

FENBENDAZOLE

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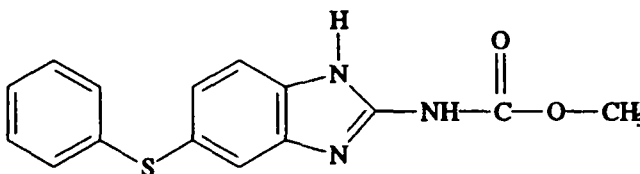
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IDENTITY

Fenbendazole is a member of a well-known and widely used chemical class of compounds known as the benzimidazoles. It is related in chemical structure and pharmacological properties to other compounds such as thiabendazole, febantel, oxibendazole, mebendazole, oxfendazole and triclabendazole.

Chemical name: Methyl 5-(phenylthio)-2-benzimidazolecarbamate

Structural formula:



Fenbendazole

CAS number: 43210-67-9

Synonyms: PANACUR®, SAFE-GUARD®, HOE 881, AXILUR®

Molecular formula: C₁₅H₁₃N₃O₂S

Molecular weight: 299.35

CONDITIONS OF USE

Fenbendazole is an anthelmintic used for the treatment and control of helminth infections in many mammalian

and avian species (e.g. cattle, sheep, goats, horses, pigs, ...). Fenbendazole has a broad spectrum of activity against all stages of gastrointestinal nematodes including larval stages, cestodes and lungworms. It is administered as a single therapeutic dose or over several days in divided doses depending on the species.

Dosage

Typical single therapeutic doses for cattle, sheep, goats, horses and pigs are 5-10, 5-10, 5, 5-10 and 5 mg/kg, respectively.

PREVIOUS REVIEWS

Febantel, fenbendazole and oxfendazole were previously reviewed at the 38th meeting of JECFA.

The Committee recommended temporary MRLs for febantel, fenbendazole and oxfendazole of 100 $\mu\text{g}/\text{kg}$ for muscle, fat and kidney (cattle, sheep, and pigs); 500 $\mu\text{g}/\text{kg}$ for liver (cattle, sheep, and pigs); and 100 $\mu\text{g}/\text{L}$ for milk (cattle). The temporary MRLs are for febantel, fenbendazole, and oxfendazole individually or in combination. The MRL value is the sum of the concentrations of fenbendazole, oxfendazole, and oxfendazole sulfone, calculated as oxfendazole sulfone equivalents.

The Committee requested the results of the following residue studies for evaluation:

1. Studies on the total residues of the three metabolites (fenbendazole, oxfendazole, and oxfendazole sulfone), measured as oxfendazole sulfone, in the edible tissues of cattle and sheep and in the milk of cattle over a 28-day withdrawal period after treatment of animals with fenbendazole or oxfendazole. In particular, information is requested on the use of the pelleted form of fenbendazole in cattle and sheep.
2. Studies on the total residues of the above three metabolites, measured as oxfendazole sulfone, in the edible tissues of pigs given fenbendazole and observed over a 7-14 day withdrawal period.
3. Information on the bioavailability of bound residues in liver after administration of febantel to one of the following species: cattle, pigs, or sheep.
4. Development of a suitable method for the determination of total residues of the three metabolites (fenbendazole, oxfendazole, and oxfendazole sulfone, measure as oxfendazole sulfone) in milk.

1995 DATA SUBMISSION

There were no new data submitted for either febantel or oxfendazole. The residue data submitted for fenbendazole consisted of the following studies:

1. An analytical method titled "Determination of Residues of Fenbendazole (HOE 881, Panacur®) and its Metabolites in Bovine Fatty Tissue, Liver, Kidney and Muscle."
2. Numerous residue depletion studies (including milk) in cattle, sheep, pigs and horses using various formulations, dosing levels and dosing regimes. The studies were designed primarily to determine withdrawal periods for each of the formulations. Some of the depletion studies included the analysis of blood samples in order to compare the pharmacokinetic profile of fenbendazole and its metabolites. The residue studies used an analytical method that converted fenbendazole and its metabolites (oxfendazole and oxfendazole sulfone) to oxfendazole sulfone. The total residue of oxfendazole sulfone was then determined quantitatively, after high pressure liquid chromatography separation with fluorescence detection. The limit of quantitation of the assay in all tissues is 5 $\mu\text{g}/\text{kg}$. One of two milk depletion studies in dairy cattle used both the method that converts the residues to oxfendazole sulfone and an older method using UV-detection with a limit of quantitation of 5-10 $\mu\text{g}/\text{l}$. The UV-detection method measures fenbendazole, oxfendazole and oxfendazole individually. Two milk residue studies in sheep used the summation method.

