COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

APRAMYCIN

SUMMARY REPORT (2)

1. Apramycin is an aminoglycoside antibiotic which is used in the treatment of colibacillosis and salmonellosis in calves, bacterial enteritis in pigs, colibacillosis in lambs and *Escherichia coli* septicaemia in poultry. It is also administered to rabbits. Apramycin is not authorised for use in laying birds nor for use in cattle or sheep producing milk for human consumption. The available products include an oral doser intended for oral administration to neonatal pigs at a dose of 10 to 20 mg apramycin sulphate/kg bw/day for 3 to 5 days and neonatal lambs at a dose of 10 mg/kg bw/day for 3 to 5 days, a premix for incorporation into pig feed at a rate of 100 mg/kg feed (equivalent to 3 to 7 mg/kg bw) for 28 days, a soluble powder for administration *via* the drinking water or milk replacer for calves at a rate of 20 to 40 mg/kg bw/day for 5 days, pigs at a rate of 7.5 to 12.5 mg/kg bw/day for 7 days, poultry at a rate of 250 to 500 mg active ingredient/l (equivalent to 25 to 50 mg/kg bw) for 7 days and an injectable formulation for intramuscular administration to calves at a rate of 20 mg/kg bw/day for 5 days. In rabbits, apramycin is administered in the drinking water at a concentration of 50 to 100 mg/l (equivalent to 10 to 15 mg/kg bw) for 5 to 8 days or in the feed at a concentration of 50 to 100 mg/kg feed (equivalent to 5 to 10 mg/kg bw) for up to 3 weeks.

Currently, apramycin is included in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Apramycin	Apramycin	Bovine	1000 µg/kg 1000 µg/kg 10 000 µg/kg 20 000 µg/kg	Muscle Fat Liver Kidney	For use in non-lactating cattle only. Provisional MRLs expire on 1.7.1999
		Porcine	1000 µg/kg 1000 µg/kg 1000 µg/kg 5000 µg/kg	Muscle Fat+skin Liver Kidney	Provisional MRLs expire on 1.7.1999

2. In a series of *in vitro* studies using isolated smooth and cardiac mucle preparations, apramycin elicited a slight increase in contraction rate in guinea pig atria and a slight decrease in the response of rat aorta to phenylephrine at a concentration of 10^{-5}M, no significant effects were observed in ileum, trachea, vas deferns or uterus. Intravenous administration of apramycin to anaesthetised dogs resulted in increased blood pressure and heart rate at doses of 10 to 25 mg/kg bw, probably due to a slight sympathomimetic action. These effects were not observed at 5 mg/kg bw, and no effects of electrocardiograms, cardiac output or respiratory function were observed at any dose. An intravenous dose of 25 mg/kg bw or oral doses of 250 or 400 mg apramycin/kg bw had no effect on neuromuscular transmission in the rat. An oral dose of 50 mg/kg bw in the rat produced a statistically significant reduction in urine volume and increased electrolyte concentrations, probably due to increased antidiuretic hormone secretion, or a direct effect on the renal tubule, the NOEL was 10 mg/kg bw. An overall oral pharmacological NOEL of 10 mg/kg bw was identified based on the effects on renal function in the rat.

3. Following oral administration of 4 mg ^{14}C-apramycin to rats, 99.5% of the administered dose was recovered from the faeces and around 0.5% from the urine. When the same dose was administered subcutaneously, 93% was recovered from the faeces and around 7% from the urine. Small amounts of radioactivity remained in the kidney. The residues in the kidney and the urine consisted almost entirely of unmetabolised apramycin. In dogs, serum concentrations were monitored in the 6-month and 1-year repeated dose studies in which doses of 25 to 100 mg/kg bw/day were employed. Peak serum concentrations were directly proportional to the dose administered and were achieved 1 to 2 hours after dosing and were below the limit of detection 24 hours later. Urinary excretion corresponded to 0.3 to 10.5% of the administered dose. The data suggested that apramycin was poorly absorbed after oral administration but the percentage oral bioavailability was not determined.

