The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

RIFAXIMIN (Extension to topical use)

SUMMARY REPORT (3)

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* sp., *Pseudomonas* sp., *Proteus* sp.). In veterinary medicine, it is intended for use in cattle, 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. The recommended dose is 100 mg of rifaximin per quarter and 50 to 200 mg/animal for intramammary and intrauterine treatments, respectively.

   A microbiological ADI of 2 µg/kg bw (i.e. 60 µg/person) was previously established for rifaximin by the Committee for Veterinary Medicinal Products (CVMP)

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

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Rifaximin	Rifaximin	Bovine	60 µg/kg	Milk	Provisional MRL expires on 01.06.1998

   For tissues other than milk, rifaximin is included in Annex II to Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal Species	Other provisions
Rifaximin	Bovine	For intramammary use - except if the udder may be used as food for human consumption - and intrauterine use only

   The Committee for Veterinary Medicinal Products (CVMP) has in the meantime recommended the inclusion of rifaximin in Annex I to Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Rifaximin	Rifaximin	Bovine	60 µg/kg	Milk	

   An application for extension of the current entries to include topical use of rifaximin has now been submitted for cattle, sheep, goats, horses and rabbits for foot and skin bacterial infections. When applied as spray, the recommended dose is approximately 2 to 9 mg of rifaximin per animal, once or twice daily for 5 to 10 days (dose ranging from 0.34 mg/kg bw/day to 2.44 mg/kg bw/day according to the species).

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2. Data on the absorption of rifaximin after dermal application have been provided for rats, for the target species (cattle, pigs, sheep and rabbits) and for humans.

3. In groups of 6 rats, 1, 3 and 6 hours after a single topical application of 100 mg/kg bw of rifaximin on shaved skin, no rifaximin could be detected in serum. Only traces were measured in the interstitial fluid collected below the site of application on the abdominal region of 4, 3 and 2 rats sacrificed at 1, 3 and 6 hours after treatment. Similar results were obtained after repeated administrations of 100 mg/kg bw/day for 14 days. However, due to the poor quality of the experimental design and of the microbiological analytical method used to measure the concentrations of rifaximin in the biological fluids and in absence of value for the limits of detection and of quantification, these results should be treated with caution.

4. In eleven lactating cows, after single topical application of 5 to 9 mg of rifaximin per animal on non-intact dermal tissue (foot lesions, post partum vaginal lesions, skin lesions or docked tail), rifaximin could not be detected in serum at 12, 24 and 36 hours after treatment. Rifaximin concentrations were analysed by an HPLC method using UV detection (limit of quantification: 10 µg/l, limit of detection: 8 µg/l).

   In a new study carried out in 5 veal calves, it was shown that after repeated topical applications of rifaximin on non-intact dermal skin (epidermal mechanical abrasions) at the recommended dosage, i.e. two applications per day for 10 days corresponding to 0.34 mg/kg bw/day, rifaximin could not be detected in plasma during the treatment (HPLC method, limit of detection: 8 µg/l).

5. In an old study carried out in three lactating ewes, after single topical application of 5 to 9 mg of rifaximin per animal on non-intact dermal tissue (foot rot), rifaximin could not be detected in serum at 4, 6, 12 and 24 hours after treatment. Rifaximin concentrations were analysed by an HPLC method using UV detection (limit of quantification: 10 µg/l, limit of detection: 8 µg/l).

6. In a new study carried out in six pigs, rifaximin was applied on non-intact skin (epidermal mechanical abrasions) at twice the recommended dosage (two applications per day for 10 days corresponding to 0.9 mg/kg bw/day). During the treatment, the concentrations of rifaximin were too low to be quantified (less than 30 µg/kg, HPLC method) in plasma and rifaximin could not be even detected in 90% of the samples assayed.

7. The absorption of rifaximin from non-intact skin was also followed investigated in fourteen rabbits. Rifaximin was applied twice daily for 10 days on the skin at the recommended dosage of 2.44 mg/kg bw/day. Rifaximin could not be detected in rabbit plasma (limit of quantification 12 µg/kg, HPLC method) during the treatment.

8. In a new depletion study carried out in five veal calves, rifaximin was applied on non-intact dermal tissue (epidermal mechanical abrasions) at the recommended dosage (two applications per day for 10 days corresponding to 0.34 mg/kg bw/day). Rifaximin could not be detected in the muscle underlying the application site (limit of detection: 10 µg/kg) immediately after the last application (less than 2 hours after the last applications). Rifaximin concentrations were analysed by an HPLC method using UV/Vis detection (limit of quantification: 30 µg/kg,). As rifaximin was detected neither in plasma nor in muscle, rifaximin was not assayed in the other edible tissues.