TISSUE RESIDUE DEPLETION STUDIES

Nonradiometric Residue Depletion Studies

Cattle

Four new studies were reported, two with the 10% suspension, one with the 22% granules and one with the 1.5% pellet formulation. All four used a 7.5 mg/kg b.w. dose of fenbendazole. With the 10% suspension dose, residues were measured at 5, 9, 14, 21 and 28 days in one study and at 7, 11, 15, 18 and 21 days in the second. In both studies, residues in liver tissue were below the temporary MRL by day 9 and 7, respectively, following drug administration (from 19-46 $\mu\text{g}/\text{kg}$ at day 9 in the first study, and 150-237 $\mu\text{g}/\text{kg}$ at day 7 in the second study). Residues were below the limit of quantitation (LOQ) in all other tissues (less than 5 $\mu\text{g}/\text{kg}$) at these same time points. In the 22% granules formulation study, residues were measured at 5, 9, 14 and 21 days post treatment. At day 9 post treatment, liver residues were 37-86 $\mu\text{g}/\text{kg}$ and below the LOQ in all other tissues. In the study using 1.5% pellets, animals were sampled at 7, 14 and 28 days post treatment. At 14 days post treatment, liver residues were 7-15 $\mu\text{g}/\text{kg}$ and below the LOQ in all other tissues.

The pharmacokinetics data indicated that there were statistically significant differences in the pharmacokinetics of fenbendazole and oxfendazole with the different formulations. The pelleted formulation was about 400% more bioavailable than the 10% suspension formulation. The data did not permit a determination of whether this has any impact on the depletion patterns of fenbendazole and its metabolites in tissue. Although the pelleted formulation is more bioavailable, the clearance of fenbendazole and metabolites from plasma is similar, based on the time for all samples to reach the LOQ (144-168 hours). The data are summarized in Table 1.

Table 1. Pharmacokinetics Data on 1.5% Pellet Formulation Versus 10% Suspension in Cattle

Formulation	Analyte	C_{max} $\mu\text{g}/\text{L}$	T_{max} (h)	Post Treatment Hours To All Values < LOQ
1.5% Pellets	FBZ	704	32	144
	FBZ-SO	1152	48	168
	FBZ-SO ₂	392	80	168
10% Suspension	FBZ	169	24	168
	FBZ-SO	305	24	168
	FBZ-SO ₂	134	48	168

FBZ = fenbendazole, FBZ-SO = oxfendazole, FBZ-SO₂ = oxfendazole sulfone

Two studies on total residues in bovine milk were reported, using the 1.5% pelleted formulation and the 10% oral suspension, at a dose of 7.5 mg/kg. In the study using the pelleted formulation, milk samples were collected twice daily until 14 days post treatment. Residues were measured by the older HPLC (LOQ of 5-10 $\mu\text{g}/\text{L}$) and the new summation method (described below). Results from both analyses indicate that total residues were below the temporary MRL (100 $\mu\text{g}/\text{kg}$) by day 5 post treatment. In the second study using the 10% oral suspension administered to 4 high and 4 low yielding cows, the total residue were less than 100 $\mu\text{g}/\text{L}$ by 58 and 72 hours, respectively, for the high and low yielding cows. These data also indicate that the 1.5% pelleted formulation has higher bioavailability than the 10% oral suspension formulation.

Sheep

Four tissue residue studies were reported for sheep, two with a 2.5% suspension and two with a 250 mg bolus formulation. Both formulations were evaluated at 5 and 10 mg/kg b.w. The 1.5% pelleted formulation is not

approved for use in sheep. In the studies using the 2.5% suspension, blood samples were also collected.

Using a 5 mg/kg b.w. treatment with the 2.5% suspension, blood samples were collected up to 168 h and tissue samples over a 28-day period. Nine days post treatment all tissues except liver were less than 100 µg/kg. Liver residues persisted through day 28, but were below the temporary MRL (500 µg/kg) in all sheep by day 14. At 21 days post treatment liver residues were 10-114 µg/kg and at day 28, residues were 14-19 µg/kg (one animal was below the LOQ). Plasma concentrations were below the LOQ (10 µg/L) by 168 h. The time to reach maximum concentration was 8 h for parent drug, 24 h for the oxfendazole and 48 h for the oxfendazole sulfone metabolites. Maximum concentrations were 137, 226, and 83 µg/L, respectively. Residues of fenbendazole were below the LOQ at 96-120 h; for oxfendazole the corresponding post treatment times were 120-168 h, and for oxfendazole sulfone, low concentrations of this metabolite were still present after 7 days (168 h) in some animals.

