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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ALBENDAZOLE

SUMMARY REPORT (2)

1. Albendazole is a benzimidazole carbamate which is used as an anthelmintic in veterinary medicine and also in human medicine.

2. Albendazole-containing products are available in liquid form or as pellets, both of which are administered orally. Products are available for sheep and cattle. In cattle and sheep, oral doses of 5 to 7.5 mg/kg bw are used for the treatment of gastrointestinal infestations with roundworms, lungworms and tapeworms; and doses of 7.5 to 10 mg/kg bw are used for the treatment of adult flukes *Fasciola hepatica*. In human medicine, a dose of 400 mg/person is recommended for the treatment of gastrointestinal parasitic infestations.

3. The Committee for Veterinary Medicinal Products (CVMP) has previously considered albendazole. Based on the data available at the time of their initial assessment, the CVMP recommended the following provisional MRLs for albendazole:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Albendazole	Sum of albendazole and metabolites which are measured as 2-amino-benzimidazole sulphone	Bovine, ovine	100 µg/kg 500 µg/kg 1000 µg/kg	Muscle, fat, milk Kidney Liver	Provisional MRLs expire on 1. 1.1998

The provisional MRLs have been renewed once and are due to expire 1 January 1998.

When albendazole was first entered into Annex III, further information on the relationship of marker residue to total residues and data to determine a marker residue for milk was requested. When these data were submitted it was found that the marker residue was not adequately justified, and a fully validated analytical method for the detection of the major components of the residue (i.e. albendazole, albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone) in edible tissues and milk of cattle and sheep was requested.

4. The mode of action of albendazole is by binding strongly with the tubulin in the cells of nematodes. The intestinal cells of the nematode are particularly affected, resulting in a loss of absorptive function which causes the nematodes to starve to death.

5. In ruminants, oral doses of albendazole are readily absorbed from the gut (cattle absorb about 50% of oral doses of albendazole). Mice and rats absorb about 20 - 30% of oral doses of albendazole.

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6. The principal route for the primary metabolism of albendazole was by rapid first pass oxidation of its sulphide group to form albendazole sulphoxide, then further oxidation to form albendazole sulphone, and deacetylation of the carbamate group to form an amine. Albendazole, albendazole sulphoxide, albendazole sulphone and albendazole-2-aminosulphone were the main components of the residue in tissues irrespective of whether the animals were dosed with netobimin, albendazole or albendazole sulphoxide. Other metabolites have been detected only at much lower concentrations.

7. Experience from use of albendazole in human medicine shows that oral doses of albendazole are not well absorbed from the human gut: about 1% is absorbed. Thus oral exposure to albendazole would be expected to be less toxic to humans than to laboratory animals or farm animals.

8. Albendazole was of low acute toxicity when given by the oral route to mice, rats, hamsters, guinea pigs and rabbits.

9. Albendazole was tested in several repeat oral dose studies in mice, rats and dogs. Its main effects were hepatotoxicity and testicular toxicity. An NOEL of 7 mg/kg bw/day has been identified for these effects, based on the results from a rat study which exposed rats to albendazole for over 60 days in one generation (including dosing during mating, gestation and the post-natal period) and then exposed their offspring for 24 months. Netobimin and albendazole sulphoxide both caused similar hepatotoxicity and testicular toxicity to this, but at higher doses.

10. A comprehensive series of developmental studies in mice, rats, rabbits, and sheep showed albendazole to be teratogenic. The malformations included visceral, craniofacial and bone defects (including shortened limbs). The lowest NOEL for any of the studies was 5 mg/kg bw/day for albendazole administered orally to rats or rabbits. Netobimin and albendazole sulphoxide were also teratogens with similar potency to albendazole.

11. Reproductive effects of albendazole were investigated in multigeneration oral-dosing studies in rats. It caused reduced survival and growth of pups during the post-natal lactation period, with an NOEL for this effect of 5.8 mg/kg bw/day.

12. Albendazole produced negative results in bacterial mutation tests using strains TA1530, TA1532, TA1534, TA1537, TA98, TA100, LT2 his- and G46 of *Salmonella typhimurium*. It produced no clastogenicity in an *in vitro* metaphase analysis of Chinese hamster ovary (CHO) cells, and was negative in an *in vitro* cell transformation assay in BALB/3T3 mouse cells. However, an *in vivo* mouse bone marrow micronucleus test on albendazole, which had been isolated from a formulated product, gave a positive result. This result indicated that albendazole was an *in vivo* somatic cell mutagen. In the absence of any tests on germ cells, it remains unclear whether or not albendazole can induce heritable mutations. The results of the mutagenicity tests on albendazole and those on netobimin and albendazole sulphoxide were consistent with these substances all being *in vivo* aneugens. A level of exposure to albendazole which presents no mutagenic risk to consumers has not been identified.

13. Albendazole has been adequately tested in carcinogenicity bioassays, giving no evidence of neoplasia in either rats or mice.

14. No irritancy studies on albendazole have been seen, but albendazole sulphoxide was found to be non-irritant to the skin or eyes of rabbits.

15. No sensitisation tests on albendazole have been seen, but a positive result in a guinea-pig maximisation test showed albendazole sulphoxide to be a potential skin sensitizer.

16. In human field trials of albendazole 17 women in the first trimester of pregnancy were inadvertently given a single oral dose of 400 mg/person without any adverse effects on mother or child being apparent.

