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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SPECTINOMYCIN

SUMMARY REPORT (1)

1. Spectinomycin is an aminocyclitol antibiotic produced by *Streptomyces spectabilis*. It exerts its bacteriostatic effect by binding to the 30S subunit of bacterial ribosomes and inhibiting the translation of protein synthesis.

2. It is indicated for use via the oral and intramuscular routes in the treatment of a variety of enteric, respiratory and other infections of cattle, sheep, pigs and poultry.

3. The hydrochloride and sulphate salts are similar in their acute toxicity and pharmacokinetics, and so a single MRL for spectinomycin base is justified.

4. Pharmacokinetic data indicate that absorption is poor via the oral route in humans and in animals, but rapid and extensive after intramuscular injection. Spectinomycin is not extensively bound to proteins either in serum or in milk. Plasma elimination half lives range from 1 to 3 hours in various species (sheep, cattle, dog, man) when administered via the oral, i.m. and i.v. routes. Spectinomycin is rapidly and extensively excreted in the urine. The data available suggest that spectinomycin is not extensively metabolised in animals or in humans.

5. Spectinomycin has low acute toxicity in mice, rats and dogs when administered by various routes.

6. In numerous repeat dose studies where spectinomycin was administered by injection (i.m, i.v, s.c) the only significant findings were injection site reactions. Spectinomycin is irritant on i.m injection. Studies in rats and dogs where the substance was administered by oral route for 90 days suggests an NOEL of 50-750 mg/kg bw/day based on the most common finding, namely changes in the consistency of faeces.

7. Spectinomycin did not adversely affect reproductive performance (litter size), and was not teratogenic in animal studies. However, there were some indications that foetal development may be delayed in certain strains of rats at high doses (300 mg/kg, TUC/SPD rats). A multigeneration study in the rat showed no adverse effects on reproductive parameters up to the highest dose used, 400 mg/kg bw/day using the oral route. Hepatocellular changes, notably clumped basophilic material in the cytoplasm and hepatocellular swelling was noted in some animals in the F_{1b} generation. The NOEL was 100 mg/kg/bw/day in *in vitro* tests. No chronic toxicity studies were performed (>90 days) which could be validated, however, the chemical structure of spectinomycin does not indicate carcinogenic potential.

8. Spectinomycin was not mutagenic in a range of well conducted *in vivo* and *in vitro* tests.

9. Spectinomycin was not ototoxic in cats or humans.

10. Although sensitisation potential was not addressed, spectinomycin did not cross-react with penicillins in human clinical trials and there is no evidence of sensitisation from a long history of clinical use in humans.

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

11. The potential for adverse effects on the human gut flora was studied *in vitro* in a wide range of organisms including both animal and human pathogens. The MIC data for a number of bacterial species representative of the anaerobic flora in humans was examined including *Bacteroides*, *Peptostreptoccus*, *Fusobacterium*, *Eubacterium*, and *Clostridium* spp. Many had a MIC_{50} of greater than 50 µg/ml. *Bifidobacterium* were more sensitive with MIC values for spectinomycin in the range of 2-32 µg/ml. The modal MIC was 16 µg per ml with an inoculum density of 10^6 and 8 µg/ml with an inoculum density of 10^4. The value of 16 µg/ml was used to calculate the ADI using the formula developed by the 38th meeting of JECFA.

$$\text{upper limit of ADI (µg/kg body weight)} = \frac{\text{concentration without effect on human gut flora (µg/ml)}^{(1)} \times \text{daily faecal bolus (g)}}{\text{fraction of oral dose available}^{(2)} \times \text{safety factor}^{(3)} \times \text{weight of human (60 kg)}}$$

$$= \frac{16 \times 150}{1 \times 1 \times 60} = 40 \text{ µg/kg bw/day}$$

The safety factors were chosen as follows :

(1) factor; to account for the range of MIC values to cover sensitive bacteria, anaerobic environment, bacterial density and pH - sufficient information was presented and no specific factors were required to adjust the modal MIC of 16 µg/ml.

(2) availability; the absorption of spectinomycin from the gastrointestinal tract is very poor so the worst case was assumed with 100% of the spectinomycin ingested available in the gut (therefore a factor of 1.0)

(3) variability among exposed individuals; a substantial amount of MIC data were presented, covering a variety of organisms. Recently published data suggested that variability among populations was low. Consequently, a safety factor of 1.0 was chosen.

Taking into account all of these factors, an ADI of 0-40 µg/kg bw/day was established for spectinomycin. In view of the extensive range of organisms examined, and as data were provided on the effects of pH, inoculum density and resistance to spectinomycin, it was considered that this should be a full ADI.

12. Spectinomycin tissue depletion studies have been carried out in pigs, cattle, turkeys and chickens, and residues were measured using microbiological methods, or more sensitive HPLC methods. In all the studies, kidney had the highest and most persistent residues of spectinomycin and this was chosen as the target tissue. Concentrations were lower in liver, and very low in muscle and fat. After multiple IM doses in cattle, the highest levels occurred in kidneys at 8 hours withdrawal (15.5 mg/kg tissue) declining to 1.4 mg/kg at 7 days. Residues in liver depleted from 3.3 mg/kg tissue at 8 hours to 0.6 mg/kg at 7 days. Residues in muscle 7 days after the last injection were <0.1 µg/g. Similar findings were noted in pigs given multiple injections; the residues had depleted to 0.8 mg/kg kidney by 96 hours. Milk from cows given IM injection of 20 mg/kg bw twice daily for 3 consecutive days showed residues below 0.2 µg/ml at the fifth milking after the last treatment. There were no residues data available from sheep, or in eggs.

13. Spectinomycin can be assayed routinely in plasma urine, milk, and tissues using a microbiological cylinder plate assay with a limit of detection of 1.0 µg/g or with HPLC methods with a detection limit of 0.1 µg/g and a limit of quantification of 0.2 µg/g for tissues in all species and milk with a detection limit of 0.1 µg/g.

14. As a result, MRLs of 5000 µg/kg for kidney, 2000 µg/kg for liver, 300 µg/kg for muscle, 500 µg/kg for fat in pigs, cattle and poultry (chickens and turkeys) and 200 µg/l for milk are established. Using these values, the theoretical maximum daily intake of spectinomycin residues is 865 µg/day. Some of the reports used in the evaluation are interim reports, and until the final reports are available, the MRLs will remain provisional. No MRLs can be established for eggs or sheep tissues.