AMINOGLYCOSIDES (Veterinary—Systemic)

This monograph includes information on the following aminoglycoside aminocyclitols: Amikacin; Dihydrostreptomycin*; Gentamicin; Neomycin; Streptomycin†. It also contains information on the following aminocyclitol: Apramycin.

Some commonly used *brand names* are:

Amifuse E [Amikacin]	*GentaVed 50* [Gentamicin]
Amiglyde-V [Amikacin]	*GentaVed 100* [Gentamicin]
Amiglyde-V Injection [Amikacin]	*Gentocin Solution Injectable* [Gentamicin]
Amiglyde-V Intrauterine Solution [Amikacin]	*Gentozen* [Gentamicin]
Amiject D [Amikacin]	*Legacy* [Gentamicin]
Amikacin C Injection [Amikacin]	*NeoMed 325* [Neomycin]
Amikacin E Solution [Amikacin]	*Neomix 325* [Neomycin]
Apralan [Apramycin]	*Neomix AG 325* [Neomycin]
Biosol Liquid [Neomycin]	*Neomix AG 325 Medicated Premix* [Neomycin]
CaniGlide [Amikacin]	*Neomix Soluble Powder* [Neomycin]
Equi-Phar EquiGlide [Amikacin]	*Neomycin 200* [Neomycin]
Ethamycin [Dihydrostreptomycin]	*Neomycin 325* [Neomycin]
Garasol Injection [Gentamicin]	*Neo-Sol 50* [Neomycin]
Gen-Gard [Gentamicin]	*Neosol Soluble Powder* [Neomycin]
GentaMax 100 [Gentamicin]	*Neoved 200* [Neomycin]
Gentamicin Sulfate Pig Pump Oral Solution [Gentamicin]	*Neovet 325/100* [Neomycin]

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* section(s).

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*Not commercially available in the U.S. as a single entity.
†Not commercially available in Canada as a single entity.

Category: Antibacterial (systemic).

Indications

Note: The text between [ELUS]and [EL] describes uses that are not included in U.S. product labeling. Text between [ELCAN]and [EL] describes uses that are not included in Canadian product labeling.

The [ELUS] or [ELCAN] designation can signify a lack of product availability in the country indicated. See the *Dosage Forms* section of this monograph to confirm availability.

General considerations

Aminoglycosides are utilized primarily in the treatment of infections caused by aerobic gram-negative organisms.[R-107; 108; 116] They are not active against anaerobic organisms. In addition to their strength in the treatment of gram-negative pathogens, aminoglycosides can be effective against some gram-positive organisms, such as *Staphylococcus aureus*,[R-107; 108] some mycobacteria,[R-116; 124] some mycoplasma strains,[R-116] and some spirochetes.[R-263] They are sometimes administered concurrently with other antibacterials for a possible synergistic effect. However, the use of aminoglycosides in the treatment of infection in animals has been tempered by toxicity considerations in the animal treated.[R-116] Often, systemic use is limited to the treatment of serious gram-negative infections resistant to less toxic medications. Also, local environment at the therapeutic site can affect the efficacy of these drugs, acidic or purulent conditions can hamper their effect,[R-5; 7; 20; 116; 160] and the presence of cations (calcium or magnesium ions, for example) can decrease antibacterial effect.[R-266]

Streptomycin was the earliest aminoglycoside introduced.[R-116] It is active against mycobacteria, *Leptospira*,[R-243; 244] *Francisella tularensis*, and *Yersinia pestis*, but only some mycoplasma, gram-negative organisms, and *Staphylococcus* species.[R-116] Dihydrostreptomycin is chemically very similar to streptomycin.[R-116] The introduction of newer aminoglycosides has eclipsed the significance of dihydrostreptomycin and streptomycin in the face of increasing bacterial resistance,[R-122; 235; 239] although some dosage forms of these medications are still available.

Neomycin became available for use a few years after streptomycin. Neomycin has been effective against many gram-negative organisms and *Staphylococcus aureus*.[R-116] However, the use of neomycin is limited by a relatively high risk of toxicity with systemic use;[R-116] it is not available for parenteral administration.

Gentamicin has been widely used in the treatment of gram-negative organisms and some gram-positive organisms.[R-5] As with other aminoglycosides, use is limited by risk of toxicity. *In vitro* tests have shown gentamicin to be active against *Salmonella arizonae (Arizona hinshawii)*,[R-7] *Enterobacter aerogenes*,[R-7; 125] *Escherichia coli*,[R-1; 5; 7; 125] *Klebsiella* species,[R-1; 5; 7; 125] *Neisseria*,[R-5; 7; 125] most indole-positive and some indole-negative *Proteus* species,[R-1; 5; 7; 125] some *Pasteurella multocida*,[R-122; 127] *Pseudomonas aeruginosa*,[R-1; 5; 7; 125] *Salmonella*,[R-5; 7; 125] *Serratia marcescens*,[R-5; 7; 125] *Shigella*,[R-5; 7; 125] *Staphylococcus* species,[R-1; 5; 7; 109-111; 123; 125] including *Staphylococcus intermedius*,[R-109-111] and some *Streptococcus* species.[R-1; 5; 7; 125]

Amikacin was developed from kanamycin, the first less toxic alternative to older aminoglycosides.[R-116] Because amikacin has the broadest spectrum of activity of the aminoglycosides, including superior activity against pathogens such as *Pseudomonas* species and kanamycin-resistant *Enterobacteriaceae*,[R-37; 178] it eclipsed the use of kanamycin, a drug with a very similar pharmacokinetic profile.[R-178] Amikacin is considered effective against strains not susceptible to other aminoglycosides because it resists some aminoglycoside inactivating enzymes.[R-91; 137; 178] In addition to those organisms listed above for gentamicin, *in vitro* tests have shown amikacin to be effective against *E. coli*, *Klebsiella* and *Pseudomonas* species resistant to gentamicin,[R-143; 266] *Citrobacter freundii*, *Listeria monocytogenes*, and *Providencia* species.[R-91; 92] There are reports in the U.S. and abroad of some *in vitro* resistance to gentamicin and other aminoglycosides by *Salmonella* species,[R-113; 117-119] but the strains tested are still susceptible to amikacin.[R-118; 199; 250]

