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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FEBANTEL

SUMMARY REPORT (3)

1. Febantel is a prodrug metabolised *in vivo* to fenbendazole which is a benzimidazole anthelmintic that is administered orally to pigs, sheep and cattle for treatment and control of gastro-intestinal roundworms, lung worms and tapeworms. The Committee for Veterinary Medicinal Products (CVMP) agreed that there was no need to estimate a separate ADI for febantel since it is metabolised to oxfendazole and oxfendazole appeared to be the more toxic. This compound is not used in human medicine.

2. The CVMP previously agreed adopt the oxfendazole ADI for fenbendazole and its prodrug febantel as all three compounds share a common metabolism and oxfendazole (the common metabolite formed *in vivo*) appeared to be the most toxic. Using the sum of fenbendazole, oxfendazole and oxfendazole sulphone oxidised to the common oxide (oxfendazole sulphone) as the marker residue, provisional MRLs were adopted as stated in Council Regulation (EEC) No 2377/90:

Pharmacologically active substance (s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Febantel	Combined residues of oxfendazole, oxfendazole sulphone and fenbendazole	All food producing species	1000 µg/kg 10 µg/kg 10 µg/kg	Liver Muscle, kidney, fat Milk	provisional MRLs expire on 1 July 1997. The MRLs cover all residues of febantel, fenbendazole and oxfendazole
Fenbendazole	Combined residues of oxfendazole, oxfendazole sulphone and fenbendazole	All food producing species	1000 µg/kg 10 µg/kg 10 µg/kg	Liver Muscle, kidney, fat Milk	provisional MRLs expire on 1 July 1997. The MRLs cover all residues of febantel, fenbendazole and oxfendazole
Oxfendazole	Combined residues of oxfendazole, oxfendazole sulphone and fenbendazole	All food producing species	1000 µg/kg 10 µg/kg 10 µg/kg	Liver Muscle, kidney, fat Milk	provisional MRLs expire on 1 July 1997. The MRLs cover all residues of febantel, fenbendazole and oxfendazole

3. When fenbendazole, oxfendazole and febantel were previously considered by the CVMP, the applicants were asked to provide further information on the following: (1) additional residues data in milk, (2) additional residues data in edible tissues and (3) additional information on the nature of extractable residues. The applicants responded jointly in the form of a supplementary residue file containing all the residue studies undertaken using the modified analytical methods proposed for routine surveillance for all three compounds.

4. In ruminants, the rumen acts as a reservoir releasing the drugs slowly into the remainder of the gastro-intestinal tract; in monogastrics there is no reservoir effect and repeat doses over several days are needed for greater efficacy. Absorption of febantel was reported to be moderate in the rat with around 25-30% of the oral dose excreted in the urine, although 70% biliary excretion

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after parenteral dosing suggests the initial absorption after oral administration may be higher. In sheep around 20% of an oral dose of febantel was excreted in urine during the next 4 days. The liver appears to be the main target tissue for febantel-related residues in all species tested. Febantel is metabolised by cyclization to fenbendazole which is then converted to oxfendazole. Fenbendazole and oxfendazole are metabolically interconvertible *in vivo*. In addition, febantel oxidation at the sulphur atom of febantel results in the corresponding sulphoxide which undergoes hydrolytic cleavage and cyclisation to produce oxfendazole.

5. Febantel was shown to be of low acute toxicity. Oral LD_{50} values in laboratory rats and mice were greater than 10000 mg/kg bw.

6. In a study in which groups of Wistar rats (15 per sex) were given daily oral doses of 0, 20, 50 or 250 mg/kg bw per day of febantel for 3 months, fatty infiltration of the liver was the only substance-related effect. The NOEL was 50 mg/kg bw per day.

7. Groups of Beagle dogs (3 per sex) were given daily oral doses of 0, 20, 60 or 180 mg/kg bw per day febantel in gelatin capsules for 13 weeks. Haematological effects, reduced testicular weights and hypoplasia were seen in dogs exposed in all groups. In an extension to the study, doses of 0, 5 or 10 mg/kg bw per day were administered in capsules; no substance-related effects were observed at any dose level. In a 52-week study, groups of Beagle dogs (4 per sex) were fed diets containing the equivalent of 0, 0.1, 5 or 25 mg/kg bw per day of febantel. At the top dose, 3 dogs died (one accidentally), there were reductions in haematocrit, haemoglobin and erythrocyte counts, hepatic enzyme levels were elevated, and testicular and lymphofollicular atrophy of the lymph nodes (including the spleen) were observed. The NOEL was 5 mg/kg.