4. Apramycin was of low acute toxicity when administered orally. Acute oral LD_{50} values were greater than 1 250 mg/kg bw in Hartley guinea pigs, greater than 1 600 mg/kg bw in NZW rabbits, greater than 1 000 mg/kg bw in Beagle dogs, greater than 8 000 mg/kg bw in Wistar rats and greater than 10 000 mg/kg bw in ICR mice. There were no deaths at any of the dose levels used in the rat, mouse or dog studies. Apramycin was more toxic when administered parenterally. Acute intravenous LD_{50} values ranged from 162 to 1 640 mg/kg bw and depended on the purity of the material tested.

5. Three repeated-dose toxicity studies were carried out in rats using oral administration and duration of 3 to 6 months. The adverse effects were generally limited to mild anaemia and diarrhoea which may have resulted from the effects of the substance on the gut flora. Evidence of nephrotoxicity was found only in one study, in 3 out of 15 males fed the top dose level of 1% apramycin in the feed. The overall NOEL from these studies was 20.9 and 26.1 mg/kg bw/day for males and females, respectively.

6. Three repeated-dose toxicity studies were carried out in dogs using oral administration and duration of 3 months to 1 year. The adverse effects were mild reductions in haematology values and some changes in organ weights which did not correlate with any pathological findings. The NOEL for the 6-month study was 25 mg/kg bw and for the 1-year study the NOEL was 50 mg/kg bw.

In the classical repeated-dose toxicity studies, there was little evidence for either ototoxicity or nephrotoxicity. This was probably due to the poor absorption of the substance following oral administration. A special study was carried out in 2 male and 2 female cats using daily subcutaneous administration of a 20% aqueous solution of apramycin for up to 30 days. The righting reflex remained normal in all the cats and the duration of post-rotatory nystagmus was unaffected in 3 out of 4 cats. At termination, histopathological examination of the kidneys revealed severe nephrosis. It can be concluded that apramycin has greater potential for inducing nephrotoxicity when administered parenterally.

7.   Target species tolerance studies were carried out in all the target species. The tolerance studies included special tests for ototoxicity in swine: no such effects were observed. The most frequent adverse effects were irritation at the injection site and diarrhoea following the administration of large doses.

8.   No adverse effects on reproductive performance were observed in a multi-generation study, in which diets containing up to 1.0% apramycin (equivalent to 785 mg/kg bw/day) were fed to Fischer 344 rats, throughout 4 successive generations.

9.   In a teratogenicity study, there was no evidence of maternal toxicity, foetotoxicity or teratogenicity at any dose level following oral administration of doses of 0, 250, 500 or 1000 mg/kg bw/day apramycin to pregnant Wistar rats from days 6 to 15 of gestation.

Oral doses of 0, 2, 8 and 32 mg/kg bw/day were administered from days 6 to 18 of gestation in a rabbit teratology study. There were dose-related reductions in maternal food consumption and bodyweight gain in all treated groups. There was dose-related increase in the numbers of dams aborting. The incidence of resorptions was significantly increased at the top dose. Foetotoxicity was apparent at all dose levels with a dose-related reduction in foetal weight. One case of cleft palate and one case of omphalocele were found at 32 mg/kg bw; the significance of these findings was unclear because only 5 dams with 24 foetuses in this group survived to the scheduled kill. There was a dose-related increase in the incidence of supernumerary ribs though only the incidence in the 32 mg/kg bw group exceeded that of the historical controls. No NOELs were established for maternal toxicity or foetotoxicity. In this study the effects on the foetus were probably secondary to the severe maternal toxicity. Rabbits are highly susceptible to the effects of antibiotics on their gut flora. For this reason, the rabbit is not a suitable species for teratogenicity studies with antibiotics.

10. Apramycin was not mutagenic in 3 *in vitro* assays. Negative results were obtained in an *in vitro* bacterial assay for gene mutation using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538, an *in vitro* assay for gene mutation in mammalian cells (mouse lymphoma assay) and an *in vitro* unscheduled DNA synthesis assay in primary rat hepatocytes.