Apramycin is an aminocyclitol antibiotic with a chemical structure very similar to that of the aminoglycosides but different enough to leave it unaffected by many aminoglycoside inactivating enzymes.[R-245] At low concentrations, apramycin is more effective in inhibiting bacterial protein synthesis than amikacin, gentamicin, or streptomycin.[R-96] Apramycin is active against *Staphylococcus aureus*, many gram-negative organisms, and some mycoplasma strains.[R-163] Apramycin has been reported to be effective *in vitro* against *E. coli* and *Salmonella species* that are resistant to streptomycin and neomycin.[R-96; 164; 167; 173]

Resistance to aminoglycosides is produced primarily by enzymes encoded by genes located on bacterial plasmids.[R-116; 168] The enzymes act inside the bacterium to modify the aminoglycoside, thereby preventing it from binding to ribosomes.[R-116; 168] This type of plasmid-associated resistance is transferable between

bacteria. A single type of plasmid may confer cross-resistance to multiple aminoglycosides[R-116; 117; 120; 145] and also resistance to other unrelated antimicrobials.[R-7; 114; 115; 120; 145; 168] In some cases, a single plasmid gene encoding for one enzyme, an acetyltransferase, may confer resistance to several aminoglycosides.[R-171] For example, the enzyme aminoglycoside 3-*N*-acetyltransferase IV allows the bacterium to be resistant to apramycin, gentamicin, netilmicin, and tobramycin.[R-171] A single bacterial isolate may have any one of a variety of combinations of resistance to different antibiotics conferred by the particular plasmid it carries.[R-168] As an example, an *E. coli* strain may be resistant to ampicillin, apramycin, chloramphenicol, gentamicin, kanamycin, sulfonamide, streptomycin, tetracycline, and trimethoprim.[R-168] Other *E. coli* isolates cultured from the same geographic region may carry resistance to a few or many of the same antibiotics in different combinations.[R-168] The nature of resistance in organisms such as *E. coli* and *Salmonella* species has been a focus of international research because of concerns about potential transference of antimicrobial resistance from animal to human pathogens.[R-168-172]

Bacteria may also utilize other methods of reducing the efficacy of aminoglycosides. Some strains of bacteria are less permeable to aminoglycosides, requiring much higher concentrations of aminoglycosides to kill them and, therefore, can be selected during treatment.[R-116] Resistance developed by chromosomal resistance is minimal and develops slowly for most of the aminoglycosides, with the exception of streptomycin or dihydrostreptomycin; resistance to streptomycin can occur from a single-step mutation.[R-116]

Accepted

ELUSBacteremia (treatment)EL; or

ELUSSepticemia (treatment)EL—*Cats* and *dogs:* ELCANAmikacin injectionEL and gentamicin injection are indicated in the treatment of bacteremia or septicemia caused by susceptible organisms.[R-7; 93; 264]

ELUS,CANBone and joint infections (treatment)EL—*Cats* and *dogs:* Amikacin injection and gentamicin injection are used in the treatment of bone and joint infections caused by susceptible organisms.[R-93; 264]

Enteritis (treatment)—The primary treatment for enteritis in many cases is aggressive fluid replacement. Treatment of enteritis with antimicrobials should rely on a specific diagnosis and knowledge of pathogen susceptibility.

ELCAN*Calves*EL: Neomycin sulfate Type A medicated article is indicated in the control and treatment of enteritis caused by susceptible *Escherichia coli.*[R-94] Streptomycin oral solution is indicated in the treatment of bacterial enteritis caused by susceptible organisms.[R-181; 182]

Cattle and *sheep:* ELCANNeomycin sulfate Type A medicated articleEL, neomycin sulfate powder for oral solution[R-97; 104] and neomycin sulfate oral solution[R-98; 103] are indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli.* If systemic signs develop, medications that are well absorbed systemically should be considered for addition to or substitution for therapy with this medication.[R-98]

Chickens: ELUSNeomycin sulfate powder for oral solutionEL, [R-104] ELUSneomycin sulfate oral solutionEL, [R-103] and ELCANstreptomycinEL[R-181; 182] are indicated in the control and treatment of bacterial enteritis in chickens.

ELCAN*Goats*EL: Neomycin sulfate Type A medicated article, neomycin sulfate powder for oral solution[R-97; 104] and neomycin sulfate oral solution[R-98; 103] are indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli.* If systemic signs develop, medications that are well absorbed systemically should be considered for addition to or substitution for therapy with this medication.[R-98]

ELCAN*Kids* and *lambs*EL: Neomycin sulfate Type A medicated article

is indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli.*[R-94]

Piglets: ELUSApramycin sulfate powder for oral solutionEL, [R-96] ELUSdihydrostreptomycin injectionEL, [R-106] gentamicin injection,[R-7;125] ELCANgentamicin oral solutionEL, [R-11; 14] ELCANgentamicin powder for oral solutionEL, [R-15] neomycin sulfate oral solution,[R-98; 103] neomycin sulfate powder for oral solution,[R-97; 104] ELCANneomycin sulfate Type A medicated articleEL, [R-94] and ELCANstreptomycinEL[R-181; 182] are indicated in the control and treatment of enteritis (weanling pig scours) in piglets caused by susceptible *E. coli.* If systemic signs develop, medications that are well absorbed systemically should be considered.[R-98]

Pigs: Neomycin sulfate oral solution,[R-98; 103] neomycin sulfate powder for oral solution[R-97; 104] and ELCANneomycin sulfate Type A medicated articleEL are indicated in the control and treatment of enteritis caused by susceptible *E. coli.*[R-94]

ELUS*Horses*EL: Neomycin sulfate oral solution[R-103] and neomycin sulfate powder for oral solution[R-97; 104] are indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli.* If systemic signs develop, medications that are well absorbed systemically should be considered for addition to or substitution for therapy with this medication.

