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

EMEA/MRL/080/96-FINAL
April 1996

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DEMBREXINE

SUMMARY REPORT

1. Dembrexine is a mucolytic agent which reduces the viscosity of respiratory mucus. Dembrexine also possesses an anti-tussive effect. It is indicated for use in horses only at a dose of 0.3 mg/kg bodyweight, twice daily. Treatment is initiated with an intravenous loading dose followed by oral maintenance therapy for up to 15 days.

2. Dembrexine is rapidly and almost completely absorbed following oral administration in animals. The compound is rapidly eliminated from plasma. Enterohepatic recirculation leads to a second phase of absorption with submaximum concentrations reached at 6 hours post dosing. Metabolism to conjugates with glucuronic acid and sulphate occurs with elimination mainly via the urine.

3. Dembrexine has a low order of acute toxicity, doses of 5 g per kg bodyweight orally being well tolerated in several laboratory species.

4. Repeated dose studies were conducted in rats, rabbits and dogs. In rats given doses up to 400 mg/ kg bw for 90 days, no clinical signs of intolerance and no organ damage at necropsy were observed. At the doses administered, dembrexine had no effect on the bodyweight development in treated rats and no effect on haematological or biochemical parameters. Administration of dembrexine at doses of 0, 2, 50 and 200 mg/kg bw for 90 days to dogs did not induce any serious abnormalities or organ damage. However, at 50 and 200 mg/kg dose levels dembrexine had a catabolic effect (reduction in bodyweight development). Haematological examinations and urin analysis of all groups of treated dogs did not reveal any substance related effects. A slight increase in blood urea nitrogen (BUN) in 1 out of 6 dogs dosed with 2 mg/kgbw at the interim (week 7) sampling period was observed; however all animals in this group had normal BUN levels at the terminal sampling period (week 13). Histological examination of the organs on all treated groups revealed no substance related abnormalities. From the repeated dose studies in dogs a NOEL of 2 mg per kg bodyweight per day was established.

5. Dembrexine was not teratogenic in rabbits or rats. Studies on the effects of dembrexine on reproductive parameters were not carried out. However, Segment I, II and III studies on a related compound - ambroxol- were carried out in rats, and in other laboratory species. The studies on ambroxol showed no effect on fertility and reproduction in rats at doses up to 640 mg/kg bw, no teratogenic effects in gravid mice, rats and rabbits at doses up to 3,000 mg/kg bw and no effect on perinatal or postnatal development in rats at doses up to 110 mg/kg bw.

6. Mutagenicity tests on dembrexine in the Ames test, Chinese hamster V79 forward mutation assay and in the mouse micronucleus test were negative.

7. No carcinogenicity studies were carried out using dembrexine. Studies on a related compound ambroxol, which were carried out in accordance with GLP, showed no neoplastic potential in either mice or rats.

8. Tolerance studies in horses demonstrated that dosages up to 15 times the recommended therapeutic dose given for 7 days were well tolerated. No clinical abnormalities, no haematological and no biochemical abnormalities were found in treated animals.

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9. Bioavailability data from humans show that dembrexine is rapidly absorbed and eliminated. The maximum plasma concentration is reached within 15 minutes of oral administration. Eight hours following administration the plasma concentration was only 6% of the maximum level.

   Dembrexine is not used in human medicine and a pharmacological NOEL has not been established.

10. It was considered that the toxicological effects in laboratory animals were more relevant than the pharmacological effects (changes in mucous secretion volumes) in establishing the ADI.

    Using a NOEL of 2.0 mg/kg bw from the 90 day oral toxicity study in dogs and applying a safety factor of 100, an acceptable daily intake (ADI) for humans of 1.2 mg/person/day is established.

11. Residue studies in horses show that sulphate and glucuronide conjugates were also present in these animals. The major metabolites in liver, kidney and muscle of treated horses were either parent compound (approximately 60% of total residues) or the cis-isomer (32-38% of total residues).

    Dembrexine is rapidly eliminated from treated horses. Total residues present in muscle, fat, liver and kidneys of treated animals amounted to 1.3 mg at one day post dosing with 3 times the recommended therapeutic dose administered for 10 days using ^{14}C-radiolabelled dembrexine.

    Residues of dembrexine in animals treated with the recommended therapeutic dose are likely to be well below the ADI within 24 hours of last treatment.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- dembrexine is intended for use in a small number of individual animals;
- treated horses are unlikely to be sent for slaughter immediately after treatment;
- dembrexine is rapidly and extensively detoxified and excreted.

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

Pharmacologically active substance(s)	Animal species	Other provisions
Dembrexine	Equidae	