In the 10 mg/kg b.w. study using the 2.5% suspension, at 9 days post treatment, muscle, kidney and fat residues were less than 100 µg/kg but liver residues in all sheep were 540-990 µg/kg. At 14 days post treatment, muscle, kidney and fat were below the LOQ and corresponding liver residues were 11-129 µg/kg. By day 21, liver residues were 8-26 µg/kg.

With fenbendazole administered at 5 mg/kg b.w. using the 250 mg bolus (tablet), by day 9, muscle, kidney and fat residues were less than 100 µg/kg and all liver samples were greater than 500 µg/kg. At day 14 two of the four sheep had liver residues of 546 and 532 µg/kg, by 21 days post treatment muscle, kidney and fat residues were below the LOQ and liver residues were 6-65 µg/kg. Plasma residues for fenbendazole and its metabolites are summarized in Table 2. The LOQ for plasma residues was 10 µg/L.

Table 2. Comparative Pharmacokinetics Data on 2.5% Suspension and 250 mg Bolus in Sheep

Formulation	Analyte	C _{max} (µg/L)	T _{max} (h)	Time Post Treatment To Residues < LOQ
2.5% Suspension	FBZ	137	8	120
	FBZ-SO	226	24	168
	FBZ-SO ₂	83	48	168
250 mg Bolus (Tablet)	FBZ	242	6	96
	FBZ-SO	302	24	144
	FBZ-SO ₂	93	24	168

The pharmacokinetics data indicate that the bolus formulation has approximately 30% more bioavailability than the 2.5% suspension. It was also noted that doubling the dose of the 2.5% suspension fenbendazole formulation resulted in higher liver residues at the day 5 post treatment, but residues were slightly higher at longer post treatment times for the lower dose. It was noted that with the benzimidazoles, both diet and manipulation of feeding can influence the pharmacokinetics of these compounds. However, because of the controlled nature of the studies, inconsistencies in tissue residues between the two dose rates must be a reflection of the variability in absorption and metabolism in sheep following drug treatment.

In the 10 mg/kg treatment using the 250 mg bolus, tissue residues were monitored over a 28 day period post treatment. As in the above studies, at day 9, in muscle, kidney and fat, residues were less than the temporary MRL of 100 µg/kg while all liver samples had residues greater than 500 µg/kg. By day 14 the liver residues in all sheep were 78-471 µg/kg and residues in muscle, kidney and fat were below the LOQ. At day 28, two of the four sheep had liver residues of 11-21 µg/kg.

Two milk residue studies in lactating sheep were reported, one using the 2.5% suspension, the other using the 250 mg bolus at a dose rate of 5 mg/kg b.w. Residues were measured by the new analytical method (HPLC)

that determines all residues as the oxfendazole sulfone.

In the first study using the 2.5% suspension in eight ewes at 5 mg/kg b.w., residues in all ewes were below 100 µg/L at 24-72 h, and below the LOQ (5 µg/L) at 96-156 h. In the second study using the 250 mg bolus in eight ewes, residues were below the temporary MRL for cattle milk (100 µg/L) at 36-72 h and below the LOQ at 96-132 h.

Pig

Five studies were conducted in pig, one with the 1.5% pellet formulation and the other four with the 4% powder formulation. In two of the studies fenbendazole was given once in the feed at 5 mg/kg b.w. In the remaining three, the drug was administered in feed over several days. Residues were determined using the new analytical procedure and reported as oxfendazole sulfone.

In the first study using the 4% powder formulation at 3 mg/kg b.w. daily for three days, residues were determined at 5, 7, 10 and 14 days. At day 5, one of the six pigs has residues of 10 µg/kg in fat, all muscle, kidney and liver tissue residues were below the LOQ (5 µg/kg). Residues at day 14 in fat were 6-88 µg/kg in four of the six animals.

In two studies, fenbendazole was given as a single dose at 5 mg/kg b.w. using the 1.5% pellet and 4% powder formulation. Residues were determined over a 21 and 27 day post treatment, respectively. Following administration of the 1.5% pellet, residues were detected only sporadically at less than 10 µg/kg in skin, fat, muscle and liver of one or two pigs over the 21-day treatment period. With the 4% powder formulation at 5 mg/kg b.w., residues were detected at only 7 µg/kg once in the skin of one of the five pigs at 5 days post administration. All other tissue residues were below the LOQ at day 5.