ELUS*Turkeys*EL: Neomycin sulfate powder for oral solution[R-104] and neomycin sulfate oral solution[R-103] are indicated in the control and treatment of bacterial enteritis in turkeys.

E. coli infection (treatment)—

Chicks, 1-day-old: Gentamicin injection[R-8] is indicated in the prevention of early mortality in chicks caused by susceptible *E. coli.*

Turkeys, growing: Neomycin sulfate powder for oral solution is indicated in the control of mortality associated with susceptible *E. coli* in growing turkeys.[R-2]

Paracolon (treatment)—*Turkey poults,* 1- to 3-day-old: Gentamicin injection is indicated in the treatment of infections in turkeys caused by susceptible *Salmonella arizonae.*[R-7; 8]

Pseudomonas aeruginosa infection (treatment); or

Salmonella typhimurium infection (treatment)—*Chicks,* 1-day-old: Gentamicin injection is indicated in the prevention of early mortality in chicks caused by suceptible *Pseudomonas aeruginosa,* and *Salmonella typhimurium.*[R-8]

Respiratory tract infections, bacterial (treatment)—*Cats* and *dogs:* ELUSGentamicin injectionEL[R-7] and ELUS,CANamikacin injectionEL[R-264] are indicated in the treatment of susceptible respiratory tract infections, including pneumonia and upper respiratory tract infections.

Skin and soft tissue infections, bacterial (treatment)—

ELUS*Cats*EL: Gentamicin injection[R-7; 123] and ELCANamikacin injectionEL[R-139; 140; 264] are indicated in the treatment of susceptible skin and soft tissue infections.

Dogs: ELCANAmikacin injectionEL[R-91] and ELUSgentamicin injectionEL[R-7] are indicated in the treatment of susceptible skin and soft tissue infections. In the case of staphyloccocal dermatitis, although the *in vitro* susceptibility of canine *Staphylococcus intermedius* to gentamicin is persistently high,[R-109-111] practical administration and toxicity considerations with long-term therapy have limited the usefulness of aminoglycosides.[R-109]

ELCANSwine dysentery (treatment)EL—*Pigs:* Gentamicin powder for oral solution[R-15] and gentamicin oral solution[R-11] are indicated in the treatment of swine dysentery caused by susceptible *Treponema hyodysenteriae.*

Urinary tract infections, bacterial (treatment)—

ELUS*Cats*EL: Gentamicin injection[R-7] and ELCANamikacin injectionEL[R-139; 140; 264] are indicated in the treatment of urinary tract infections, such as cystitis, caused by susceptible organisms.

Dogs: ELCANAmikacin injectionEL[R-264] and gentamicin injection[R-4; 7] are indicated in the treatment of urinary tract infections

caused by susceptible organisms.
Uterine infections, bacterial (treatment)—

[EL US,CAN]*Cats*[EL]: Amikacin injection,[R-139; 140; 264] and gentamicin injection[R-264] are indicated in the treatment of endometritis in cats.[R-93]

Dogs: [EL US]Gentamicin injection [EL][R-7] and [EL US,CAN]amikacin injection[EL][R-264] are indicated in the treatment of uterine infections (metritis) in dogs caused by susceptible organisms.

Horses: Amikacin uterine solution,[R-92] [EL CAN]gentamicin uterine infusion[EL],[R-1] and [EL US]gentamicin injection[EL][R-7] are indicated in the control of bacterial infections of the uterus caused by susceptible organisms.

Potentially effective

Infections, bacterial (treatment)—

[EL US,CAN]*Calves* and *cattle*[EL]: The extralabel use of aminoglycosides in cattle has been strongly discouraged because of the long duration of drug residues in some tissues (see the *Regulatory Considerations* section). However, in the case of bacterial infections susceptible to gentamicin in cattle that will *not* be used for food production, there are pharmacokinetic data available to estimate dosing for amikacin in calves[R-141; 144] and gentamicin in calves and cattle.[R-21; 22; 25] Use of aminoglycosides should be restricted to susceptible bacterial infections caused by pathogens resistant to antimicrobials that are less likely to produce prolonged residues.

[EL US,CAN]*Donkeys, foals, horses,* and *ponies*[EL]: Although the safety and efficacy have not been established, amikacin has been recommended in the treatment of susceptible bacterial infections in donkeys, foals, horses (systemic administration), and ponies, based on pharmacokinetic studies[R-130-132; 136; 137] and *in vitro* antimicrobial susceptibility of common pathogens.[R-159; 253]

Although the safety and efficacy have not been established, gentamicin has been recommended in the treatment of susceptible bacterial infections in foals and horses, based on pharmacokinetic studies[R-46-52; 53; 55] and *in vitro* antimicrobial susceptibility of common pathogens.[R-159; 253]

[EL US,CAN]*Minor species*[EL]: Although the safety and efficacy have not been established, amikacin has been suggested for the treatment of susceptible bacterial infections in *African gray parrots,*[R-150] *ball pythons,*[R-155] *goats* that will not be used for food production,[R-151] *gopher snakes,*[R-154] *gopher tortoises,*[R-156] *guinea pigs,*[R-152] and *red-tailed hawks,*[R-147] based on pharmacokinetic studies.

Although the safety and efficacy have not been established, gentamicin has been suggested for the treatment of susceptible bacterial infections in the following species, if not used for food production: *baboons,*[R-76] *budgerigars,*[R-86] *buffalo calves,*[R-78] *eagles,*[R-88] *goats,*[R-40] *hawks,*[R-88] *llamas,*[R-82] *owls,*[R-88] and *pythons,*[R-89] based on pharmacokinetic studies.

