The European Agency for the Evaluation of Medicinal Products

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ALBENDAZOLE SULPHOXIDE

SUMMARY REPORT (1)

1. Albendazole sulphoxide (also known as ricobendazole) is a benzimidazole carbamate which is used as a broad spectrum anthelmintic in veterinary medicine. It is also a metabolite of two other veterinary drugs: netobimin and albendazole.

2. Albendazole sulphoxide-containing products are available as liquid suspensions which are administered orally. Products are available for sheep and cattle. Dosages of 7.5-10 mg/kg bw of albendazole sulphoxide are recommended and should be given at approximately monthly intervals. A product is currently being developed for use in pheasants.

3. The mode of action of albendazole sulphoxide 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.

4. No data were provided on the amount of absorption of albendazole sulphoxide from the gut, but the finding of tissue residues indicated that some uptake of albendazole sulphoxide must occur in farm animals. Pharmacological studies indicated that albendazole sulphoxide was slowly metabolised to a range of metabolites by hydroxylation, oxidation to sulphones, deacetylation to form amines and reduction to albendazole. The range of metabolites found were similar to those detected following dosing with albendazole. Some binding to protein may occur.

5. Albendazole sulphoxide was found to be non-irritant to the skin or eyes of rabbits.

6. A positive result in a guinea-pig maximization test showed albendazole sulphoxide to be a potential skin sensitizer.

7. Albendazole sulphoxide was of low acute toxicity when given by the oral route to rats or to food animals (cattle, sheep and pheasant).

8. Repeat dose subchronic oral toxicity studies in rats showed slight alterations in some haematological parameters at low doses of albendazole sulphoxide, but these were interpreted as being fortuitous results which were unrelated to treatment. Hepatotoxicity, testicular atrophy and activation of the immune system were interpreted as having been caused by treatment with albendazole sulphoxide. Hepatotoxicity and testicular atrophy were seen at doses of 34 mg/kg bw/day or greater, but not at 12.9 mg/kg bw/day or less. Netobimin and albendazole both caused similar hepatotoxicity and testicular toxicity. The effects on the immune system were characterised by increased spleen weight with splenic extramedullary haematopoiesis, splenic reticular cell hyperplasia and lymph node hyperplasia with the increased spleen weight being evident in males at doses of 10.9 mg/kg bw/day or more and no effects being seen at 3.3 mg/kg bw/day or less. It is unclear whether this activation of the immune system is indicative of an adverse effect to health, but it would be prudent to assume that it is. Consequently a NOEL of 3.3 mg/kg bw/day has been identified. No repeat dose toxicity studies had been performed on albendazole sulphoxide in any species other than the rat.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

9. The results of the rat teratology studies showed that high doses of albendazole sulphoxide were embryotoxic and that lower doses caused impairment of foetal development at doses of 7 mg/kg bw/day (no effect at 6 mg/kg bw/day). It was unclear from the study report whether this developmental effect should be regarded as teratogenicity or merely foetotoxicity, but as netobimin and albendazole were both clearly teratogenic it is reasonable to assume that the developmental effect was teratogenicity. No studies have been performed on albendazole sulphoxide in species other than the rat.

10. No studies on fertility or peri-/post-natal toxicity were provided. It is noted that both netobimin and albendazole produced adverse effects on reproduction (with NOELs of 15 and 5.8 mg/kg bw/day respectively).

11. Albendazole sulphoxide gave a positive result in an *in vivo* mouse bone marrow micronucleus test. A yeast assay showed that albendazole sulphoxide had aneugenic potential and this was confirmed by studies which demonstrated *in vitro* the ability of albendazole sulphoxide to bind with tubulin. No evidence of clastogenicity was seen in an *in vitro* metaphase analysis of human lymphocytes but this study could not be relied upon as a clear negative result as insufficiently high concentrations of albendazole sulphoxide had been used. However, as albendazole was negative in a well-conducted *in vitro* metaphase analysis of CHO cells, it is reasonable to assume that albendazole sulphoxide did not have clastogenic potential. The results of the mutagenicity tests on albendazole sulphoxide and those on netobimin and albendazole were consistent with these substances all being *in vivo* aneugens in somatic cells. In the absence of any tests on germ cells, it remains unclear whether or not albendazole sulphoxide can induce aneuploidy at meiosis and thus induce heritable mutations. A level of exposure to albendazole sulphoxide which presents no mutagenic risk to consumers has not been identified.

12. No long-term/carcinogenicity studies have been performed on albendazole sulphoxide. However, albendazole has been adequately tested in carcinogenicity bioassays, giving no evidence of neoplasia in either rats or mice.