In the two remaining studies the 4% powder formulation was used. In one of these studies dosing was 1 mg/kg b.w. per day for 5 days (total dose was 5 mg/kg b.w.). Residues were determined at 5, 7, 10 and 14 days. In the second study, fenbendazole was given at a dose rate of 0.3 mg/kg b.w. per day for 15 days (total dose was 4.5 mg/kg b.w.). Tissue samples were analyzed at 5, 7 and 10 days. Residues were at the LOQ in all tissues (including skin) in all pigs at 5 days.

Horses

As a consequence of horse being considered a minor species as a food animal, only a limited residue study was conducted in four adult horses using the 18.75% paste at a dose rate of 10 mg/kg b.w. (the recommended therapeutic dose in the U.S.). The recommended single dose in Europe is 7.5 mg/kg b.w. Residues were determined at 20 days post treatment and blood samples were collected at regular intervals from drug treatment until necropsy. Fenbendazole and its metabolites were detected only during the first 24 hours post treatment. From 48 h until day 20, plasma drug levels were below the LOQ of 10 µg/L. Residues in tissues were below the LOQ (5 µg/kg) in all horses at the 20-day sampling point.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Fenbendazole and its metabolites (oxfendazole and oxfendazole sulfone) can be quantitatively determined in bovine fat, liver, kidney and muscle. Fenbendazole and its metabolites are extracted from tissue homogenates with ethyl acetate. Fenbendazole and oxfendazole are oxidized to oxfendazole sulfone with peracetic acid. The total amount of oxfendazole sulfone is quantitatively analyzed after extensive purification using HPLC with fluorescence detection, 295 nm (Ex.) and 410 nm (Em.). A calibration function is constructed using peak ratios of oxfendazole sulfone and the internal standard determined from tissue samples spiked with various concentrations of a fenbendazole-oxfendazole-oxfendazole sulfone mixture. The recovery of fenbendazole and its metabolites using incurred residues has not been determined, e.g. by using radiolabeled drug. The recovery of oxfendazole sulfone and the internal standard were determined relative to pure aqueous standard solutions. The mean recovery for fenbendazole and its metabolites (measured as FBZ-SO₂) ranged from 70.8% (muscle,

6 samples) to 87.8% (liver, 5 samples). The limit of quantitation for all tissues is 5 µg/kg; the method is linear in the range from 5 to 1000 µg/kg in liver and from 5 to 200 µg/kg in kidney, fat and muscle. The method uses an internal standard, methyl-(5-cyclopentylsulfinyl-1H-benzimidazole-2-yl)carbamate.

APPRAISAL

The Committee recommended that the MRLs for febantel, fenbendazole and oxfendazole should continue be based on the temporary ADI of 0-4 µg per kg of body weight previously allocated to oxfendazole and they should remain temporary. For a 60-kg person, this corresponds to 240 µg/day of residues of febantel, fenbendazole and oxfendazole.

The recommended temporary MRLs for febantel, fenbendazole and oxfendazole, determined as the sum of oxfendazole, fenbendazole and oxfendazole sulfone, expressed as oxfendazole sulfone equivalents, for cattle, sheep and pigs:

Muscle, kidney and fat:	100 µg/kg
Liver:	500 µg/kg
Milk (cattle & sheep):	100 µg/L

These MRLs would results in a maximum daily intake of 240 µg of residues of febantel, fenbendazole and oxfendazole, based on a daily food intake of 300 g of muscle, 100 g of liver, 50 g of kidney, 50 g of fat and 1.5 L of milk.

The Committee noted that, with increasing production of goats in developing countries, residue data would be required for establishing MRLs in this species.

The results of ongoing residue depletion studies on total residues of fenbendazole, oxfendazole and oxfendazole sulfone in cattle and sheep following the administration of febantel and oxfendazole are required for evaluation in 1998.

REFERENCES

Schmidt, D. (1995). Determination of Residues of Fenbendazole (HOE 881, Panacur®) and its Metabolites in Bovine Fatty Tissue, Liver, Kidney and Muscle. Submitted by Hoechst Veterinär GmbH, Wiesbaden, Germany. V-0079-0495-1169.

Schmid, K. (1994). Report on plasma concentrations and tissues residues of fenbendazole (FBZ) and its metabolites in cattle after oral treatment with Panacur Suspension 10% ad us. vet. at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-0793-1094.

Schmid, K. (1993). Report on residues of fenbendazole (FBZ) and its metabolites in cattle after oral treatment with Panacur Suspension 10% ad us. vet. at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-1293-1098.

Schmid, K. (1994). Report on tissue residues of fenbendazole (FBZ) and its metabolites in cattle after oral treatment with Panacur granules ad us. vet. (222 mg fenbendazole/g) at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-0394-1142.

