EMEA/MRL/008/95-FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

SUMMARY REPORT (1)

1. Streptomycin and dihydrostreptomycin are aminoglycoside antibiotics which are closely related in structure. The pharmacokinetics, toxicological profile and spectrum of antimicrobial and biological activity are similar and therefore the two compounds were evaluated together to establish a single ADI. They are used to treat bacterial diseases in cattle, pigs, sheep and poultry.

2. In animals and humans both drugs are poorly absorbed from the gastrointestinal tract and the majority of the oral dose is recovered in the feces. After parenteral dosing, the drugs are excreted in the urine.

3. Both drugs have low toxicity after oral administration to rodents (LD_{50} 9000-25000 mg/kg bw/day).

4. Parental administration of doses of 50-100 mg/kg bw/day streptomycin for 20 days to dogs resulted in renal damage. Ototoxicity was studied in guinea-pigs and cats in 90 day studies. No hearing loss occurred in guinea-pigs treated orally with 40 mg/kg bw/day dihydrostreptomycin; no hearing loss or effects on vestibular function occurred in cats given 40 mg/kg bw/day. The NOELs for ototoxicity were 40 mg/kg bw/day from these studies.

5. There were no data available on the genotoxicity of these drugs, although it has been reported that streptomycin gave conflicting results in an in vitro study for chromosome aberrations.

6. In a two year chronic toxicity study, rats were given up to 10 mg/kg bw/day dihydrostreptomycin. There were no increases in the incidences of any tumour type and an NOEL of 5 mg/kg bw/day based on decreased body weights in males was identified.

7. A number of teratology studies in mice were conducted with streptomycin with parenteral doses of up to 250 mg/kg bw/day. No teratogenic effects were seen. No teratogenic effects were noted in guinea-pigs given up to 200 mg/kg bw/day dihydrostreptomycin or streptomycin by the intramuscular route. No teratogenic effects occurred in rabbits given 5 or 10 mg/kg bw/day dihydrostreptomycin orally.

   In the mouse studies, there was evidence of ototoxicity at the highest dose of streptomycin used (250 mg/kg bw/day).

8. There were no studies of fertility or peri/postnatal effects available.

9. The spectrum of antimicrobial effects is similar for streptomycin and dihydrostreptomycin, therefore the results of studies with the latter compound were used to calculate an ADI. A range of isolates from human intestinal material was examined and the MIC_{50} for the most sensitive species (Bifidobacterium) was 32µg/ml.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard (44-20-7) 418 8400 Fax (44-20-7) 418 8447
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

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

    - the concentration without effect on the human gut flora was 32µg/ml;
    - 150 g for the human fecal bolus;
    - absorption 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.

11. From the toxicological and antimicrobial data, the toxicological data provided the most appropriate end-points for the safety evaluation of streptomycin and dihydrostreptomycin.

    A temporary ADI of 0-25µg/kg bw/day was calculated using the NOEL of 5 mg/kg bw/day derived from the two year rat study. A safety factor of 200 was used to allow for the lack of information on peri/post natal toxicity.

12. Residue studies were available for cattle, sheep, pigs, poultry and milk. Kidney was the target tissue and unchanged streptomycin or dihydrostreptomycin was the marker residue.

13. On the basis of the ADI of 30 µg/kg bw and from the results of the residue studies, the following provisional MRLs were elaborated for streptomycin and dihydrostreptomycin in cattle, sheep, pigs and poultry:-

muscle	500 µg/kg
liver	500 µg/kg
kidney	1000 µg/kg
fat	500 µg/kg
milk	200 µg/l

    These provisional MRLs expire on 1 June 2000.

    There were inadequate residue data available for eggs.

14. Validated chemical methods of analysis are available with limits of quantitation of 20 µg/kg for streptomycin and 40 µg/kg for dihydrostreptomycin. A validated LC/MS/MS method is available for measuring residues in bovine kidney with limits of quantitation of 440 µg/kg and 320 µg/kg for streptomycin and dihydrostreptomycin respectively.

LIST OF QUESTIONS

The applicant should resolve the outstanding toxicological and residues issues identified by the 43rd meeting of JECFA.

- information to assess the potential for effects on fertility and peri-/postnatal toxicity;
- an expert report or experimental studies on the metabolism of both drugs;
- residues data in eggs;
- studies to determine the relationship between the antimicrobial activity of the residues and the measurement of the residues by specific chemical methods.

The validated methods of analysis described in the JECFA evaluation must be provided to the CVMP.

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