COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NETOBIMIN

SUMMARY REPORT

1. Netobimin is a pro-benzimidazole anthelmintic which is used in cattle, sheep and goats.

2. As netobimin is rapidly but incompletely metabolised to albendazole, it is expected that netobimin will have all the toxicological characteristics of albendazole. However, it is possible that netobimin may have some toxicological properties of its own in addition to those of albendazole. Consequently, one cannot rely solely on albendazole's toxicity data in assessing the safety of netobimin and must also consider data from toxicologic studies of netobimin.

3. Netobimin was of low acute toxicity when given by oral or intravenous routes in all of the species tested. In rats and mice estimates of intravenous LD_{50} were greater than 5000 mg/kg bw.

4. Netobimin was tested in several repeat-dose oral toxicity studies, but there were shortcomings in the design and/or performance of all of these studies. The most sensitive parameters in rats were anaemia in short-term studies (NOEL = 38 mg/kg bw/day) and liver toxicity in a one-year study (NOEL < 15 mg/kg bw/day). A NOEL was not established for the liver toxicity. In addition, testicular atrophy, skin lesions (with secondary systemic infections), and other effects were seen in rats at higher doses. In short-term studies in dogs, diarrhoea was the most sensitive effect of netobimin (NOEL = 190 mg/kg bw/day), but as the effect was slight at the lowest dose and as other species were more sensitive to the toxicity of netobimin it will not be necessary for the applicant to establish a NOEL for diarrhoea in dogs.

5. Netobimin was teratogenic in both rats (NOEL = 91.4 mg/kg bw/day) and rabbits (NOEL = 7.5 mg/kg bw/day). A reproduction study in rats showed more general adverse reproductive effects (NOEL = 15 mg/kg bw/day) at doses below the limit for rat teratogenicity.

6. The positive results from an *in vivo* micronucleus test suggest that both netobimin and albendazole are mutagenic. As some benzimidazoles are known to act as anthelmintics by attacking the microtubules in the cells of helminths the hypothesis that this result was due to aneugenicity of netobimin and albendazole seems feasible, but the available evidence is insufficient to prove this. The possibility that these chemicals may be clastogenic has not been eliminated. A limited range of other tests performed *in vitro* (tests for gene mutations and DNA repair) gave no evidence to suggest that netobimin might be mutagenic. From the available evidence, it is concluded that netobimin and albendazole are *in vivo* mutagens. The mode of action (e.g. clastogenicity or aneugenicity) of the mutagenicity is not clear.

7. There are no satisfactory data on the possible carcinogenicity of netobimin. The one year rat study was of insufficiently long duration to be regarded as a carcinogenicity bioassay. The applicant's proposal for a full ADI needs further supporting data. This is because NOELs have not been established for all of the toxic effects of netobimin (e.g. liver toxicity in orally exposed rats) and because the available evidence (positive *in vivo* micronucleus test) suggest that netobimin and its metabolite albendazole are mutagenic.

   A provisional ADI of 0-0.0075 mg/kg bw may be used, pending provision of the data requested for setting a full ADI. This has been set by applying a safety factor of 1000 to the NOEL of 7.5 mg/kg bw/day for teratogenic effects in rabbits. This provisional ADI for netobimin is greater than the ADI of 0-005 mg/kg for its metabolite albendazole. Consequently, applying the same numerical values of the MRLs set for albendazole also for netobimin will ensure the safety of consumers.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

8. Netobimin appears to have no significant antimicrobial activity.

9. A series of generally well-conducted pharmacokinetic studies demonstrate that netobimin given orally or parenterally to cattle or sheep is rapidly absorbed :

	Cattle oral	Cattle parenteral	Sheep oral
C_{max}	6 µg equiv/ml	2 µg equiv/ml	7 µg equiv/ml
T_{max}	10 hours	< 1 hour	7 hours

Only netobimin, albendazole or albendazole-related metabolites are present.

10. The major metabolites present is cow and sheep milk after oral administration of a single 20 mg/kg dose of ^{14}C netobimin are albendazole sulphoxide and albendazole sulphone. After parenteral administration, parent compound is also present. In orally dosed goats a similar pattern was seen but only one study was conducted and this used only two animals.

