



COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

ALBENDAZOLE (Extrapolation to all ruminants)

SUMMARY REPORT (3)

1. Albendazole is a benzimidazole carbamate, used for the treatment of gastrointestinal infestations with roundworms, lungworms and tapeworms and adult flukes of *Fasciola hepatica*. Albendazole is currently entered into 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
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	

2. In reviewing the availability of endo- and ectoparasiticides for sheep and goats, albendazole was considered for extrapolation from bovine and ovine species to all ruminants. The considerations and criteria leading to the identification of albendazole are described in the Position Paper Regarding Availability of Veterinary Medicines – Extrapolation of MRLs (EMEA/CVMP/457/03-FINAL).
3. The scientific justification for this extrapolation was assessed in accordance with the Notes for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL) and on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL).
4. In setting the ADI in the original assessment of albendazole, the data summarised on the paragraphs below were considered.
5. 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.
6. 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 to 30% of oral doses of albendazole.

7. 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.
8. 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.
9. Albendazole was of low acute toxicity when given by the oral route to mice, rats, hamsters, guinea pigs and rabbits.
10. 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 treatment 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.
11. 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.
12. 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.
13. 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.
14. Albendazole has been adequately tested in carcinogenicity bioassays, giving no evidence of neoplasia in either rats or mice.
15. No irritancy studies on albendazole have been seen, but albendazole sulphoxide was found to be non-irritant to the skin or eyes of rabbits.
16. 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.
17. 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.

18. In 1992, the CVMP set an ADI for albendazole of 0.005 mg/kg bw, by applying a 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 1000-fold safety factor was also regarded as sufficient to cover the indications of potential mutagenic risk indicated in the *in vivo* mouse micronucleus test as it was probably due to an aneugenic effect when the ADI was reconsidered and confirmed in 1997.
19. For the extension to include all ruminant species in Annex I the information summarised in the paragraphs below was taken into account.
20. After oral treatment, residues are highest and most persistent in the liver. In cattle given ¹⁴C-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 treatment to around 6 mg/kg four days after treatment and around 1.2 mg/kg 20 days after treatment. 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, 4 days after treatment and 170 µg/kg 20 days after treatment.

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.

21. Calves were given an oral dose of 20 mg/kg bw ¹⁴C-albendazole and killed 1, 4, 6 or 10 days after treatment. One day after treatment, around 90% of the residues were extractable but from 4 days to 10 days after treatment only 20 to 30% of the residues were extractable. Residues of albendazole in calves liver accounted for 27% of the total extractable residues one day after treatment but were undetectable 4 days after treatment. Residues of albendazole sulphoxide + albendazole sulphone + the 2-amino-sulphone metabolite accounted for 52% of the total extractable residues one day after treatment, and comprised 40 to 50% of the total extractable residues for up to 10 days after treatment. Analysis of kidney samples revealed the same metabolic profile.
22. Sheep were given an oral dose of 10 mg/kg bw ¹⁴C-albendazole and killed 1, 2, 4, 6 or 8 days after treatment. Residues of albendazole were not found in any of the tissue samples. One day after treatment, around 100% of the residues were extractable but this proportion decreased to 37% at 4 days and 13% at 8 days. From 1 to 4 days after treatment, 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 to 80%. Thereafter, the percentage of extractable residues present as marker residue declined to around 40%, 8 days after treatment. 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 ¹⁴C-albendazole and the sheep killed (2 per time point) immediately after 7 or 14 days of treatment, the marker residue accounted for 80 to 100% of the total residues in muscle, 52 to 58% of the total residues in liver and 47 to 74% of the total residues in kidney.
23. Four dairy cows in different stages of lactation were given a single oral dose of 15 mg/kg bw ¹⁴C-albendazole. Within 24 hours of treatment, mean total residues in milk were around 3416 µg/kg albendazole-equivalents and depleted to 227 µg/kg by 2 days after treatment and 19 µg/kg by 3 days after treatment. Within the first 2 days of treatment, around 2 to 3% of the total residues were present as albendazole. During the first 24 hours after treatment, 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 treatment, the marker residue accounted for around 50% of the total residues.

24. Ruminant species such as bovine, ovine and caprines share a similar gastro-intestinal physiology. The available pharmacokinetic and residues depletion data do not indicate any significant variability between cattle and sheep, therefore, it was considered that other ruminants were unlikely to show any significant differences in these parameters. The existing MRLs for bovine and ovine species are identical and so it was considered appropriate to recommend the extension of the MRLs so that that the same MRL values would apply to all ruminants, including milk.
25. An analytical method based on HPLC has been validated in accordance with Volume VI¹ 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. This method should be applicable to other ruminant species and therefore from this aspect extrapolation to the tissues and milk of other ruminants is possible.

Conclusions and recommendation

Having considering that:

- an ADI of 0.005 mg/kg bw (i.e. 300 µg/person) was previously established,
- no significant differences in pharmacokinetics or residue depletion were observed in bovine and ovine species,
- MRLs were previously established in bovine and ovine species; these MRLs are identical,
- an analytical method for the monitoring of residues in tissues and milk of all ruminants was available;

the Committee for Medicinal Products for Veterinary Use recommends the modification of the current entry of albendazole for bovine and ovine species 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
Albendazole	Sum of albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone expressed as albendazole	All ruminants	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.

¹ Now Volume 8 following revision in September 2001 and June 2003