9. In a new depletion study carried out in six pigs, rifaximin was applied on non-intact skin (epidermal mechanical abrasions) at twice the recommended dosage (two applications per day for 10 days corresponding to 0.9 mg/kg bw/day). Thirty minutes after the end of the treatment, significant amounts of rifaximin (2033 ± 977 µg/kg) were measured in skin. In these animals, as the fat weight represented 33.85% of the weight of fat and skin tissues in natural proportions, it was possible to extrapolate the concentrations susceptible to be found in fat and skin in natural proportions to approximately 1350 µg/kg.

Thirty minutes after the end of this treatment, rifaximin could not be detected in the muscle and the fat underlying the application site in five animals. For one animal, the concentrations were below the limit of quantification. Rifaximin concentrations were analysed by an HPLC method. The limits of quantification were 30 and 50 µg/kg for muscle and fat respectively and the limits of detection 10 and 20 µg/kg for muscle and fat respectively.

As rifaximin was detected neither in plasma nor in muscle and fat, rifaximin was not assayed in the other edible tissues.

10. In rabbits (n equals 14), rifaximin was applied on non-intact skin (epidermal mechanical abrasions) at the recommended dosage (two applications per day for 10 days corresponding to 2.31 to 2.44 mg/kg bw/day). Immediately after the last application (within 1 hour 30 after the last application), rifaximin could be quantified in the fat of 2 of the 14 experimental animals (56.5 and 174.2 µg/kg). In all the other fat samples the concentrations were either below the limit of quantification (less than 50 µg/kg in 3 animals) or not detected (less than 20 µg/kg in 8 animals). In muscle, the concentrations were either below the limit of quantification (less than 30 µg/kg in 4 animals) or not detected (less than 10 µg/kg in 10 animals).

    As rifaximin was detected neither in plasma nor in muscle and fat, rifaximin was not assayed in the other edible tissues.

11. Although rifaximin was not assayed in kidney and liver of the target species, the CVMP considered that additional depletion studies for this administration route were not necessary with regard to the negligible potential absorption of rifaximin from the application. Firstly, no rifaximin could be detected in plasma after topical applications at the recommended dosage in cattle and in rabbits or at twice the recommended dosage in pigs, so it could be assumed that the systemic absorption of rifaximin from application site is negligible. Secondly, the physicochemical properties of rifaximin (specially ionisation constants (pka equals 6.77) and octanol:water partition coefficient (415) showed that this non lipophilic compound is ionised in plasma so that its ability to circulate through the membranes and to penetrate in edible tissues is negligible.

12. In eleven milk producing cows, after a single topical application of 5 to 9 mg of rifaximin per animal on non-intact dermal tissue (foot lesions, post-partum vaginal lesions, skin lesions or docked tail), rifaximin could not be detected in milk at 12, 24 and 36 hours after treatment. Rifaximin concentrations were analysed by an HPLC method using UV detection (limit of quantification: 10 µg/l, limit of detection: 8 µg/l).

13. In three milk producing ewes, after a single application of 5 to 9 mg of rifaximin per animal on non-intact dermal tissue (foot rot lesions), rifaximin could not be detected in milk at 4, 6, 12, 24 hours after treatment. Rifaximin concentrations were analysed by an HPLC method using UV detection (limit of quantification: 10 µg/l, limit of detection: 8 µg/l).

14. Although a MRL of 60 µg/kg has already been allocated for bovine milk without reference to an administration route, the CVMP considered that it was not necessary to set MRLs when rifaximin is applied topically as no residues of rifaximin were detected in milk after topical use.

15. A HPLC routine analytical method with a diode array detector set at 450 nm was provided for determining residues of rifaximin in ovine milk. It was validated according to the recommendations of the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Species (EMEA/CVMP/153a/97-FINAL). The limit of quantification is 20 µg/kg.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II to Council Regulation (EEC) No 2377/90 and in particular that:

- rifaximin could not be detected in plasma of pigs, cattle and rabbits during and following after repeated dermal applications. Absorption is negligible in these species and is likewise not expected in the other target species. In addition rifaximin could not be detected in milk after topical application,
- no rifaximin could be quantified in the skin or underlying fat and muscle after repeated applications in bovine and rabbits,
- in swine, the amount of residues measured in fat and skin in natural proportions thirty minutes after the end of the repeated treatment on non -intact skin lead to about 25% of the microbiological daily intake,
- the animals treated are unlikely to be sent to slaughter immediately after treatment;

the Committee concludes that there is no need to establish an MRL for rifaximin for topical use in edible tissues and milk, and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Rifaximin	All food producing mammalian species	For topical use only