in the morning compared with the evening. Following subcutaneous administration of 0.5 mg/kg bw ^{14}C-hydrocortisone to rats, 74 to 89% of the administered dose was recovered within 24 hours, mostly in the faeces. Rapid excretion was also observed in guinea pigs, however in this species, most of the dose was excreted in urine.

4. The normal blood concentrations of hydrocortisone were reported to be 130 to 293 µg/l in horses, 61 ± 7 µg/l in cattle, 224 ± 36 µg/l in sheep, 235 ± 29 µg/l in goats and 297 ± 10 µg/l in pigs.

5. In humans hydrocortisone was shown to be interconvertible with the inactive metabolite cortisone with the equilibrium favouring hydrocortisone. Cortisone was metabolised further to 20-hydroxycortisone, and then to cortolones and tetrahydrocortisone. A major metabolic pathway involved 5β-reduction to tetrahydrocortisol. The major metabolites did not retain any corticosteroid activity.

6. Single dose toxicity studies were carried out in rats and mice. The acute intraperitoneal LD_{50} in rats was reported to be 150 mg/kg bw. The acute subcutaneous LD_{50} in male Sherman rats was greater than 1800 mg/kg bw following a 7-day observation period. However many rats died in the second week after dosing due to infections which may have been related to the immunosuppressive effect of the substance. The effects observed in acute studies in rats and mice included reduced adrenal weights, liver damage, lung consolidation and gastrointestinal effects.

7. Repeated-dose toxicity studies were carried out in rabbits given intramuscular injections of 10 or 15 mg/animal of hydrocortisone or 25 mg/animal of hydrocortisone acetate per day for up to 8 days. The studies were designed to investigate hepatotoxicity and no other parameters were monitored. Hepatotoxicity was observed in all treated groups with increased liver weight, focal hepatic necrosis and increased glycogen deposition. Liver weights in rabbits which were left

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

untreated for 20 days before necropsy were comparable with the controls. No NOEL was established.

8. There were no multigeneration studies and no studies concerning the potential effects of hydrocortisone on fertility or peri/post-natal development.

9. Intramuscular doses of 15 to 50 mg/animal hydrocortisone to pregnant hamsters induced cleft palate in the foetuses. Ocular administration of 1.2 or 1.8 mg/animal of hydrocortisone was teratogenic in rabbits. In mice, ocular administration of 0.75 and 1.5 mg/animal to dams caused a dose-related incidence of cleft palate in the foetuses but no significant increase was observed following administration of 0.18 mg/animal. Cortisone, which is metabolised to hydrocortisone, also induced foetal cleft palate when administered intramuscularly to pregnant guinea pigs at doses of 320 mg/kg bw. These studies were designed primarily to investigate the induction of cleft palate and therefore did not follow OECD guidelines and used limited dosing regimes. No conclusions can be drawn regarding NOELs.

10. Hydrocortisone was not mutagenic in an *in vitro* assay for gene mutation in *Salmonella typhimurium* TA97a, TA98, TA100 or TA1535, in either the presence or absence of metabolic activation. Positive results were obtained in an *in vitro* chromosomal aberration assay in human lymphocytes though there was no dose-response over the concentration range studied (1 to 50 µg/ml). There was a dose-related increase in the numbers of micronucleated polychromatic erythrocytes in an *in vivo* micronucleus test in which mice were given single intraperitoneal injection of 1, 10 or 100 mg/kg bw hydrocortisone. Positive results were also obtained in an *in vivo* sister chromatid exchange analysis in the bone marrow of mice given single intraperitoneal injection of 0.1, 1 or 10 mg/kg bw hydrocortisone. All of the positive results were reported in a single published report and no information was provided concerning the purity of the material tested. The results conflicted with the negative results of mutagenicity studies carried out with the synthetic corticosteroids dexamethasone, prednisolone and methylprednisolone.

11. No carcinogenicity studies were provided. Carcinogenicity studies with the synthetic corticosteroid prednisolone, and its metabolite prednisone, gave no indication of carcinogenic potential.

12. In a cross-over design study, human volunteers were given a single intravenous dose of 100 or 400 mg/person hydrocortisone. Both doses caused transient decreases in lymphocyte and monocyte counts which had reverted to normal values 24 hours after dosing.

13. No data concerning potential microbiological effects were provided. It was agreed that these data were not needed for this class of substances.

14. In humans, hydrocortisone is administered as free alcohol, acetate, aceponate, butyrate, cypionate, hemisuccinate, phosphate or valerate. For replacement therapy in cases of acute or chronic adrenocortical insufficiency, the normal oral dose is 20 mg in the morning and 10 mg in the evening, to mimic the circadian rhythm of the body. Hydrocortisone may also be administered intravenously for emergency treatment of post-adrenalectomy crises or certain allergic emergencies at a dose of 100 to 500 mg, repeated 3 or 4 times every 24 hours. A range of topical preparations is also available. Adverse reactions are normally observed only after administration of high doses for a prolonged period and include gastrointestinal haemorrhage and opportunistic infections. Hydrocortisone has fewer side effects and is less likely to cause adrenal insufficiency when administered topically.

15. No NOELs were established in the pharmacology and toxicity studies which could be used as the basis for an ADI calculation. However the daily production of hydrocortisone in normal humans had been investigated in several studies and was in the range of 17 to 30 mg per person per day.

16. There were no pharmacokinetic, metabolism or residues depletion data in the target species. Given the fact that the substance is administered only as a topical preparation to the eye, residues in the edible tissues and milk are not expected. Moreover, considering that hydrocortisone is an endogenous substance, these data were not considered necessary.

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:

- hydrocortisone is an endogenously produced substance,
- hydrocortisone is used in topical preparations only;
- hydrocortisone is used for the treatment of individual animals only;
- the animals are unlikely to be sent for slaughter during or immediately after treatment,

the Committee concludes that there is no need to establish an MRL for hydrocortisone and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Hydrocortisone	All food producing species	For topical use only