8. A 2-generation reproduction study was carried out with febantel in rats, using dietary doses equivalent to 0, 2, 10 or 50 mg/kg bw per day. Litter size and viability of the offspring were reduced at 50 mg/kg bw per day. The NOEL for reproductive performance was 10 mg/kg bw per day. Histopathological examination revealed hepatocellular hypertrophy in the liver of the F_0 rats given 10 and 50 mg/kg bw per day, fatty degeneration of the liver in F_{1b} rats given 50 mg/kg bw per day and glycogen deposition in the livers of F_{2b} rats given 10 and 50 mg/kg bw per day. The overall NOEL based on hepatic effects was 2 mg/kg bw per day.

9. A developmental toxicity study was carried out in which groups of pregnant female Long Evans rats were given daily oral doses of 0, 10, 30 or 100 mg/kg bw per day febantel from days 6-15 of gestation. Maternal toxicity (reduced bodyweight gain) was observed at 100 mg/kg bw. 100 mg/kg bw was also foetotoxic causing an increased incidence of resorptions and reduced foetal weights. Teratogenic effects (anophthalmia, microphthalmia and multiple axial skeletal effects) were reported in 4 out of 25 foetuses following treatment of the dams at 100 mg/kg bw. The NOEL for maternal toxicity and teratogenicity was 30 mg/kg bw per day. In another study, unspecified teratogenic effects were reported following dosing of rats (unspecified strain) with 46-89 mg/kg febantel or 46 or 93 mg/kg oxfendazole from gestation days 8-15. The NOEL in this study was 22 mg/kg bw per day.

10. No evidence of genotoxicity was obtained with febantel in an *in vitro* Ames test with *Salmonella typhimurium* nor in an *in vitro* pol A+/A- test for DNA repair in *E.coli*. An *in vivo* cytogenetics assay in Chinese hamster marrow and spermatogonia and an *in vivo* mouse bone marrow micronucleus test also gave negative results. However, two daily oral doses of 2000 mg/kg bw febantel caused reduced fertility in male mice and increased the numbers of pre- and post-implantation losses in a dominant lethal assay. Many benzimidazole compounds are known to be mitotic spindle poisons. The microtubules of exposed cells are affected in such a way as to impair normal cell division and cause mis-segregation of chromosomes into the daughter cells resulting in aneuploidy. The mutagenicity data available for febantel, fenbendazole and oxfendazole show no evidence of genotoxicity and although no specific tests for aneugenicity have been conducted, the clastogenicity studies that have been conducted are generally reassuring.

11. Combined long-term toxicity/carcinogenicity studies with febantel in Wistar rats and NMRI mice revealed no increases in tumour incidence. In mice, liver weights were increased in the high dose group (170 mg/kg males, 250 mg/kg females) and increased hepatic fat vacuolation was seen in the high dose females only, the NOEL was 58 mg/kg. In rats, decreased bodyweight gain, increased liver weight, hepatocellular enlargement and vacuolation, and increased serum ALP were seen in both sexes of the high dose (40 mg/kg), and slight anaemia in the high dose females, the NOEL was 8 mg/kg.

12. Febantel had no significant antibacterial activity (no effects on human gut flora).

13. An ADI of 7 µg/kg bw per day for oxfendazole has been estimated by applying a safety factor of 100 to the NOEL of 0.65 mg/kg bw per day for hepatic vacuolation seen in a carcinogenicity study in rats treated with oxfendazole.

14. Two radiometric pharmacokinetic studies were presented for febantel in pigs. These studies were conducted over 18 years ago, were not GLP compliant and were produced in a poor format hindering data extraction and assessment. When pigs were dosed orally with 5 mg ^{14}C-febantel/kg bw, 10 day urine and faeces samples accounted for 40% and 51% respectively (91% total) of the administered dose. Total residues in liver and kidney were depleted from 350 and 60 µg/kg respectively 10 days after dosing to 150 and 20 µg/kg 20 days respectively after dosing; no residues were detectable in muscle samples. After oral dosing of pigs with 5 mg febantel/kg bw (a non-radiometric study), liver residue concentrations were more than ten times those in other edible tissues, on days 12, 20, and 34 after treatment; these were 402, 245, and 57 µg/kg respectively. Twelve days after dosing, tissue residue concentrations of oxidised febantel residues in muscle kidney and fat were less than 6, 12 and 100 µg/kg respectively. Thirty four days after dosing (the last timepoint studied) oxidised febantel residue concentrations had depleted to less than 6, less than 5 and 7.7 µg/kg respectively.

