The European Agency for the Evaluation of Medicinal Products

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ALBENDAZOLE OXIDE

SUMMARY REPORT (2)

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

   Albendazole oxide-containing products are available as liquid suspensions which are administered orally. Products are available for sheep, cattle and pheasants. For sheep and cattle dosages of 7.5 to 10 mg/kg bw of albendazole oxide are recommended and should be given at approximately monthly intervals. For pheasants albendazole oxide is administered in the feed at a dose equivalent to 17 mg/kg bw/day for 3 days.

   In some Member States, oral boluses containing albendazole oxide are available and are administered at dose rates of up to 15 mg/kg bw. The substance was reported to be used in goats but no data concerning this use were available.

   Currently, albendazole oxide is included in Annex III of Council Regulation (EEC) No. 2377/90 as follows:

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	100 µg/kg 100 µg/kg 100 µg/kg 1000 µg/kg 500 µg/kg	Milk Muscle Fat Liver Kidney	Provisional MRLs expire on 1 January 2000

   The information requested for the establishment of final MRLs has now been submitted.

2. The mode of action of albendazole oxide 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.

3. No data on the percentage of oral bioavailability of albendazole oxide were provided. Pharmacokinetic and metabolism studies in rodents, chickens, cattle and sheep indicated that albendazole oxide was slowly metabolised to albendazole sulphone and then to albendazole 2-aminosulphone. The range of metabolites found following treatment with albendazole oxide were similar to those detected following dosing with albendazole. Some binding to protein may occur.

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

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5. Repeated dose oral toxicity studies in rats of 13 weeks duration showed slight alterations in some haematological parameters at low doses of albendazole oxide, 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 oxide. 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 on 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 repeated dose toxicity studies had been performed on albendazole oxide in any species other than the rat.

6. The results of the rat teratology studies showed that high doses of albendazole oxide were embryotoxic and that lower doses (7 mg/kg bw/day) caused impairment of foetal development (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 oxide in species other than the rat.

7. 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).

8. Albendazole oxide gave a positive result in an *in vivo* mouse bone marrow micronucleus test. A yeast assay showed that albendazole oxide had aneugenic potential and this was confirmed by studies which demonstrated *in vitro* the ability of albendazole oxide 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 oxide had been used. However, as albendazole was negative in a well-conducted *in vitro* metaphase analysis of Chinese hamster ovary cells, it is reasonable to assume that albendazole oxide did not have clastogenic potential. The results of the mutagenicity tests on albendazole oxide 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 oxide can induce aneuploidy at meiosis and thus induce heritable mutations. A level of exposure to albendazole oxide which presents no mutagenic risk to consumers has not been identified.

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

10. Albendazole oxide was found to be non-irritant to the skin or eyes of rabbits.

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

11. Although albendazole oxide 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 oxide were so closely associated in their metabolism that use could be made of safety data from studies of albendazole to complement the albendazole oxide studies. A NOEL of 5 mg/kg bw/day was identified to cover a variety of effects: teratogenicity, immunomodulation, hepatotoxicity, and testicular toxicity. A safety factor of 1000 was applied to the NOEL to give an ADI for both albendazole oxide and albendazole of 0.005 mg/kg bw (i.e. 0.3 mg/person). The large safety factor was necessary to compensate for the severity of teratogenic effects produced by albendazole. 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.

12. Bioequivalence studies have been carried out in cattle and sheep, demonstrating that plasma levels of albendazole oxide and albendazole sulphone are similar following oral dosing with equivalent doses of albendazole or albendazole oxide. In a study in sheep, C_{max} values of 1.48 and 1.48 µg/ml were obtained for albendazole oxide 8.5 and 8.7 hours after dosing with 5 mg/kg bw albendazole oxide and albendazole respectively and C_{max} values of 0.28 and 0.30 µg/ml were obtained for albendazole sulphone around 18 hours after dosing. The respective area under the curve (AUC) values were 25206 ng.h/ml and 25140 ng.h/ml for albendazole oxide and 7432 ng.h/ml and 7912 ng.h/ml for albendazole sulphone.

