



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

RIFAXIMIN

REVISED SUMMARY REPORT

1. Rifaximin is an antibiotic belonging to the family of naphthalene-ringed ansamycins (Rifampicin, Rifamycin). Rifaximin possesses a broad spectrum of action against gram-positive bacteria (Staphylococci and Streptococci, Corynebacterium sp.) and against gram-negative bacteria (E. coli, Pasteurella spp., Pseudomonas sp., Proteus sp.). The applicant recommends this compound for the treatment and prevention of mastitis during the dry - period by intramammary route and for the treatment of post-partum metritis by intrauterine route.
2. The emergence of resistances to Rifaximin, evaluated in vitro by the method of transfers either in a solid medium or in a liquid one and in vivo (man, guinea-pig), is comparable to what is generally observed with the compounds of this family.
3. The pharmacokinetic studies were carried out by oral route in rats, man and by intramammary route in dairy cows. An oral or topical administration of Rifaximin leads to a negligible systemic absorption of the active ingredient.
After oral administration of Rifaximin to rats, plasma concentrations remained to a low level, represented less than 0.1 % of the administered dose (10 mg/kg or 100 mg/kg). After 168 hours, the faecal excretion amounts represented more than 95 % of the administered dose.
In lactating dairy cows or in cows at drying-off, no trace of Rifaximin could be detected in plasma after administration by intramammary route 100 mg of Rifaximin per quarter (2 or 4 quarter treated). The HPLC quantification and detection limits were 0.02 µg/ml and 0.01 µg/ml.
4. Single oral toxicity was only tested for rats, and the LD50 was higher than 2000 mg/kg.
5. Three and six month-toxicity studies were performed in rats and in dogs (0, 25, 50, 100 mg/kg b.w./day). The most sensitive species was rats. In rats, liver steatosis was described for the dosage equal or upper to 25 mg/kg b.w./day. The blood biochemistry revealed a significant increase in the cholesterolemia and a diminution of the ratio of esterified cholesterol to total cholesterol in animal groups at the doses of 50 and 100 mg/kg b.w./day. A NOEL of 25 mg/kg b.w./day could be retained.
6. No embryotoxic and teratogenic effects of Rifaximin could be seen in rats and rabbits after administration of 0, 50 and 100 mg of Rifaximin/kg b.w./day during the organogenesis period.
7. From the toxicological data set, a toxicological ADI of 0.25 mg/kg b.w./day could be derived from the three-month toxicity studied carried out in rats.
8. The different tests performed, Ames's test, test with Schizosaccharomyces pombe, with Saccharomyces cerevisiae, Micronucleus test, human Lymphocyte chromosomal aberration test, CHO/HGPRT test did not reveal mutagen properties for Rifaximin.

9. In the dairy technology, especially in the fabrication of yoghurts, the NOEL of Rifaximin was established at 0.098 µg/ml for *Streptococcus thermophilus*.
10. Based on the in vitro results obtained on *Bacteroides fragilis*, a microbiological ADI of 0.002 mg/kg b.w./day was calculated according to the following formula :

$$\text{ADI (}\mu\text{g/kg b.w.)} = \frac{\frac{\text{Mean MIC (0.20 } \mu\text{g/ml)} \times \text{CF}_2 (4)}{\text{CF}_1 (1)} \times \text{daily faecal bolus (150 ml)}}{\text{fraction available for micro-organism (1)} \times \text{human weight (60 kg)}}$$

with CF₁ = 1 as the MIC variability being evaluated by the calculation of the one-tailed 10 % lower confidence limit of sensitive strains,
 CF₂ = 4, the influence of the inoculum size been tested on intermediate or resistant strains.

This microbiological ADI (0.002 mg/kg b.w. per day) is about 100 lower than the toxicological ADI of 0.250 mg/kg b.w. contained from the three-month toxicity in rats.

11. As MICs of *M. tuberculosis* strains isolated from kidneys and lungs of patients affected with tuberculosis determined before and after an exposure to Rifaximin (6, 20, 90 and 270 ng/ml for 12 to 23 days) remain identical, it can be advanced that the use of Rifaximin in veterinary medicine can not lead to the development of resistance in human strains.
12. Two studies of depletion of Rifaximin in milk were performed to quantify the Rifaximin residues after treatment of lactating cows (100 mg of Rifaximin per quarter by intramammary route - two quarters treated in a first study, four quarters in the second study). Milk residues were below the limit of detection from the 18th milking. The HPLC and microbiological limits of detection were 0.01 and 0.025 µg/ml respectively.
13. In a third study, it is shown that no residues of Rifaximin could be detected in milk after calving when animals had been treated at drying - off (100 mg of Rifaximin per quarter). The limits of detection are the same as previously.
14. After intrauterine administration to cows immediately after calving, with pessaries (1200 mg/animal) or foam (200 mg/animal), plasma and milk concentrations up to 96 hours are below the quantification limit of the HPLC method used (0.01 µg/ml).
15. There is no study of residues depletion in tissues either after intramammary or intrauterine administrations. As plasma concentrations of Rifaximin were always below the limit of quantification (0.010 µg/ml) after intramammary or intrauterine administrations, the CVMP concludes that depletion studies are not required for this compound.
16. A validated routine HPLC method for the assaying of Rifaximin residues in milk is available. The limit of quantification of this method is 0.050 mg/kg.

17. In line with the recommendations of Volume VI of the Rules Governing Medicinal Products in the European Community on the analytical validation, as the limit of quantification is close to the value retained for the MRL only provisional MRL for milk could be allocated:

Conclusion and recommendation:

- Given that after intramammary use, residues of Rifaximin can be detected in milk;
- Given that after intramammary use, plasma concentrations of Rifaximin are always below the quantification limit of the HPLC method used (0.01 µg/ml);
- Given that after intrauterine administration, plasma concentrations of Rifaximin are below the quantification limit of the HPLC method used (0.01 µg/ml).

The Committee for Veterinary Medicinal Products recommends that MRLs for Rifaximin be set as indicated in the two following tables:

Annex III					
Pharmacologically active substance	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Rifaximin	Rifaximin	Bovine	0.060 mg/kg	Milk	Provisional MRL expires on 01.06.1998

Annex II		
Pharmacologically active substance	Animal Species	Other provisions
Rifaximin	Bovine	For intrauterine and intramammary uses only and for all tissues excepted milk

The applicant should provide by 1 June 1997 data on the precision of the analytical method for a level corresponding to half the value of the provisional MRL (0.030 mg/kg).