17. In 1992, the CVMP set an ADI for albendazole of 0.005 mg/kg bw, by applying a large safety factor of 1000 to the NOEL of 5 mg/kg bw/day for teratogenicity in rats and rabbits. The large safety factor was regarded as being necessary to compensate for both the severity of the teratogenicity endpoint and for the fact that teratogenic effects can be produced following a single exposure to a large dose.

    The only important data which have become available on the safety of albendazole since this ADI was set are the results of the *in vivo* mouse micronucleus test, which indicate a mutagenic risk. The existing 1000-fold safety factor is regarded as sufficient to minimise this risk to an acceptable level. Therefore the ADI of 0.005 mg/kg bw is reaffirmed.

18. After oral dosing, residues are highest and most persistent in the liver. In cattle given ^{14}C-labelled albendazole as a single dose of 15 mg/kg bw, total residues in liver depleted from more than 20 mg/kg one day after dosing to around 6 mg/kg four days after dosing and around 1.2 mg/kg 20 days after dosing. Kidney is the tissue with the next highest and most persistent residues, whilst levels in muscle and fat are much lower and deplete rapidly (e.g. for muscle, 5 mg/kg one day after treatment reducing to 64 µg/kg 4 days after treatment and 20 µg/kg after 20 days).

    In sheep given a similar dose of albendazole, a similar pattern was observed but total residues in all tissues were lower at all time points, depleting in liver from around 16 mg/kg one day after treatment to 700 µg/kg four days after dosing and 170 µg/kg 20 days after dosing.

    In cattle, total residues in milk were nearly 5000 µg/kg 11 hours after administration of a 15 mg/kg bw dose, reducing to 640 µg/kg after 35 hours and 35 µg/kg after 72 hours. Results in sheep were very similar.

19. Calves were given an oral dose of 20 mg/kg bw ^{14}C-albendazole and killed 1, 4, 6 or 10 days after dosing. One day after dosing, around 90% of the residues were extractable but from 4 days to 10 days after dosing only 20-30% of the residues were extractable. Residues of albendazole in calves liver accounted for 27% of the total extractable residues one day after dosing but were undetectable 4 days after dosing. Residues of albendazole sulphoxide + albendazole sulphone + the 2-amino-sulphone metabolite accounted for 52% of the total extractable residues one day after dosing, and comprised 40-50% of the total extractable residues for up to 10 days after dosing. Analysis of kidney samples revealed the same metabolic profile.

20. Sheep were given an oral dose of 10 mg/kg bw ^{14}C-albendazole and killed 1, 2, 4, 6 or 8 days after dosing. Residues of albendazole were not found in any of the tissue samples. One day after dosing, around 100% of the residues were extractable but this proportion decreased to 37% at 4 days and 13% at 8 days. From 1 - 4 days after dosing, the percentage of extractable residues present as the marker residue (albendazole sulphoxide + albendazole sulphone + the 2-amino-sulphone metabolite) in liver remained constant at around 70-80%. Thereafter, the percentage of extractable residues present as marker residue declined to around 40%, 8 days after dosing. Analysis of kidney samples revealed the same metabolic profile. In another study, in which 4 sheep were infused using an intraruminal catheter at a rate of 0.5 mg/kg bw per day of ^{14}C-albendazole and the sheep killed (2 per time point) immediately after 7 or 14 days of treatment, the marker residue accounted for 80-100% of the total residues in muscle, 52-58% of the total residues in liver and 47-74% of the total residues in kidney.

21. Four dairy cows in different stages of lactation were given a single oral dose of 15 mg/kg bw ^{14}C-albendazole. Within 24 hours of dosing, mean total residues in milk were around 3416 µg/kg albendazole-equivalents and depleted to 227 µg/kg by 2 days after dosing and 19 µg/kg by 3 days after dosing. Within the first 2 days of dosing, around 2-3% of the total residues were present as albendazole. During the first 24 hours after dosing, the marker residue (albendazole sulphoxide + albendazole sulphone + the 2-amino-sulphone metabolite) accounted for around 82% of the total residues. Two to three days after dosing, the marker residue accounted for around 50% of the total residues.

22. An analytical method based on HPLC has been validated in accordance with Volume VI of the Rules Governing Medicinal Products in the European Community and presented in the ISO 78/2 format and is capable of individually measuring residues of albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone in the edible tissues and milk of cattle and sheep. The limits of quantification for each analyte are 15 µg/kg for milk, 20 µg/kg for muscle and fat and 100 µg/kg for liver and kidney.

Conclusions and recommendation

Considering that:

- an ADI of 0.005 mg/kg bw (300 µg/person) had been established,
- in cattle, 90% of the residues were extractable one day after treatment but only 20-30% of the residues were extractable from 4 days after treatment; tissue binding in sheep was less extensive,
- the principal components of the extractable residue in cattle and sheep treated with albendazole were albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone and these substances accounted for essentially all the residues which were of toxicological significance at all time points; these substances represented 80-100% of the extractable residues in muscle within 24 hours of dosing, and around 50% of the extractable residues in liver and kidney for up to 10 days after dosing,
- a validated analytical method was available for the determination of residues of albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone in edible tissues and milk of cattle and sheep;

the Committee recommends the inclusion of albendazole in Annex I of Council Regulation (EEC) 2377/90 in accordance with the following table:

Pharmacologically active substance (s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Albendazole	Sum of albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone expressed as albendazole	Bovine, ovine	100 µg/kg 100 µg/kg 1000 µg/kg 500 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	

Based on these MRLs, it was calculated that the daily intake of extractable residues would amount to 310 µg/day, i.e. 103% of the ADI. It was considered that this would not constitute a risk to consumers because at least 75% of the residues in tissues were not bioavailable.