The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/044/95-FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

COLCHICINE

SUMMARY REPORT

1. Colchicine is an alkaloid of plant origin. Colchicine is used in veterinary medicine to treat papillomas and warts in cattle and horses. The recommended dosage is 5 mg every 2 days until complete disappearance (directly injected at the base of the wart or in area of papilloma).

2. Colchicine is rapidly absorbed following oral administration in human patients. The plasma peak reaches 3 µg/l between 30 min. and 2 h. after the oral administration of dose level of 1 mg.

3. After intravenous administration of H^3-Colchicine to rat, hamster, rabbit and dog (0.2-2 mg/kg), Colchicine is widely distributed. High levels have been found in the liver, kidneys, spleen and intestinal tract.

4. Bioconversion in the liver is partial (70 to 80%) and leads to inactive metabolites after de-acetylation and partial de-methylation.

   In various species, the major component in bile has been shown to be unchanged Colchicine, with variable percentages of desmethyl Colchicine, desmethyl Colchicine glucuronide, and unspecified polar metabolites.

   In human after enterohepatic circulation, most of the absorbed drug is excreted as inactive metabolites in the faeces, but in normal individuals 10-20% is excreted unchanged in the urine.

5. There is relatively little published information on the general toxicology of purified Colchicine.

   Single doses of Colchicine were severely toxic to mice (the following LD_{50} values were obtained : 5.8 mg/kg b.w (oral), 1.2 mg/kg bw (sc), 1.2, mg/kg b.w (im), 2 mg/kg bw (ip) and 1.7 mg/kg b.w.(iv)). The intravenous value of LD_{50} in cats was 0.25 mg/kg bw.

6. *In vitro* Colchicine altered the trilamellar structure of kinetochores, and inhibited tubulin assembly, 2.10^{-6} M being the 30% inhibition concentration (IC_{30}).

7. Colchicine administered in gravid mice induced malformation, pre-implantation loss and effects on embryo or foetus (foetal death). In mice and male rats injected into testicles, Colchicine causes lowered spermatogenesis. These effects on reproduction are observed at dose of 0.25 mg/kg, irrespective of the administration route.

8. Colchicine gave positive results *in vivo* and *in vitro* for gene and chromosome mutation (all mutagenicity assay). Colchicine has an aneugenic potential *in vivo* (1 mg/kg) and *in vitro* (0.006 µg/ml).

9. No data for the carcinogenicity of Colchicine in experimental animals were provided.

   Colchicine is an antimitotic compound that has an anti-tumour action.

   Colchicine binds to microtubular proteins, thereby causing depolymerization and disappearance of microtubules in cells.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

10. Colchicine is used in humans medicine for the relief of acute gout and in treatment of familial Mediterranean fever. The signs of acute toxicity appear from 0.1 mg/kg. The most frequent adverse effects of Colchicine are those involving the gastro-intestinal tract and may be associated with its antimitotic action (diarrhoea, nausea ...). Bone marrow depression with agranulocytosis, thrombocytopenia and aplastic anaemia have occurred on prolonged treatment as have peripheral neuritis, myopathy, rashes and alopecia. Effects on the neuromuscular system (myopathy, neuropathy) were also reported.

    Colchicine may have effect on the quality of sperm and on fertility.

    Historical obstetric observations for 36 woman on prolonged Colchicine therapy suggested that Colchicine increase the risk of producing trisomic offspring if conception occurs during therapy with the drug.

Conclusion and recommendation

Having considered that :

- Colchicine is genotoxicity in *in vitro* and *in vivo* systems even at low concentrations/doses,
- Colchicine has the ability to cause malformations in offspring,
- Colchicine has the ability its ability to induce effects on fertility and its
- teratogenic properties,
- there are no data on the absorption from the local administration in cattle and horses.

The Committee concluded that no ADI could be established and therefore, recommends the inclusion of Colchicine into Annex IV of Council Regulation (EEC) No 2377/90.