Schmid, K. (1993). Report on plasma concentrations of fenbendazole (FBZ) and its metabolites in bulls after oral treatment with Panacur pellets 1.5% ad us. vet. at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-0593-1119.

Scholl, T. (1994). Pharmacokinetics and statistics of HOE 881 and its metabolite FBZ-SO in suspension 10% versus pellets 1.5% in cattle. V-0079-0994-1162.

Düwel, (1994). Report on residues in milk and plasma concentrations of fenbendazole (FBZ) and its metabolites in dairy cattle after oral treatment with Panacur pellets 1.5% ad us. vet. at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-0293-1073.

Düwel, (1994). Report on residues in milk and plasma concentrations of fenbendazole (FBZ) and its metabolites in dairy cattle after oral treatment with Panacur pellets 1.5% ad us. vet. at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-0793-1099.

Schmid, K. (1994). Report on residues of fenbendazole (FBZ) and its metabolites in milk of cattle after oral treatment with Panacur Suspension 10% ad us. vet. at a dose rate of 7.5 mg FBZ/kg body weight. V-0079-0693-1118.

Schmid, K. (1994). Report on plasma concentrations and tissues residues of fenbendazole (FBZ) and its metabolites in sheep after oral treatment with Panacur Suspension 2.5% ad us. vet. at a dose rate of 5.0 mg FBZ/kg body weight. V-0079-0693-1121.

Scholl, T. and Schmid, K. (1993). Report on plasma concentrations and tissue residues of fenbendazole (FBZ) and its metabolites in sheep after oral treatment with Panacur Bolus 250 mg ad us. vet. at a dose rate of 5 mg FBZ/kg body weight. V-0079-1193-1108.

Scholl, T. (1994). Pharmacokinetics and statistics of HOE 881 and its metabolite FBZ-SO in suspension 2.5% versus bolus 250 mg in sheep. V-0079-0894-1150.

Schmid, K. (1994). Report on residues of fenbendazole and its metabolites in sheep after oral treatment with Panacur Suspension 2.5% ad us. vet. at a dose rate of 10 mg FBZ/kg body weight. V-0079-1093-1097.

Schmid, K. (1994). Report on tissue residues of fenbendazole (FBZ) and its metabolites in sheep after oral treatment with Panacur Boli 250 ad us. vet. at a dose rate of 10 mg FBZ/kg body weight. V-0079-1293-1110.

Tiefenbach, B. (1993). Report on the determination of the levels of fenbendazole (FBZ) and its metabolites in the milk of sheep treated orally with the Panacur susp. 2.5% for veterinary use at a dose rate of 5.0 mg fenbendazole/kg body weight. V-0079-0593-1070.

Tiefenbach, B. and Scholl, T. (1993). Report on the determination of the levels of fenbendazole (FBZ) and its metabolites in the milk of sheep treated orally with the Panacur Boli 250 for veterinary use at a dose rate of 5.0 mg fenbendazole/kg body weight. V-0079-0593-1071.

Schmid, K. (1993). Report on plasma concentrations and tissue residues of fenbendazole (FBZ) and its metabolites in pigs after oral treatment with Panacur powder 4% ad us. vet. at a dose rate of 3 mg FBZ/kg body weight daily for 3 days. V-0079-0793-1092.

Scholl, T. and Schmid, K. (1993). Report on plasma concentrations and residues of fenbendazole (FBZ) and its metabolites in pigs after oral treatment with Panacur pellets 1.5% ad us. vet. at a dose rate of 5 mg FBZ/kg b.w. V-0079-0993-1117.

Schmid, K. (1993). Report on tissue residues of fenbendazole (FBZ) and its metabolites in pigs after oral treatment with Panacur powder 4% ad us. vet. at a dose rate of 5 mg FBZ/kg body weight. V-0079-1193-1120.

Schmid, K. (1994). Report on tissue residues of fenbendazole (FBZ) and its metabolites in pigs after oral treatment with Panacur Powder 4% ad us. vet. at a dose rate of 1 mg FBZ/kg body weight/day for 5 days. V-0079-1293-1111.

Schmid, K. (1994). Report on tissue residues of fenbendazole (FBZ) and its metabolites in pigs after oral treatment with fenbendazole at 0.3 mg/kg body weight/day for 15 days (Panacur Powder 4% ad us. vet.). V-0079-0294-1130.

Scholl, T. and Schmid, K. (1993). Report on plasma levels and tissues residues of fenbendazole and its metabolites in horses after oral treatment with Panacur Paste ad us. vet. at a dose rate of 10 mg FBZ/kg b.w. V-0079-1293-1109.