Note: [EL US]Leptospirosis (treatment)[EL]—*Cattle, dogs,* and *pigs:* Canadian product labeling includes the use of dihydrostreptomycin in the treatment of leptospirosis in cattle, dogs, and pigs.[R-106] Studies have shown that, while shedding of leptospires in the urine of cattle can be halted for at least 2 months by the administration of a single dose of dihydrostreptomycin, carriers are not necessarily eliminated.[R-243; 244] Equally effective alternative medicines exist.

Unaccepted

[EL US,CAN]Mastitis (treatment)[EL]—*Cattle* and *pigs:* Although, at one time, Canadian product labeling listed the use of dihydrostreptomycin in the treatment of mastitis in cows and sows, there is no published evidence that this treatment is effective. Dihydrostreptomycin is irregularly distributed into milk when administered at the labeled dose.[R-247] Another member of this drug family, gentamicin, has been shown in some studies to be ineffective in the treatment of coliform mastitis.[R-259-260]

[EL US]Pneumonia (treatment)[EL]—*Calves* and *cattle:* Although Canadian product labeling includes the use of dihydrostreptomycin in the treatment of bacterial pneumonia in calves,[R-106] there is no published evidence available pertaining to efficacy of this therapy. Such use is not recommended by the USP Veterinary Medicine Advisory Panel[R-258] due to the lack of efficacy data and the potential for extended tissue withdrawal times.

[EL US]Uterine infections (treatment)[EL]—

Cattle: Although Canadian product labeling includes the use of gentamicin injection administered by the *intrauterine* route in the treatment of uterine infections in cattle,[R-7] this use is not recommended. Intrauterine gentamicin dosage regimens necessary to produce therapeutic concentrations in uterine tissue other than the endometrium can lead to significant systemic drug distribution and a risk of long-term tissue residues of gentamicin.[R-28-30]

Dogs: Although Canadian product labeling includes the use of gentamicin injection administered by the *intrauterine* route in the treatment of uterine infections in dogs, such use is not recommended.[R-258]

Regulatory Considerations

U.S.—

Because drug residues can persist in some tissues for many months, the extralabel use of aminoglycosides in food-producing animals should be avoided when there are no established scientific data on residue depletion. A voluntary resolution against the administration of aminoglycosides to cattle has been instituted by the Academy of Veterinary Consultants, the American Association of Bovine Practitioners, the National Cattlemen's Beef Association, and the American Veterinary Medical Association (AVMA).[R-257] The AVMA position on aminoglycosides states "Until further scientific information becomes available, aminoglycoside antibiotics should not be used in cattle, except as specifically approved by the FDA.[R-257]" At issue is the need for a clearer understanding of the complexity of aminoglycoside residue depletion for food-producing animals.[R-25; 32; 34; 36] Drug residues can persist in some tissues for many months.

Gentamicin is not labeled for use in horses intended for human consumption. Neomycin is not labeled for use in veal calves.

Withdrawal times have been established for the use of gentamicin sulfate oral solution and gentamicin sulfate powder for oral solution in pigs; gentamicin injection in chicks and turkey poults; neomycin sulfate oral solution, neomycin sulfate powder for oral solution, or neomycin sulfate Type A medicated article in cattle, goats, pigs, and sheep; and streptomycin sulfate oral solution in calves, chickens, and pigs. See the *Dosage Forms* section.

Canada—

Gentamicin is not labeled for use in horses intended for human consumption.

Withdrawal times have been established for the use of apramycin sulfate powder for oral solution in pigs; dihydrostreptomycin injection in cattle and pigs; gentamicin injection in chickens, cows, piglets, and turkey poults; and neomycin sulfate oral solution and neomycin sulfate powder for oral solution in cattle, chickens, pigs, sheep, and turkeys. See the *Dosage Forms* section.

Chemistry

Source:

Amikacin—Semi-synthetic; derived from kanamycin.[R-91]

Apramycin—Produced by fermentation of *Streptomyces tenebrarius.*[R-18; 96]

Gentamicin—Created from fermentation of *Micromonospora purpurea.*[R-1; 5; 18]

Neomycin—The sulfate of an antibacterial substance produced by

Streptomyces fradiae.[R-256]

Streptomycin—Prepared from fermentation of *Streptomyces griseus,* an actinomycete organism isolated from soil.[R-256]

Chemical group:

Amikacin, dihydrostreptomycin, gentamicin, neomycin, and streptomycin—Aminoglycoside antibiotics.

Apramycin—Aminocyclitol.

Note: The aminoglycosides are defined by their mechanism of action, binding with the 30S ribosomal subunit.[R-251] The term aminocyclitol describes the structure of both the aminoglycosides and apramycin; however, the structure of apramycin differs just enough from other aminoglycosides that it may be listed as an aminocyclitol rather than specifically an aminoglycoside. It is very similar physicochemically to other aminoglycosides.[R-164]

Chemical name:

Amikacin sulfate—D-Streptamine, O-3-amino-3-deoxy-*alpha*-D-glucopyranosyl-(1→6)-O-[6-amino-6-deoxy-*alpha*-D-glucopyranosyl-(1→4)]-N^1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy, (*S*)-, sulfate (1:2) (salt).[R-18]

Apramycin—D-Streptamine, 4-O-[(8R)-2-amino-8-O-(4-amino-4-deoxy-*alpha*-D-glucopyranosyl)-2,3,7-trideoxy-7-(methylamino)-D-*glycero-alpha*-D-*allo*-octodialdo-1,5:8,4-dipyranos-1-yl]-2-deoxy-.[R-18]

Dihydrostreptomycin sulfate—Dihydrostreptomycin sulfate (2:3) (salt).[R-18]

Gentamicin sulfate—A complex antibiotic substance with three major components, sulfates of gentamicin C_1, gentamicin C_2, and gentamicin C_{1A}.[R-18]

Neomycin sulfate—Neomycin sulfate.[R-18]

