



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### DIMETRIDAZOLE (3)

#### SUMMARY REPORT

1. Dimetridazole is a 5-nitroimidazole drug traditionally used for the prevention and treatment of histomoniasis in turkeys, the treatment of trichomoniasis in pigeons, genital trichomoniasis in cattle and the prevention and treatment of haemorrhagic enteritis in pigs.
2. The safety of dimetridazole residues in food for human consumption has been assessed on the basis of the mutagenic and carcinogenic potential of these compounds.
3. Dimetridazole has shown mutagenic activity in several bacterial tests carried out. However, it has been shown that this activity was linked to the enzyme activity of the nitroreductases of the bacteria used in the tests. Results from other *in vitro* and *in vivo* tests suggested that dimetridazole was not a genotoxic compound.

However, recent data from other nitroimidazoles suggest that these agents may be genotoxic as they induced chromosomal aberrations in human lymphocytes *in vitro* and *in vivo* at high therapeutic dose levels. It was recognised that information about the possible genotoxicity of dimetridazole under conditions favouring reduction metabolism (e.g. in mammalian tissues and gut microorganisms) was not available. Therefore, the possibility that dimetridazole might be genotoxic could not be excluded.

4. The carcinogenicity studies carried out with dimetridazole have been found to be inadequate. The only complete study involved only one species of animal : the rat. It showed that dimetridazole produces an increase in the incidence of benign mammary tumours. This effect occurs in males at a dose of 2000 ppm and in females at doses of 2000 and 400 ppm. Doses of 10 and 100 ppm have no effect. However, a high level of spontaneous benign mammary tumours was observed in the female controls.
5. A two-month toxicity study in male and female rats after oral administration of dimetridazole at 100, 2000 and 5000 ppm, revealed that the progesterone levels in females increased at 2000 ppm (+112%) and at 5000 ppm (+167%). The applicant suggested that the development of benign mammary tumours could be the result of hormonal modification (plasma progesterone increase). However, no difference in progesterone levels could be seen in male rats treated.
6. It is possible that the increase in benign mammary tumours, as observed in the rat, and the induction of elevated progesterone levels could be coincidental rather than causally related; progesterone levels were raised only in female rats but tumours occurred in rats of both sexes. Moreover, the Working Group recognised that carcinogenicity studies with other nitroimidazoles indicate that these substances can cause malignant tumours in mice. For dimetridazole, chronic carcinogenicity data in mice are not available but such studies had not been specifically requested by the Working Group.

No ADI could be established as a NOEL could not be identified.

7. Dimetridazole is absorbed from the gastrointestinal tract in both laboratory and target species. About 88% of the administered dose is eliminated from turkeys within three days, whereas about 76% is eliminated from pigs within seven days. In both turkeys and pigs, the predominant oxidative metabolite found in urine of pigs and turkeys is 2-hydroxymethyl-1-methyl-5-nitroimidazole.

Although there was inadequate information on biotransformation of dimetridazole in the target species and it was still not possible to establish the ratio between the hydroxylated derivative of dimetridazole and total residues, this metabolite has nevertheless been recognized by the 34th JECFA as the major one in tissues.

8. Information on the quantity of bound residues was evaluated from two depletion studies, performed in turkeys and pigs with [<sup>14</sup>C] - Dimetridazole following oral dosing (one animal per slaughtering point). In both species, about 50% of the total radioactivity were not extracted. However, the nature of bound residues was unclear.
9. Two new residue depletion studies were carried out (submitted in 1993) in pigs and turkeys at the therapeutic dosage regimen. In both species, dimetridazole and its major hydroxylated metabolite were assayed and could be detected in skin/fat of pigs until 9 days and in turkeys until 12 days after treatment.

Moreover, other shortcomings identified in the previous assessments had still not been adequately addressed. There was inadequate information on biotransformation of dimetridazole in the target species, and it was still not possible to identify a marker residue or target tissues.

Routine analytical methods were inadequate due to the lack of information, as the toxicological and analytical significance of the metabolites measured (dimetridazole and its hydroxylated derivative) were not clear.

10. No validated analytical methods for assaying residues in edible tissue were provided.
11. No MRL values could be established for dimetridazole in tissues of pigs and turkeys. The compound should therefore be inserted in Annex IV to Regulation N° 2377/90.