11. There was no evidence of carcinogenicity in a study in which B6C3F1 mice were fed diets containing up to 4.5% apramycin for up to 2 years. Pathological changes involving the non-brush border cortical tubular epithelium were observed in mice given 0.5% apramycin and above. No NOEL was established for this study due to the reduced bodyweight gain at 0.15%, the lowest dose level tested. There was no evidence of carcinogenicity in a study in which Fischer 344 rats were fed diets containing up to 5.0% apramycin for 2 years. Bodyweight gain was significantly reduced in both sexes given the top dose and terminal liver and kidney weights were also reduced at this dose. The NOEL was 0.25%, equivalent to 124 mg/kg bw/day in males and 154 mg/kg bw/day in females.

12. Apramycin was not a skin sensitiser in 2 non-standard tests for delayed hypersensitivity in the guinea pig.

13. Apramycin is not used in human medicine. There were no data concerning possible effects in humans.

14. A NOEL of 25 mg/kg bw/day was established in a 6-month repeated dose toxicity study in Beagle dogs, based on mild anaemia and slight changes in organ weights. A similar NOEL was established in a 90-day repeated dose toxicity study in Wistar rats. A toxicological ADI of 0.25 mg/kg bw was calculated by applying a safety factor of 100 to the overall NOEL of 25 mg/kg bw/day.

15. For the establishment of the microbiological ADI the following standard formula was used:

$$\text{ADI} \ (\mu g/kg \ bw) = \frac{\dfrac{MIC_{50} \text{ most sensitive organism} \times CF2}{CF1} \ (\mu g/ml) \times \text{daily faecal bolus (150 ml)}}{\text{fraction of an oral dose available for microorganisms} \times \text{weight of human (60 kg)}}$$

In vitro MIC data were provided for a wide range of bacteria of both human and veterinary origin. Many of the strains were insensitive to apramycin. It was decided to base the microbiological ADI on the MIC_{50} for *Escherichia coli* because:

- an adequate number of human isolates had been studied,

- data supplied for veterinary strains indiated that the veterinary strains were also sensitive to apramycin and gave MIC values in the same range as the human isolates,

- although some strains of human gut bacteria gave lower MIC values, e.g. *Bacteroides ureolyticus,* only this one strain was sensitive; all the other strains of *Bacteroides* were insensitive with MIC_{50} values greater than 64 µg/ml.

And therefore the microbiological ADI was calculated as indicated below:

$$\text{ADI} = \frac{\dfrac{8 \times 2}{1} \times 150}{1 \times 60} = 40 \ \mu g/kg \ bw \ i.e. = 2400 \ \mu g/person$$

The following assumptions were made:

- 8 µg/ml was the *in vitro* MIC_{50} for the most relevant sensitive gut organism (*Escherichia coli*) tested under aerobic conditions,

- CF1 = 1 because the MIC_{50} for the most sensitive predominant and relevant organism was used,

- CF2 = 2 because of the conversion from aerobic to anaerobic conditions; it was not considered necessary to correct for changes in pH or bacterial density. The MIC_{50} value used was the one obtained at the higher of the 2 bacterial densities tested (10^8 CFU/ml),

- 150 g was weight of daily faecal bolus,

- the proportion of dose available to the microorganisms at the distal part of the gastrointestinal tract was considered to be 1,

- 60 kg for the human bodyweight.

16. Pharmacokinetics and metabolism studies were carried out in which 2 pigs and a calf were given intramuscular injections of ^{14}C-labelled apramycin. Peak radioactivity concentrations were found in blood 0.5 hours after treatment and declined to around the limit of detection 24 hours later. Almost all of the radiolabelled material in blood and more than 90% of the material in excreta was microbiologically-active and appeared to be unmetabolised apramycin. The pigs were slaughtered 6 days after treatment and the calf was slaughtered 5 days after treatment and the total residues in tissues were determined. Residues of apramycin in liver and kidney were also determined using a microbiological assay. The majority of the residues in these tissues of both species appeared to consist of unmetabolised apramycin. Another study in pigs and calves using oral administration of ^{14}C-labelled apramycin gave similar results. The excreta consisted almost entirely of unmetabolised apramycin and more than 75% of the radiolabelled material in liver and kidney consisted of unmetabolised apramycin. It was concluded that apramycin is an appropriate marker residue for bovine and porcine tissues.