Streptomycin sulfate—D-Streptamine, O-2-deoxy-2-(methylamino)-*alpha*-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-*alpha*-L-lyxofuranosyl-(1→4)-N,N'-bis(aminoiminomethyl)-, sulfate (2:3) (salt).[R-18]

Molecular formula:

Amikacin sulfate—$C_{22}H_{43}N_5O_{13}\cdot2H_2SO_4$.[R-18]

Apramycin—$C_{21}H_{41}N_5O_{11}$.[R-18]

Dihydrostreptomycin sulfate— $(C_{21}H_{41}N_7O_{12})_2\cdot3H_2SO_4$.[R-18]

Gentamicin—

Gentamicin C_1: $C_{21}H_{43}N_5O_7$.[R-17]

Gentamicin C_2: $C_{20}H_{41}N_5O_7$.[R-17]

Gentamicin C_{1A}: $C_{19}H_{39}N_5O_7$.[R-17]

Streptomycin sulfate—$(C_{21}H_{39}N_7O_{12})_2\cdot3H_2SO_4$.[R-18]

Molecular weight:

Amikacin sulfate—781.76.[R-18]

Apramycin—539.58.[R-19]

Dihydrostreptomycin sulfate—1461.42.[R-18]

Gentamicin—

Gentamicin C_1: 477.61.[R-17]

Gentamicin C_2: 463.59.[R-17]

Gentamicin C_{1A}: 449.56.[R-17]

Streptomycin sulfate—1457.38.[R-18]

Description:

Amikacin Sulfate USP—White, crystalline powder.[R-19]

Dihydrostreptomycin Sulfate USP—White or almost white, amorphous or crystalline powder. Amorphous form is hygroscopic.[R-19]

Gentamicin Sulfate USP—White to buff powder.[R-19]

Neomycin Sulfate USP—White to slightly yellow powder, or cryodesiccated solid. Is odorless or practically so and is hygroscopic.[R-19]

Streptomycin Sulfate USP—White or practically white powder. Is odorless or has not more than a faint odor. Is hygroscopic, but is stable in air and on exposure to light. Its solutions are acid to practically neutral to litmus.[R-19]

pKa:

Amikacin—8.1.[R-256]

Dihydrostreptomycin—8.8.[R-254]

Gentamicin sulfate—8.2.[R-254]

Neomycin sulfate—8.3.[R-254]

Solubility:

Amikacin Sulfate USP—Freely soluble in water.[R-19]

Apramycin sulfate—Highly soluble in water and slightly soluble in the lower alcohols.[R-96]

Dihydrostreptomycin Sulfate USP—Freely soluble in water; practically insoluble in acetone, in chloroform, and in methanol.[R-19]

Gentamicin Sulfate USP—Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether.[R-19]

Neomycin Sulfate USP—Its solutions are dextrorotatary. Freely soluble in water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether.[R-19]

Streptomycin Sulfate USP—Freely soluble in water, very slightly soluble in alcohol; practically insoluble in chloroform.[R-19]

Pharmacology/Pharmacokinetics

Note: See also *Tables I* and *II* at the end of this monograph.

Mechanism of action/Effect:

Aminoglycosides—Bactericidal.[R-107; 116] Aminoglycosides enter susceptible bacteria by oxygen-dependent active transport (making anaerobes impervious to them) and by passive diffusion.[R-37; 107] Once the antibiotic has gained access, it binds irreversibly to a receptor protein on the 30S ribosomal subunit[R-5; 107] and blocks the formation of a complex that includes mRNA, formylmethionine, and tRNA.[R-107] As a result, the tRNA is translated incorrectly, producing a nonfunctional protein.[R-107] Aminoglycosides also disrupt protein synthesis by disruption of polysomes and may prevent the initiation of DNA replication.[R-107]

Aminocyclitols—Apramycin is bactericidal. It also acts against bacteria by inhibiting protein synthesis at the ribosome level.[R-96] Like the aminoglycosides, it inhibits the translocation step of protein synthesis and induces translation errors.[R-96]

Absorption:

Intramammary administration—In cows with mastitis, gentamicin is well absorbed systemically following intramammary administration. With a single dose (1.1 mg per kg of body weight), concentrations of antibiotic in the serum (measured in one study up to 1.09 ± 0.15 mcg per mL) could result in prolonged tissue residues.[R-26]

Intramuscular or subcutaneous administration—Amikacin, dihydro-streptomycin and gentamicin generally are rapidly and well absorbed from intramuscular and subcutaneous routes of administration.[R-230; 247]

Intrauterine administration—*Cows:* In healthy cows, 39% of a total intrauterine dose of 2500 mg, administered once a day for 3 days, was absorbed systemically and produced serum concentrations of up to 6.6 mcg/mL.[R-28] In cows with endometritis, absorption was similar, with 36% of an intrauterine dose of 4 mg/kg of body weight administered once a day for 3 days absorbed systemically, producing peak serum concentrations of 6 to 11 mcg/mL.[R-29] A smaller total intrauterine dose of 225 to 275 mg produced plasma concentrations of 0 to 2.5 mcg/mL,[R-30] while 70% of the dose administered remained in the lumen of the uterus.[R-17; 30].