11. The major metabolites present in the edible tissues of cows and sheep are albendazole, albendazole sulphoxide and albendazole amine sulphone in the solvent extractable fraction and albendazole amine sulphone in the acid extractable fraction.

12. Final netobimin residue depletion studies were conducted using 3 animals per time point. In cattle oral and subcutaneous administration were studied; in sheep only oral administration was studied. No studies were carried out in goats. The HPLC analysis methods were not fully validated.

13. Final milk residue depletion studies were conducted in cattle and sheep using either 5 or 7 animals per species and route of administration. No such study was conducted in goats. Again HPLC analysis was used and the methods employed for milk were better validated and documented than those used for tissues.

14. No full MRLs can be elaborated for the following reasons :

    - no full ADI is established;
    - the relationship between the proposed marker residue and total residues is not adequately demonstrated;
    - the proposed marker residues (i.e. 2-amino-benzimidazole sulphone in tissues and the sum of albendazole sulphoxide, albendazole sulphone and netobimin in milk) are inappropriate for a compound whose metabolites are largely similar to those of albendazole;
    - there is no regulatory surveillance method available for measurement of the marker residues proposed by the applicant.

15. As netobimin is metabolised to albendazole and to metabolites of albendazole, the provisional MRLs which were set for albendazole may be applied to netobimin for a limited period of time.

    Data are still required for setting a full MRL for netobimin. Following provisional MRLs are proposed :

muscle	0.1 mg/kg
fat	0.1 mg/kg
kidney	0.5 mg/kg
liver	1.0 mg/kg
milk	0.1 mg/l

    The marker residue is the sum of netobimin and albendazole and metabolites of albendazole measured as 2-amino-benzimidazole sulphone. The target species are cattle, sheep and goats.

    The provisional MRLs expire on 1 January 1999 (4 years)

    Additional information is required before 1 January 1998 (3 years) relating to the following aspects :

LIST OF QUESTIONS

1. Clarification is required regarding which routes of administration of the drug are used in which species in the member states. If parenteral use is recommended, is subcutaneous or intramuscular injection specified ? (Note : most of the information on parenteral administration refers to subcutaneous administration).

2. The applicant should establish a NOEL for liver toxicity in orally-exposed rats.

3. The applicant should eliminate the possibility of netobimin having clastogenic properties. An *in vitro* metaphase analysis may be used, but if this gives a positive result an *in vivo* metaphase analysis will be needed.

4. The possible carcinogenicity of netobimin should be discussed.

5. On the basis of the forthcoming information the applicant should establish a permanent ADI.

6. The metabolites of netobimin are, with the exception of the parent compound after parenteral administration, essentially similar to those of albendazole. The applicant should justify their choice of marker residues in view of the fact that the provisional MRLs for albendazole are expressed as the 2-aminosulphone. The applicant should provide more convincing evidence of the claimed relationship between the proposed marker residue and total residues.

7. Information on residues on goats' milk is scant, i.e. based on one radioactive study using only 2 animals. The applicant should propose MRLs for goat meat.

8. Clarification is required as to whether the figures quoted for albendazole amine sulphone residues in bovine tissues include solvent-extractable and bound residues. Comment is also required on the amount and biological significance of the bound residues.

9. With regard to residues in bovine tissues following subcutaneous injection, the applicant should explain why the residues detected in radioactive studies are so much lower than those from the non-radioactive study (approximately 10^3 for most tissues).

10. The MRLs need to more accurately reflect the level of residues found in different tissues. In particular, the new proposals need to take account of the high level of residues found in injection sites (under the proposed withdrawal period the residues found in injection sites are well above the proposed MRL for muscle). Also the relationship between residues in liver and kidney needs to be re-examined (the applicant claims that residues in liver are 5 times those in kidney but in the case of parenteral administration of netobimin to cattle, the levels in kidney are in fact higher than those in liver).

11. In cattle, adults excreted more of the dose in urine and had higher levels of residues in their tissues than did their calves. The applicant should comment on the possible cause of this age effect and provide data on the existence of comparable age effects in sheep and goats.

12. Considering the information to be forwarded in regard of the questions mentioned above the applicant should submit a fully validated surveillance method. A confirmation of the availability of analytical standards should be provided.