This is provisional English translation of an excerpt from the original full report.

Risk Assessment Report
Rifaximin (veterinary medicines)

Food Safety Commission of Japan (FSCJ)
June 2008

Executive summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of rifaximin (CAS No. 80621-81-4), which is an antibiotic being used overseas in the treatment and/or prevention of nonlactating mastitis in cows; treatment of postpartum uteritis in cows; and treatment of bacterial infections in feet and skins of cows, sheep, goats, horses and rabbits. The risk assessment was carried out using three risk assessment reports of the European Medicines Evaluation Agency (EMEA), a FSCJ' survey report, and one relevant document including data available in these reports[1].

The data included administration tests (rats, humans, and cows), residue tests (dermal administration: rats, rabbits, cows, pigs, and sheep; intramammary administration: milk; and intramammary administration: cows), acute toxicity tests (rats), subacute toxicity tests (rats and dogs), developmental toxicity tests (rats and rabbits), genotoxicity tests, and microbiological effects tests. Rifaximin is belonging to the family of naphthalene-ringed ansamycins (as rifampicin and rifamycin). Rifaximin possesses a broad antibacterial spectrum against gram-positive and gram-negative bacteria. The systemic absorption of an orally or topically administered active agent is negligible. No rifaximin can be detected in the milk of postpartum cows that received rifaximin during the nonlactating period. Neither embryotoxicity/teratogenicity nor *in vitro*/*in vivo* genotoxicity was demonstrated.

The lowest no observed adverse effect level in the toxicity tests was 25 mg/kg body weight/day in a 3-month subacute toxicity test in rats. The EMEA established a toxicological acceptable daily intake (ADI) by applying a safety factor of 100 to the no observed effect level (NOEL) of 25 mg/kg body weight/day. Neither chronic toxicity tests nor carcinogenicity tests were conducted in the EMEA assessment. Hence, the FSCJ established a toxicological ADI of 0.025 mg/kg body weight/day by applying a safety factor of 1,000 (a factor of 10 in addition to a safety factor of 100). A microbiological ADI of 0.00045 mg/kg body weight/day was established from the microbiological effects based on a current internationally recognized formula established by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). This microbiological ADI is much smaller than the toxicological ADI of 0.025 mg/kg body weight/day calculated by applying the additional safety factor, thereby ensuring toxicological safety.

In conclusion, the ADI for rifaximin was determined to be 0.00045 mg/kg body weight/day.

[1] The following reports and the documents were used in the risk assessments: EMEA,COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS:RIFAXIMIN REVISED SUMMARY REPORT, 1995; EMEA,COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS: RIFAXIMIN SUMMARY REPORT(2), 1997; EMEA,COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS : RIFAXIMIN (Extension to topical use) SUMMARY REPORT(3), 1998; FSCJ Comprehensive Food Safety Survey in 2006 (a survey of the microbiological effects of veterinary antibacterial agents, written only in Japanese); and Goodman's and Gilman's The Pharmacological Basis of Therapeutics (Japanese Editon, Hirokawa Publishing Co.) 2002, p1621-1624.

Food safety risk assessment (extracted from Part III of the original risk assessment report)

1. Toxicological ADI

Neither chronic toxicity tests nor carcinogenicity tests for rifaximin were conducted by EMEA. Rifaximin was not found to be genotoxic because it tested negative in all *in vitro* and *in vivo* genotoxicity tests. Thus the FSCJ decided that a toxicological ADI should be determined using an additional safety factor.

In toxicity tests of the EMEA assessment reports, indicators for adverse effects of rifaximin at the lowest doses were elevation of blood cholesterol levels and reduction of ratio of esterified cholesterol to total cholesterol in a 3-month subacute toxicity test in rats. In addition, the no observed adverse effect level (NOAEL) was determined to be 25 mg/kg body weight/day. Further, in the EMEA reports, the NOEL was calculated to be 25 mg/kg body weight/day and consequently a toxicological ADI of 0.25 mg/kg body weight/day was established. However, considering the absence of the results of chronic toxicity tests and carcinogenicity tests, FSCJ decided that the toxicological ADI should be 0.025 mg/kg body weight/day using a factor of 10 in addition to a safety factor of 100.

2. Microbiological ADI

The EMEA currently uses only the *in vitro* minimum inhibitory concentration (MIC) to assess microbiological effects. The mean MIC (lower limit of 90% confidence limit) of *Bacteroides fragilis* susceptible in human intestinal flora is 0.0002 mg/ml. In calculating a microbiological ADI by EMEA, 0.0002 mg/ml, 150 g of feces, 1 fraction of exposed bacteria, and 60 kg of human body weight were applied to the formula defined by the Committee for Medicinal Products for Veterinary Use (CVMP), as follows:

$$\text{Microbiological ADI (mg/kg body weight/day)} = \frac{\dfrac{0.0002 \times 4^{*b}}{1^{*a}} \times 150}{1 \times 60}$$

$$= 0.002$$

*a: A correction value of 1 was used from the MIC variability against susceptible bacteria, calculated with the 10% or less confidence limit (lower limit of a 90% confidence limit) of a one-tailed test.

*b: The EMEA uses a correction value of 4 to take into account the effects of inoculum amount.

On the other hand, in this risk assessment, it was decided to use detailed findings obtained from a comprehensive FSCJ food safety survey conducted in 2006 on microbiological effects of veterinary antibacterial agents. The findings were sufficient for estimation of microbiological ADI according to VICH guidelines. A MIC_{calc} was calculated, consequently to establish a microbiological ADI, according to the internationally recognized formula available in the VICH Guidelines[2].

[2] VICH GL36 (SAFETY), namely "Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI", have been adopted in Japan since March 2006.

The microbiological ADI is established by applying 0.000122 mg/ml of the MIC_{calc} for rifaximin, 220 g of colon content, 100% fraction of exposed bacteria and 60 kg of human body weight to the VICH formula, as follows:

$$\text{Microbiological ADI (mg/kg body weight/day)} = \frac{0.000122^{*c} \times 220^{*d}}{1^{*e} \times 60^{*f}} = 0.00045$$

*c: Lower limit of the 90% confidence limit of the mean MIC_{50} (active against test agents) of the most relevant bacterial genera
*d: Colon contents = 220 g
*e: Ratio of biologically available oral dose
*f: Human body weight (kg)

It was considered appropriate to adopt the current VICH formula in calculation of the microbiological ADI.

3. ADI calculation

The EMEA uses the microbiological ADI of 0.002 mg/kg bw/day as rifaximin's ADI because the microbiological ADI is much lower than the toxicological ADI of 0.25 mg/kg body weight/day. In this risk assessment, the microbiological ADI of 0.00045 mg/kg body weight/day calculated using the VICH formula is much smaller than the toxicological ADI of 0.025 mg/kg body weight/day, which is calculated by applying the additional safety factor, thereby ensuring toxicological safety. Thus, the ADI should be set at 0.00045 mg/kg body weight/day for establishing the criteria for rifaximin residue.

4. Conclusion

The following value should be used as an ADI for rifaximin:

Rifaximin: 0.00045 mg/kg body weight/day

Ministry of Health Labour Welfare will estimate the amount of human exposure to rifaximin and elaborate new or revised maximum residue limits (MRLs) for rifaximin in food concerned, not to exceed the ADI above. The proposed MRLs will be reviewed by the FSCJ for any advice, where necessary.