Because of the demonstrated intrauterine absorption of aminoglycosides, some clinicians have warned that intrauterine administration is likely to result in residues above regulatory limits in food-producing animals.[R-60]

Oral administration—In general, aminoglycosides and apramycin are very poorly absorbed from oral administration in adult animals, including cattle, chickens, and pigs.[R-46; 96; 166; 230] However, 11% of an oral neomycin dose of 30 mg per kg of body weight (mg/kg) was absorbed in 3-day-old calves and 1

to 2% of the dose was absorbed by 2-month-old calves, regardless of ruminant status.[R-238] In very young calves, this absorption can be significant. When neomycin was administered orally to 2- to 4-day-old calves at a dose of 33 mg/kg for 14 days, absorption was significant enough to produce relatively high concentrations of drug in the kidneys (approximately 300 mcg per gram of tissue).[R-240] Some absorption of apramycin has also been shown to occur in neonatal pigs.[R-296] Damage to the gastrointestinal mucosa can also lead to increased aminoglycoside absorption.[R-166; 230] Moderate enteritis from induction of coccidial infection in chickens caused a significant increase in absorption of a 43-mg/kg dose of apramycin for 5 days.[R-166] Serum concentrations were increased from 0.04 to 0.06 mcg/mL and tissue concentrations were also increased.[R-166]

Distribution: Aminoglycosides are distributed primarily into the extracellular space[R-46] and over time accumulate in tissues.[R-25] The amount of antibiotic in most tissues appears to be dependent on the total dose administered over time rather than the size of each individual dose.[R-25; 34] Aminoglycosides do not distribute well across membrane barriers and, therefore, are not found at high concentrations in brain tissue, cerebrospinal fluid, ocular fluid, or respiratory secretions.[R-20; 153; 230]
Systemic administration—
   Otic tissue: Aminoglycosides concentrate in the perilymph of the inner ear. The damage to the ciliated cells can result in deafness; vestibular nerve injury may result as well.[R-263]
   Renal tissue: When aminoglycosides are administered systemically, the predominant site of drug accumulation is the renal cortex in most species tested, including cats, cattle, pigs, and sheep.[R-20; 25; 34; 42; 67; 230] Therapeutic concentrations are also reached in other tissues and slow depletion from some tissues may prolong the presence of residues.[R-25; 230] For cats, cattle, pigs, and sheep, the following general relative gentamicin concentrations are reached over time with repeated doses, from highest to lowest concentrations: renal cortex; renal medulla; liver/lung/spleen; skeletal muscle.[R-25; 34; 42; 67; 230] Renal proximal tissues actively take up and accumulate aminoglycosides by pinocytosis.[R-265] Once within the tubular cells, the drug may cause dysfunction in lysosomes, mitochondria, proximal tubule cell plasma membrane phospholipids and enzymes, and glomerular filtration.[R-37]
   Other tissues:
   Cats: Amikacin is distributed into uterine tissue so that tissue concentrations are about 25% of the current serum concentration.[R-140]
   Horses:
      Amikacin—Amikacin is distributed into peritoneal fluid and synovial fluid in the horse with a peak of 13.7 ± 3.2 mcg/ mL and 16.8 ± 8.8 mcg/mL, respectively, at the first sample, 1 hour after an intravenous dose of 6.6 mg per kg of body weight.[R-137]
      Gentamicin—Gentamicin is distributed into endometrial tissue so that tissue concentration is higher than plasma concentrations reached after 7 days of intramuscular therapy with a dose of 5 mg/kg every 8 hours.[R-53]
      Gentamicin is distributed into synovial fluid in normal horses to produce a peak of 6.4 mcg/mL at 2 hours with a single 4.4 mg/kg intravenous dose.[R-58] However, local inflammation may increase drug concentrations in the joint and concentrations may increase with repeated doses.
      Gentamicin is distributed into jejunal and colonic tissue with a maximum gentamicin concentration of 4.13 ± 1.8 mcg/mL measured in the large colon at 0.5 hour after administration and 2.26 ± 1.35 mcg/mL measured in jejunum at 0.33 hour.[R-59]

Intra-articular administration—Horses: Intra-articular administration of 150 mg of gentamicin resulted in a peak synovial concentration of 1828 ± 240 mcg/mL 15 minutes after administration.[R-61] The intra-articular administration of buffered gentamicin produced more synovitis and higher gentamicin concentrations (2680 ± 1069 mcg/ mL) than unbuffered gentamicin;[R-61] however, synovial concentrations 12 hours later were very similar for buffered and unbuffered gentamicin. Synovial concentrations remained >10 mcg/mL for at least 24 hours.[R-61] A peak plasma concentration of 0.69 mcg/mL at 15 minutes after intra-articular administration was measured;[R-61] gentamicin was no longer detectable in plasma at 6 hours.
Intrauterine administration—Horses:
   Amikacin—Intrauterine administration of a total dose of 2 grams produces a peak of greater than 40 mcg per gram of endometrial tissue within 1 hour after infusion.[R-92] Twenty-four hours after infusion, 2 to 4 mcg of amikacin per gram of endometrial tissue is still present.[R-92]
   Gentamicin—Intrauterine administration of 2.5 grams of gentamicin once daily for 5 days resulted in endometrial tissue concentrations of 41.65 ± 17 mcg/gram 24 hours after the last dose.[R-60] The addition of progesterone, administered concurrently, increased the sample to 100.33 ± 19.27 and the administration of estradiol concurrently with gentamicin increased the sample to 74.09 ± 8.6 mcg/gram.[R-60] At the same time, measured serum concentrations of gentamicin peaked at 0.64 ± 0.06 for gentamicin administered alone; the concurrent administration of progesterone or estradiol increased gentamicin serum concentrations to a peak of 8.34 ± 1.34.[R-60]
Regional limb perfusion—Horses: Amikacin—Regional intravenous perfusion of amikacin (125 mg diluted in 60 mL of electrolyte solution) into the distal limb of horses produced sufficiently high concentrations of antibiotic in local joint fluid, bone, and serum in the limb to be effective in the treatment of most susceptible organisms.[R-179]

Protein binding:
   Amikacin—Calves: 6% at a concentraton of 5 to 150 mcg per mL of serum (mcg/mL).[R-141]
   Dihydrostreptomycin—
      Cows: 8%, at a concentration of 2.5 to 5 mcg/mL.[R-129]
      Ewes: 12%, at a concentration of 2.5 to 5 mcg/mL.[R-129]
   Gentamicin—Horses and foals: < 30%.[R-1; 47]
   Neomycin—
      Cows: 45%, at a concentration of 5 to 10 mcg/mL.[R-129]
      Ewes: 50%, at a concentration of 5 to 10 mcg/mL.[R-129]
   Spectinomycin—Cows: 6%, at a concentration of 12.5 to 25 mcg/mL.[R-129]

Biotransformation: In many species, aminoglycosides are eliminated in the form of the administered drug;[R-96; 143; 150; 180; 238] that is, they are not biotransformed.