13. Tissue residue depletion studies have been carried out in cattle and sheep. In both cases, residues of albendazole oxide 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. In a study in which sheep were given an oral dose of 9.6 mg/kg bw albendazole oxide, and slaughtered in groups of 4 animals per time-point, concentrations of both the metabolites in all samples of muscle, liver, kidney and fat had fallen to less than 25 µg/kg by 7 days after dosing. In a study in which cattle were given a single oral dose of 12 mg/kg bw albendazole oxide, and slaughtered in groups of 4 animals per time point, mean residues of 294 µg/kg albendazole oxide and 2953 µg/kg albendazole sulphone were found in liver one day after dosing and the residues of both analytes had depleted to below 5 µg/kg by 3 days after dosing. In kidney, mean residues of 233 µg/kg albendazole oxide and 1355 µg/kg albendazole sulphone were found one day after dosing and had depleted to below 5 µg/kg by 2 days after dosing. Although the 2-aminosulphone metabolite which is found after administration of albendazole was not assayed, the results for the other two metabolites show that residues depletion is virtually identical to that after administration of albendazole.

    Data provided for chickens indicated that albendazole was metabolised in avian species via the same metabolic pathway as in mammals. Pheasants were given albendazole oxide orally in the feed at a dose equivalent to 17 mg/kg bw/day for 3 days. Groups of 5 male and 5 female birds were killed at 1, 2, 3 and 7 days after the end of dosing and residues of albendazole oxide and albendazole sulphone in tissues were determined using HPLC. In addition, residues of a metabolite which was believed to be albendazole 2-aminosulphone were detected only in liver. The mean residues in liver (albendazole oxide + albendazole sulphone) depleted from 479 µg/kg at one day to 90 µg/kg at 3 days and 45 µg/kg at 7 days. Mean residues of albendazole 2-aminosulphone in liver were 24 µg/kg at one day, 168 µg/kg at 3 days and 99 µg/kg at 7 days. Mean residues in kidney depleted from 366 µg/kg at one day to 15 µg/kg at 3 days and were undetectable at 7 days. Mean residues in samples of skin with fat were 84 µg/kg at 7 days and were undetectable at later time points. Mean residues in muscle depleted from 168 µg/kg at one day to 15 µg/kg at 2 days and were undetectable at later time points.

14. Milk residues depletion studies have also been carried out in cattle and sheep. Albendazole oxide, albendazole sulphone and albendazole 2-aminosulphone 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.

15. Albendazole oxide is a primary metabolite of albendazole, hence, the same marker residue is applicable for both compounds. It was previously agreed that the final marker residue for albendazole should be the sum of albendazole oxide, albendazole sulphone and albendazole 2-aminosulphone (to be expressed in terms of albendazole) and this marker includes all the extractable residues which are of toxicological significance following treatment with either albendazole or albendazole oxide.

16. A fully validated HPLC method with UV detection which is capable of separating and individually measuring albendazole oxide, albendazole sulphone and albendazole 2-aminosulphone in bovine and ovine tissues and milk was provided. The limits of quantification, based on acceptable accuracy and precision are 100 µg/kg for each metabolite in liver and kidney, 20 µg/kg for each metabolite in muscle and fat and 15 µg/kg for each metabolite in milk. This equates to a total limit of quantification of 300 µg/kg for liver and kidney , 60 µg/kg for muscle and fat and 45 µg/kg for milk. This method is the same as that submitted in connection with albendazole. The method was not satisfactorily validated for pheasant tissues.

Conclusions and recommendation

Considering that:

- an ADI of 0.005 mg/kg bw (i.e. 300 µg/person) had been established,
- the main components of the extractable residues in tissues of cattle and sheep treated with albendazole oxide were qualitatively and quantitatively similar to those in animals treated with albendazole, i.e. albendazole oxide, albendazole sulphone and albendazole 2-aminosulphone, and these substances accounted for essentially all the residues which were of toxicological significance at all time points,
- for the sake of consistency and taking into account the comparable pharmacokinetics of albendazole oxide and albendazole, it was considered that the choice of marker residue and the numerical values of the MRLs should be the same as established for albendazole,
- a validated analytical method was available for the determination of residues of albendazole oxide, albendazole sulphone and albendazole 2-aminosulphone in edible tissues and milk of cattle and sheep,
- the analytical method is not satisfactorily validated for pheasant tissues and therefore no final MRLs could be proposed for pheasants;

the Committee recommends the inclusion of albendazole oxide 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 oxide	Sum of albendazole oxide, albendazole sulphone and albendazol 2-aminosulphone, 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	