13. No substantive safety data arising from human exposure to albendazole sulphoxide were available.

14. Although albendazole sulphoxide had not been tested in the full range of studies indicated in Volume VI of the Rules Governing Medicinal Products in the European Community, it was considered that albendazole and albendazole sulphoxide were so closely associated in their metabolism that use could be made of safety data from studies of albendazole to complement the albendazole sulphoxide studies. A NOEL of 5 mg/kg bw/day was identified to cover a variety of effects: teratogenicity, immunomodulation, hepatotoxicity, and testicular toxicity. A large safety factor of 1000 was applied to the NOEL to give a group ADI for albendazole sulphoxide and albendazole of 0-0.005 mg/kg bw. The large safety factor was necessary to compensate for the severity of teratogenic effects produced by albendazole and the fact that albendazole and albendazole sulphoxide may cause developmental effects after a single exposure. Also, although no level of exposure which was free of mutagenic risk had been identified, it was considered that the use of this large safety factor would ensure that the risk was minimal.

    Group ADI (albendazole sulphoxide + albendazole) = 0-0.005 mg/kg bw (equivalent to 0.3 mg/person/day for a 60 kg person).

15. Bioequivalence studies have been carried out in cattle and sheep, demonstrating that plasma levels of albendazole sulphoxide are similar following oral dosing of albendazole or albendazole sulphoxide, i.e. both are readily absorbed from the gut in ruminants. No pharmacokinetic studies have been carried out in pheasants.

16. Meat residue depletion studies have been carried out in cattle, sheep and pheasants. In all cases, albendazole sulphoxide and albendazole sulphone were measured. These studies demonstrate that, as for albendazole, residues are highest and most persistent in liver followed by kidney, then muscle and fat. Levels of both the metabolites assayed had fallen to less than 25 µg/kg by 7 days after dosing in all three species. Although the 2-amino sulphone metabolite was not assayed, the results for the other two metabolites show that residue depletion is virtually identical to that after administration of albendazole.

17. Milk residue depletion studies have been carried out in cattle and sheep. Albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone were measured and the results demonstrated that, even when the dose administered was higher than the maximum recommended dose, residues in milk had fallen below 100 µg/kg by 48 hours after treatment.

18. Since albendazole sulphoxide is a primary metabolite of albendazole, it seems sensible for the same marker residue to be used for both compounds. It has been proposed that the marker residue for albendazole should be established as the sum of albendazole, albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone (to be expressed in terms of albendazole). In practice, no residues of albendazole have been found in the edible tissues following administration of albendazole sulphoxide, but this could nevertheless be included in the marker residue definition.

19. The applicant has submitted an HPLC method with UV detection which is capable of separating and individually measuring albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone in bovine and ovine tissues. The limits of quantification, based on acceptable accuracy and precision are 100 µg/kg for each metabolite in liver and kidney and 20 µg/kg for each metabolite in muscle and fat. This equates to a total limit of quantification of 300 µg/kg for liver and kidney (i.e. 30% and 60% of the MRLs, respectively) and 60 µg/kg for muscle and fat (i.e. 60% of the MRLs). Further information on storage stability and possible interference from other benzimidazoles is required before this method can be considered fully validated.

Conclusions and recommendation

Having considered that :

- a toxicological ADI has been set at 0-0.005 mg/kg bw;
- the physico-chemical analytical method available is not fully validated,

the Committee recommends the inclusion of albendazole sulphoxide into Annex III 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 sulphoxide	Sum of albendazole, albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone,expressed as albendazole	Bovine, ovine, pheasant	1000 µg/kg 500 µg/kg 100 µg/kg 100 µg/kg	Liver Kidney Muscle Fat	Provisional MRLs expire on 01.01.1998
		Bovine, ovine	100 µg/kg	Milk	

Based on the standard daily intake of 100 g liver, 50 g kidney, 300 g muscle, 50 g fat and 1.5 litres milk, this adds up to a daily intake of 310 µg. This is slightly in excess of the ADI proposed in paragraph 13 above, but in view of the large safety factor, this is not considered to constitute a consumer hazard.

LIST OF QUESTIONS

1. Before the MRLs for cattle and sheep can be entered into Annex I of Council Regulation (EEC) No 2377/90, the applicant must provide the following information :

   – With regard to the analytical method for cattle and sheep tissues, information on possible interference from other benzimidazoles, together with further information on storage stability, especially at levels nearer the MRLs and in incurred tissues.

   – A fully validated analytical method presented in an internationally recognized format (e.g. ISO 78/2) for the determination of the marker residue in ovine and bovine milk.

2. Before the MRLs for pheasant tissues can be enterd into Annex I of Council Regulation (EEC) No 2377/90, the applicant must provide the following information in accordance with the CVMP's policy on minor species :

   – Some evidence (possibly from *in vitro* studies) that metabolism in pheasants is essentially similar to that in the mammalian species already studied.

   – A fully validated analytical method presented in an internationally recognized format (e.g. ISO 78/2) for the determination of the marker residue in pheasant tissues.