Elimination: Parenterally administered aminoglycosides are predominantly excreted unchanged in the urine.[R-96; 164; 180] Only a small amount is excreted in the bile in some species, such as cattle.[R-1] For amikacin in dogs and gray parrots, and gentamicin in calves, cows, horses, and sheep, 75 to 100% of the dose is eliminated unchanged in the urine in the first 8 to 24 hours.[R-1; 7; 20; 22; 32; 143; 150; 178; 204]

Because the kidney is the site of predominant accumulation and elimination of drug, the analysis of elimination seems straightforward. However, researchers have described a dose-dependent slow elimination phase (gamma phase) many times longer than the initial elimination phase.[R-32] It is postulated that gentamicin is bound to tissues by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound by another process is released more slowly.[R-25;

[32; 34; 36] It is not known if these processes are tissue-specific.

Precautions to Consider

Pregnancy/Reproduction

Amikacin—

Dogs: Reproductive studies have not been performed in dogs.[R-91]

Horses: No evidence was found of impaired fertility in mares given an intrauterine dose of 2 grams of amikacin 8 hours before natural breeding.[R-92] In *in vitro* studies, equine sperm exposed to 0.1 mg of benzethonium chloride per mL of solution, present in some amikacin products, showed impaired viability.[R-92] Product labeling recommends that mares not be bred for 8 hours after intrauterine treatment with amikacin.[R-92]

Apramycin—No adverse effects have been observed in laboratory animals pertaining to mutagenicity, teratology, or reproduction.[R-96]

Dihydrostreptomycin—*Bulls:* No effect was noted on spermatogenesis, seminal pH, ejaculate volume, percentage of motile spermatozoa, rate of spermatozoal motility, or concentration of spermatozoa from nine beef bulls on the third or seventh days after the second dose of 22 mg of dihydrostreptomycin per kg of body weight every 12 hours for two doses.[R-242]

Gentamicin—

Cats and *dogs:* Reproductive studies have not been performed with gentamicin in cats and dogs.

Horses: Intrauterine treatment of mares with gentamicin is not recommended the day of breeding.

Rats: Ototoxicity has been shown to be a risk even before the auditory organs have begun to function in developing rats.[R-188]

Lactation

Because of poor lipid solubility, aminoglycosides have relatively poor penetration from plasma into milk.[R-22; 26] In general, parenteral administration of gentamicin has not been shown to produce therapeutic milk concentrations (greater than 3 to 5 mcg/mL) for the treatment of most gram-negative mammary pathogens.[R-22; 23; 25] At any one time, approximately 10 to 15% of plasma gentamicin levels may appear in milk.[R-22; 26] Intramammary administration of gentamicin to cows with experimental mastitis results in significant systemic absorption (88%), leading to long persistence of drug residues in some tissues, such as renal tissue.[R-23; 26]

Apramycin—*Cows, goats,* and *sheep:* Apramycin has limited distribution from parenteral administration into milk in healthy glands.[R-163] It is distributed into bovine milk at higher concentrations during acute clinical mastitis, but it is not known if concentrations would be high enough to have clinical effect without significant residue and toxicity considerations.[R-163]

Dihydrostreptomycin—*Cows:* When administered at an intramusuclar dose of 11 mg/kg, dihydrostreptomycin is irregularly distributed into the milk for at least 18 hours.[R-247]

Gentamicin—*Cows:* With an intramuscular dose of 5 mg/kg, a peak concentration of 1.5 to 1.8 mcg/mL is measured 2 to 6 hours after administration.[R-22; 26]

Pediatrics

The susceptibility of young animals to toxicity from aminoglycosides may be species-specific and drug-specific. Young dogs, rabbits, and rats have shown resistance to gentamicin nephrotoxicity in some studies,[R-177; 219] while 2- to 3-month-old foals may be more susceptible than adults to toxicity.[R-208; 219] The renal function of young rats, 21-days old, was more strongly affected by the administraton of amikacin than was the renal function of adults given the same dose.[R-192]

Young animals typically have a higher percentage of extracellular water and, therefore, have a higher volume of distribution compared with adults. Higher doses may be necessary in animals less than 6 weeks old compared with adults.[R-266]

Very young animals may absorb significant amounts of orally administered apramycin or neomycin. See *Absorption,* above in this monograph.

Geriatrics

In a case report study of dogs, advanced age of more than 8 years appeared to be a risk factor in susceptibility to gentamicin nephrotoxicity.[R-215] However, it is not known if these dogs had subclinical renal compromise, which is known to increase the nephrotoxicity of gentamicin,[R-217] or some other dysfunction associated with aging.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Aminoglycosides, two or more concurrently[R-91]
(concurrent administration may increase the risk of ototoxicity, nephrotoxicity, or neuromuscular blockade)

Calcium
(intravenous calcium supplementation may decrease nephrotoxicity associated with aminoglycosides; in horses, 20 mg of intravenous calcium gluconate per kg of body weight administered every 12 hours decreased nephrotoxicity of high dose gentamicin [20 mg/kg every 8 hours for 14 days] administered to adult ponies)[R-223]

Calcium channel blocker
(an increased risk of neuromuscular blockade may occur with concomitant administration with an aminoglycoside)[R-232]

Halothane anesthesia
(horses administered gentamicin, 4 mg/kg, while under halothane anesthesia have significant changes in the pharmacokinetics of gentamicin; total body clearance and volume of distribution decrease while half-life of elimination increases; a longer gentamicin dosing interval after anesthesia may help correct for the changes, but serious consideration should be given to choice of another antimicrobial)[R-204]