17. A residues depletion study was carried out in which pigs were given apramycin in the drinking water at a dose equivalent to 25 mg/kg bw/day for 7 days. The residues in tissues were

determined using a microbiological assay with a limit of detection of 100 µg/kg. Detectable residues were found only in kidney and in fat samples taken within one day of the end of treatment. Within one day of the end of treatment, mean residues in kidney were 2500 µg/kg and declined to 200 µg/kg, 14 days after the cessation of treatment. Within one day of the end of treatment, mean residues in fat were 100 µg/kg and were undetectable at later time points.

In a GLP study, pigs were given daily oral doses of 20 mg/kg bw/day (the maximum indicated dose) for 7 consecutive days and residues in tissues were determined using HPLC. Detectable residues were found only in kidney. Residues of apramycin depleted in the range of 5 800 to 15 300 µg/kg, one day after the end of treatment, 2500 to 3100 µg/kg, 7 days after treatment and were below the limit of detection (210 µg/kg), 14 days after treatment.

18. A residues depletion study was carried out in which 2 to 7 day old calves were given daily intramuscular injections of 20 mg apramycin/kg bw/day for 5 days. Residues in tissues were determined using a microbiological assay. The residues declined from mean values of 60 000 µg/kg in kidney, 5 000 µg/kg in liver, 1 500 µg/kg in fat, 1 000 µg/kg in muscle and 1 000 µg/kg at the injection site, 7 days after the end of treatment, to 8 000 µg/kg in kidney, 6 000 µg/kg in liver, 300 µg/kg in fat, 200 µg/kg in muscle and less than 200 µg/kg at the injection site, 28 days after treatment.

In a GLP study, using the same dosage regime and 3-week old calves, the residues in tissues were determined using HPLC. The residues declined from the range of 296 600 to 435 300 µg/kg in kidney, 8 700 to 14 700 µg/kg in liver, 6 200 µg/kg (mean value) in fat, 1 900 to 3 400 µg/kg in muscle and 23 600 to 65 100 µg/kg at the injection site, 4 hours after the last treatment, to 1200 to 14 500 µg/kg in kidney, 3 500 to 4 200 µg/kg in liver, 400 µg/kg (mean value) in fat, below the limit of detection (268 µg/kg) in muscle and less than 268 to 4 600 µg/kg at the injection site, 28 days after treatment. The pattern of residues depletion monitored using HLPC paralleled that obtained using the microbiological method.

19. A residues depletion study was carried out in which 2 to 7 day-old calves were given daily oral doses of 40 mg apramycin/kg bw/day for 5 consecutive days, in the milk replacer. Residues in tissues were determined using a microbiological assay. The residues in tissues declined from the range of 5 000 to 20 000 µg/kg in kidney, 400 to 4 000 µg/kg in liver, 100 to 200 µg/kg in fat and less than 50 µg/kg in muscle, 7 days after treatment, to 1 600 to 3 200 µg/kg in kidney, 1 000 to 2 000 µg/kg in liver and less than 50 µg/kg in fat and muscle, 21 days after treatment. In a modern GLP study, 3-week old calves were given daily oral doses of 40 mg/kg bw/day for 5 days and the residues in tissues were determined using HPLC. Residues in kidney declined from the range of 2 800 to 21 700 µg/kg 7 days after treatment, to 200 to 9 400 µg/kg 21 days after treatment. Residues in bulked fat samples declined from 900 µg/kg 4 hours after treatment, to 100 µg/kg 7 days after treatment and were below the limit of detection on subsequent occasions. Residues in muscle samples were below the limit of detection except for one sample (out of 4) taken 21 days after treatment; a residue of 800 µg/kg was found in this sample and may have resulted from contamination. Residues in liver were very variable between individual animals and ranged from below the limit of detection to 1 200 µg/kg 7 days after treatment to 400 to 700 µg/kg 21 days after treatment. Again the pattern of residues depletion monitored using HPLC paralleled that obtained using the microbiological method.

20. A residues depletion study was carried out in which lambs were given daily oral doses of 10 mg apramycin/kg bw on 3 consecutive days. The lambs were killed (3 per time-point) within one day of the end of treatment, 21, 28 or 35 days after the end of treatment, and residues in tissues were determined using a microbiological assay. Residues in liver and muscle were less than 500 µg/kg at all time points. Residues in fat were below the limit of detection (less than 500 µg/kg) at all time points except in the samples taken 21 days after treatment when concentrations in the range less than 500 to 960 µg/kg were found. Residues in kidney were in the range of less than 500 to 2860 µg/kg immediately after treatment and declined to the range 1200 to 1730 µg/kg, 21 days after treatment, to less than 500 µg/kg, 35 days after treatment.