15. In a previously reported radiometric study, total liver residue concentrations in cattle dosed orally with 7.5 mg ^{14}C-febantel mg/kg were 2500, 800 and 300 µg/kg on days 10, 14 and 28 after treatment; all other tissues contained concentrations below the analytical limit of quantification (10 µg/kg) 14 days after treatment. New GLP compliant non-radiometric febantel tissue depletion studies (4 animals/timepoint) were conducted in cattle. Seven days after oral dosing cattle with febantel (7.5 mg/kg bw) tissue concentrations of oxidised febantel residues were above the analytical limit of quantification (5µg/kg) only in the liver (115 µg/kg) and fat (19 µg/kg).

16. The mean concentrations of oxidised febantel residues in cows' milk samples at 0, 10, 24, 34, 58, 72, 82, 96, 106, 120 and 130 hours after treatment were: less than 5, 172, 256, 268, 107, 44, 19, less than 5 to 20, less than 5 to 10, less than 5, and less than 5 µg/kg respectively.

17. When 3 female sheep were given a single intraruminal dose of 5 mg/kg bw ^{14}C-febantel; around 85% of the dose was excreted within 4 days; 19% in urine and 66% in faeces. Peak serum concentrations were 400-700 µg/kg, 12-24 hours after dosing. Total residues in liver, kidney, muscle and fat declined from 5000, 235, 35 and 100 µg/kg, 4 days after dosing, to 2500, 75, 10 and 15 µg/kg, 8 days after dosing. New GLP-compliant non-radiometric febantel tissue depletion studies (4 animals/timepoint) were conducted in sheep. Three days after oral dosing sheep with febantel (5 mg/kg bw) oxidised febantel residue concentrations were 40, 4617, 199, and 133 µg/kg in muscle, liver, kidney, and fat respectively. Seven days after dosing, residues in liver, kidney and fat were 941.5, 10.8 and 8.5 µg/kg respectively. Residue concentrations in all tissues were below the analytical limit of quantification by day 28 after dosing.

18. Fourteen days after dosing sheep oxidised febantel residue concentrations were: less than 5, 942, 11 and 9 µg/kg in muscle, kidney, liver and fat respectively. Twenty eight days after treatment all tissue residue concentrations had depleted to below the analytical limit of quantification (5 µg/kg). The mean concentrations of oxidised febantel residues in sheep's milk samples at 0, 10, 24, 34, 48, 58, 72, 82, 96, 106, 120 and 130 hours after treatment were less than 5, 357, 260, 158, 73, 42, 20, 15, 9, less than 5 to 11, less than 5 to 7 and less than 5 µg/kg respectively.

19. In horses no specific studies were conducted with febantel. However, in a study with fenbendazole, 5 days after repeated oral dosing for 5 days (10 mg/kg bw) concentrations of the combined fenbendazole, oxfendazole and oxfendazole sulphone residues were below the analytical limit of quantification (10 µg/kg) in muscle, fat liver and kidney. Tissue concentrations at earlier points were not reported.

20. The Joint FAO/WHO expert Committee on Food Additives (JECFA) proposed temporary MRLs for febantel, oxfendazole and fenbendazole of 500 µg/kg in liver and 100 µg/kg in muscle, kidney and fat. However, these MRLs do not reflect the tissue distribution according to the new data submitted for febantel in cattle, sheep and pig tissues.

21. A routine analytical method was presented for quantifying febantel residues in tissues from cattle, sheep, pigs, and horses. With slight changes to the solvent extraction process this method was also proposed for the routine analysis of milk samples. In the method, residues were extracted from sample matrices in acetonitrile, then oxidised (peracetic acid) to oxfendazole sulphone and quantified by HPLC with fluorescence detection. Sample extracts were quantified by comparison to calibration standards made by extracting blank matrix samples spiked with fenbendazole, oxfendazole and oxfendazole sulphone (1:1:1 w/w/w; 5-1000 µg/kg or litre). The method and its validation data were well presented and both met the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community. The validation data demonstrated no interference from blank sample matrices but no other compounds were tested. The limit of quantification of the method was shown (in terms of accuracy and precision) to be 5 µg/kg or litre for all samples matrices. When investigated the limit of detection of the analytical method was shown to be 2-3 µg/kg or litre (equivalent to a signal of 3.5-5 times the background noise).

Conclusions and recommendation:

Having considered that :

- *in vivo*, febantel is transformed into fenbendazole which in turn is oxidised to oxfendazole,
- an ADI of 7 µg/kg bw per day for oxfendazole has been established,
- a validated analytical method for residues monitoring purposes is available;

The Committee recommends the inclusion of febantel in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Febantel	Sum of extractable residues which may be oxidised to oxfendazole sulphone	Bovine, ovine, porcine, equidae	50 µg/kg 50 µg/kg 500 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	
		Bovine, ovine	10 µg/kg	Milk	

Based on these MRL values, the daily intake will represent about 17% of the ADI; this margin allows for total residue correction.