The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/006/95

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NEOMYCIN
(INCLUDING FRAMYCETIN AND SOFRAMYCIN)

SUMMARY REPORT (1)

1. Neomycin is an aminoglycoside antibiotic consisting of 3 components, A, B and C. Component B is the largest component of commercial preparations of neomycin (over 90%). Framycetin (also known as soframycin) is largely component B. Component A is present only in traces (<1%). Neomycin is used to treat bacterial infections of cattle, sheep, pigs, goats and poultry.

2. It is poorly absorbed from the gastrointestinal tract of humans and animals, and it has low absorption from the udder. It undergoes negligible biotransformation after parenteral administration. Excretion after oral doses is in the feces, but after parenteral administration it is excreted in the urine.

3. Neomycin has low acute toxicity (LD_{50} values in excess of 2000 mg/kg bw) after oral administration but it is more toxic after intravenous dosing (LD_{50} in mice 100 mg/kg bw/day).

4. After repeated parenteral administration, nephrotoxic effects were noted in mice (subcutaneous, 30-300 mg/kg bw/day), guinea-pigs (subcutaneous, 10-60 mg/kg bw/day) and in dogs (intramuscular, 24-96 mg/kg bw/day). Ototoxicity was noted in guinea-pigs given repeated doses of neomycin. The lowest NOEL from these studies was 10 mg/kg bw/day neomycin sulphate equivalent to 6 mg/kg bw/day neomycin for ototoxicity in the guinea-pig.

5. Only 3 genotoxicity studies were available and two of these (an in vitro chromosome aberration assay in human lymphocytes and an in vivo cytogenetics assay in mouse bone marrow) gave positive results.

6. There was no increased tumour incidence in a 2 year oral carcinogenicity study in rats. However, hearing was impaired and the NOEL was 12.5 mg/kg bw/day.

7. In a multigeneration study in rats, no adverse effects on reproduction parameters were noted with doses of up to 25 mg/kg bw/day, the highest dose used. A teratogenicity study was conducted with the F_{2b} females. Neomycin was administered in feed at 0-25 mg/kg bw/day from days 0-6 and 16-20 of gestation. Doses were increased to 0-250 mg/kg bw/day in the day 16-20 period. There was no evidence of teratogenic effects in this study.

8. Several in vitro studies were conducted using various bacteria, most isolated from humans. An MIC_{50} of 64µg/ml was derived from the relevant bacterial species under conditions of high innoculum density. In a mouse study using animals with a human gut flora a NOEL of 125 mg/kg bw/day was identified. Effects on human gut flora in patients occurred at doses equal to or greater than 30 mg/kg bw/day.

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9. In determining the microbiological ADI, the following equation and parameters were used:

   - the concentration without effect on the human gut flora was 64 µg/ml;
   - 150 g for the human fecal bolus;
   - absorption of neomycin from the gut is low so a factor of 1.0 was used to represent 100% availability to gut micro-organisms;
   - a safety factor of 1.0 to cover variability between humans.

$$\text{microbiological ADI} = \frac{64 \times 150}{1 \times 1 \times 60} = 160 \text{ µg/kg or } 9.6 \text{ mg/person/day}$$

10. From the toxicological and antimicrobial data, the toxicological data provided the most appropriate end-point for the safety evaluation of neomycin. A temporary ADI of 0-30 µg/kg bw/day was calculated using the NOEL of 6 mg/kg bw/day in the guinea-pig. A safety factor of 200 was used to allow for the deficiencies in the genotoxicity data.

11. Residues data were available for cattle, sheep, goats, pigs, chickens, turkeys, ducks and milk. Residue levels in tissues, eggs and milk were low at zero withdrawal, after oral administration. Kidney was the target organ and neomycin the marker residue.

12. On the basis of the ADI of 30 µg/kg bw and from the results of the residues studies, the following provisional MRLs were elaborated for cattle, sheep, goats, pigs, chickens, turkeys and ducks (neomycin, framycetin, soframycin):

muscle	500 µg/kg
liver	500 µg/kg
kidney	5000 µg/kg
fat	500 µg/kg
eggs	500 µg/kg
milk	500 µg/l

    These MRLs expire on 1 June 2000.

13. There are validated HPLC and mass spectrometric methods of analysis with limits of quantification of 100 µg/kg.

LIST OF QUESTIONS

The following list takes into account the questions developed during the 43rd meeting of JECFA and those previously adopted by the CVMP.

Safety file

1. Data about the effects on the human gut flora and micro-organisms used in the food industry are required.

2. NOELs for oto- and nephro-toxicity are required.

3. Information concerning potential for teratogenicity in a second species should be provided. Human epidemiological evidence would be acceptable.

4. A batterty of mutagenecity studies conducted in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community are required. At least :

   - a gene mutation assay, in eukaryotic cells;
   - a study of chromosome aberrations in vivo.

The possible requirement for further carcinogenicity studies will be considered after a full evaluation of the mutagenicity test results.

Residue file

1. Residues depletion data, in all relevant tissues, including injection sites and species, in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community should be provided.

2. A validated analytical method, with specificity for the determination of Neomycin and Framycetin in tissues should be provided.

This information should be provided to the CVMP by 1 January 2000.