In a more recent study, lambs were given daily oral doses of 10 mg apramycin/kg bw/day for 5 consecutive days. The lambs were killed (4 per time point) at 6, 12, 18, 24 or 30 days after the last dose. Residues of apramycin in tissues were determined using the proposed routine analytical method based on HPLC. The limits of quantification of the assay were 500 µg/kg for muscle and fat and 2500 µg/kg for liver and kidney and the limits of detection were for 124 µg/kg for muscle, 42 µg/kg for fat, 368 µg/kg for liver and 394 µg/kg for kidney. Residues in all samples of muscle and fat at all time-points were below the limits of detection for those tissues. Low residues of apramycin were found in liver and kidney at all time points with no apparent decline over the time points studied. In liver, residues at 6 days ranged from below 368 to 600 µg/kg and at 30 days from 450 to 700 µg/kg. In kidney, residues at 6 days ranged from 1000 to 1200 µg/kg and at 30 days from 1300 to 1700 µg/kg.

21. A total residues depletion study was carried out in which broilers were given drinking water containing 500 mg ^{14}C-apramycin/l for 5 days. Mean total residues in kidney declined from 3230 µg equivalents/kg within one day of treatment, to 1470 µg equivalents/kg, 7 days later, and 470 µg equivalents/kg, 14 days after treatment. Over the same time period, mean total residues in liver declined from 420 µg equivalents/kg to 150 µg equivalents/kg to 80 µg equivalents/kg and mean total residues in skin from 200 µg equivalents/kg to 60 µg equivalents/kg to 30 µg equivalents/kg. Mean total residues in muscle declined from 70 µg equivalents/kg within one day of treatment to 20 µg equivalents/kg, 7 days after treatment. The liver and kidney samples were also analysed using a microbiological assay. From the results it was concluded that more than 80% of the residues in liver and kidney consisted of unmetabolised apramycin.

22. Broilers were given drinking water containing 559 mg apramycin sulphate/l for 5 days. The birds were killed (6 per time point) within one day of the end of treatment and then 7, 10 or 14 days after the end of treatment. The residues in tissues were measured using a microbiological assay. Residues in all samples of muscle were less than 50 µg/kg. Residues in skin were detectable only in samples taken on the day of treatment (range 60 to 200 µg/kg). Mean residues in fat were 150 µg/kg on the day of treatment and were less than 50 µg/kg on subsequent occasions. Residues in liver were variable between individual birds and were 260 to 540 µg/kg on the day of treatment, 60 to 210 µg/kg, 7 days later, and 50 to 230 µg/kg, 14 days after treatment. In a more recent study broiler chickens were given drinking water containing 500 mg apramycin/l of water for 5 consecutive days. The birds were killed (10 per time point) at 3, 6, 9 and 12 days after the withdrawal of the medicated water. Residues of apramycin in tissues were determined using the proposed routine analytical method based on HPLC. The limit of quantification was 500 µg/kg for all tissues. The limits of detection were 470 µg/kg for liver, 133 µg/kg for kidney, 319 µg/kg for muscle and 32 µg/kg for skin and fat. Residues of apramycin in all samples of muscle were below the limit of detection. Residues of apramycin were detectable in only one liver sample taken at the first time point of 3 days: 480 µg/kg. Residues in skin and fat were in the range less than 32 µg/kg to 620 µg/kg at 3 days and were below the limit of detection (32 µg/kg) in all samples taken at 9 days. Residues in kidney were in the range 430 to 1100 µg/kg at 3 days and depleted to less than 133 to 600 µg/kg at 9 days.

23. Male and female rabbits were administered apramycin in the drinking water at a concentration of 100 mg/l of water for 7 consecutive days. The rabbits were killed (5 per time-point), at 0, 3, 7, 14 or 21 days after the end of treatment. Residues in tissues were determined using the proposed routine analytical method based on HPLC. The limits of detection of the method were 100 µg/kg for liver, 600 µg/kg for kidney, 500 µg/kg for muscle and 200 µg/kg for fat. Residues in all tissues were below the limit of detection at all time points.

24. The proposed routine analytical method was based on HPLC with fluorescence detection. The method had satisfactory specificity and it was shown that residues of other aminoglycosides did not interfere in the assay. Validation data were provided for all edible tissues of all the target species.

The limits of quantification in cattle were 5000 µg/kg for kidney and liver, and 500 µg/kg for muscle and fat. The limits of detection were 396, 229, 268 and 129 µg/kg for liver, kidney, muscle and fat.

In pigs the limits of quantification were 2500 µg/kg in kidney and 500 µg/kg in liver, muscle and skin+fat. The limits of detection were 253, 212, 314 and 60 in liver, kidney, muscle and skin and fat, respectively. For ovine tissues, the limits of quantification were 500 µg/kg for muscle and fat and 2500 µg/kg for liver and kidney, and the limits of detection were 394 µg/kg for muscle, 368 µg/kg for liver, 42 µg/kg for fat and 394 µg/kg for kidney.The limit of quantification was 500 µg/kg for chicken liver, kidney, muscle and skin and fat; the limits of detection for these tissues were 470, 133, 319 and 32 µg/kg, respectively. For rabbit tissues, the limits of quantification were 500 µg/kg for muscle, liver and fat and 2500 µg/kg for kidney.

The stability of residues in edible tissues was shown to be satisfactory following storage at -20°C for several weeks.

25. Details of a microbiological method with a limit of detection of 100 µg/kg for all tissues was also provided. However, as for all microbiological methods the requirements for specificity were not fulfilled.

26. Residues were highest in neonatal calves and residues were even higher when calves were dosed parenterally reflecting the better absorption via this route; it was agreed to propose MRLs for cattle based on the residue distribution. In contrast, low residues were found in all the other species in which apramycin was administered orally. Residues of apramycin were not detectable in porcine muscle and liver at any time point and residues in porcine skin+fat samples were detectable only within one day of treatment. It was estimated that consumer intake of microbiologically-active residues from porcine tissues taken within one day of the end of treatment would represent less than 13% of the ADI.

27. No residues of apramycin were found in ovine or chicken muscle or in ovine fat at any time point and low residues were found in some samples of liver and chicken skin and fat at early time-points. It was estimated that consumer intake of microbiologically-active residues from ovine tissues would represent less than 15% of the ADI and total residues from poultry tissues would represent approximately 6% of the ADI. Residues in all rabbit tissues were below the limit of detection at all time points. Therefore, it was considered that no MRLs were necessary for pigs, sheep, rabbits and chickens.

Conclusions and recommendation

Having considered that:

- an ADI of 40 µg/kg bw (i.e. 2400 µg/person) was established for apramycin,
- apramycin was identified as the marker residue and represents more than 75% of the residues in tissues of cattle and pigs 5 to 6 days after dosing,
- a fully validated physico-chemical analytical method is available to determine residues of apramycin in the tissues of the target species,
- apramycin was poorly absorbed after oral administration to pigs, sheep, chickens and rabbits,
- within one day of the end of oral treatment, the intake of total residues from chicken tissues represents approximately 6% of the ADI,
- within one day of the end of oral treatment, the intake of microbiologically-active residues from porcine tissues represents less than 13% of the ADI,
- within one day of the end of oral treatment, the intake of microbiologically-active residues from ovine tissues represents less than 15% of the ADI,
- residues of apramycin in rabbit tissues were below the limit of detection within a few hours of the end of treatment;

the Committee for Veterinary Medicinal Products recommends the inclusion of apramycin in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Apramycin	Apramycin	Bovine	1 000 µg/kg 1 000 µg/kg 10 000 µg/kg 20 000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption

Based on these MRLs the daily intake will not exceed 97% of the ADI.

In addition, the Committee for Veterinary Medicinal Products concludes that there is no need to establish MRLs for apramycin for pigs, sheep, chickens, and rabbits and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Apramycin	Porcine, rabbits	For oral use only
	Ovine	For oral use only. Not for use in animals from which milk is produced for human consumption
	Chicken	For oral use only. Not for use in animals from which eggs are produced for human consumption