Iron, supplemental
(the risk of auditory and renal toxicity might be increased when aminoglycosides are administered with iron supplements; guinea pigs administered gentamicin at 100 mg/kg a day for 30 days showed a more rapid and profound hearing loss within the treatment period with concurrent administration of supplemental iron at a dose of 2 to 6 mg/kg a day; the effect was iron dose–dependent;[R-198] a study in rats showed increased renal tubular damage when gentamicin was administered at a dose of 100 mg/kg a day to rats given iron supplementation)[R-202]

Ketorolac,[R-224]

Phenylbutazone,[R-203] or

Nonsteroidal anti-inflammatory drugs (NSAIDs), other
(in one study, concurrent administration of phenylbutazone with gentamicin to horses affected the pharmacokinetics of gentamicin by decreasing the half-life of elimination by 23% and decreasing the volume of distribution [area] by 26%; the pharmacokinetics of phenylbutazone did not appear to be affected;[R-203] also, the nephrotoxic potential of NSAIDs can increase the risk of renal toxicity, as ketorolac does when administered to rats concurrently with gentamicin;[R-224] however, flunixin was shown to have no effect on the pharmacokinetics of gentamicin when administered concurrently to adult horses[R-265])

Loop diuretics, including[R-143]
  Ethacrynic acid[R-143; 197; 229] or
  Furosemide[R-91; 185; 207]
(because these medications can cause ototoxicity in patients with

renal compromise, the risk of potentiating toxicity during
concurrent use with aminoglycosides should be considered;[R-143]
concurrently administered systemic gentamicin and ethacrynic
acid causes more profound ototoxicity in guinea pigs than either
drug administered alone[R-229])

Nephrotoxic medications, other or
Ototoxic medications, other
    (concurrent use may increase the risk of ototoxicity or
    nephrotoxicity)
Neuromuscular blocking agents or drugs with neuromuscular blocking
    activity,[R-186; 187; 199-201] other
    (concurrent use with aminoglycosides can increase the risk of
    neuromuscular blockade, particularly during anesthesia[R-186] but
    there may be little clinical significance; administration of
    gentamicin [2 to 6 mg/kg dose] does potentiate the neuromuscular
    blocking effect of atracurium in inhalant-anesthetized cats, dogs,
    and horses; however, minimal to no effect on recovery from
    anesthesia was noted;[R-199-201] edrophonium reversed any
    remaining neuromuscular block during recovery;[R-199-201] calcium
    supplementation can also help reverse neuromuscular blockade
    [see *Treatment of overdose*])

Human drug interactions[R-255]

In addition to the above drug interactions reported in animals, the
    following drug interactions have been reported in humans, and are
    included in the human monograph, *Aminoglycosides (Systemic)* in
    USP DI Volume I; these drug interactions are intended for
    informational purposes only and may or may not be applicable to
    the use of aminoglycosides in the treatment of animals:
Antimyasthenics
    (concurrent use of medications with neuromuscular blocking
    action may antagonize the effect of antimyasthenics on
    skeletal muscle; temporary dosage adjustments of
    antimyasthenics may be necessary to control symptoms of
    myasthenia gravis during and following use of medications
    with neuromuscular blocking action)
Beta-lactam antibiotics
    (aminoglycosides can be inactivated by many beta-lactam
    antibiotics [cephalosporins, penicillins] *in vitro* and *in vivo* in
    patients with significant renal failure; degradation depends on
    the concentration of the beta-lactam agent, storage time, and
    temperature)
Indomethacin, intravenous
    (when aminoglycosides are administered concurrently with
    intravenous indomethacin in the premature neonate, renal
    clearance of aminoglycosides may be decreased, leading to
    increased plasma concentrations, increased elimination half-
    lives, and risk of aminoglycoside toxicity; dosage adjustment
    of aminoglycosides based on measurement of plasma
    concentrations and/or evidence of toxicity may also be
    required)
Methoxyflurane or
Polymyxins, parenteral
    (concurrent and/or sequential use of these medications with
    aminoglycosides should be avoided since the potential for
    nephrotoxicity and/or neuromuscular blockade may be
    increased; neuromuscular blockade may result in skeletal
    muscle weakness and respiratory depression or paralysis
    [apnea]; caution is also recommended when methoxyflurane
    or polymyxins are used concurrently with aminoglycosides
    during surgery or in the postoperative period)

Laboratory value alterations

The following have been selected on the basis of their potential
    clinical significance (possible effect in parentheses where
    appropriate)—not necessarily inclusive (» = major clinical
    significance):
With physiology/laboratory test values
    Aspartamine aminotransferase (AST [SGOT]), serum and
    Lactate dehydrogenase (LDH), serum

(in galahs [cockatoos] and macaws, values are reported to
increase with therapeutic gentamicin administration of 5
mg/kg every 12 hours)[R-205]

Human laboratory value alterations[R-255]

In addition to the above laboratory value alterations, the following
    alterations have been reported in humans, and are included in the
    human monograph *Aminoglycosides (Systemic)* in the *USP DI
    Volume I;* these laboratory value alterations are intended for
    informational purposes only and may or may not be applicable to
    the use of aminoglycosides in animals:
With physiology/laboratory test values
    Alanine aminotransferase (ALT [SGPT]), serum and
    Alkaline phosphatase, serum and
    Aspartate aminotransferase (AST [SGOT]), serum and
    Bilirubin, serum and
    Lactate dehydrogenase (LDH), serum
        (values may be increased)
    Blood urea nitrogen (BUN) and
    Creatinine, serum
        (concentrations may be increased)
    Calcium, serum and
    Magnesium, serum and
    Potassium, serum and
    Sodium, serum
        (concentrations may be decreased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been
    selected on the basis of their potential clinical significance
    (reasons given in parentheses where appropriate)—not necessarily
    inclusive (» = major clinical significance).

***Except under special circumstances, this medication should not be
    used when the following medical problems exist:***
»   Dehydration, hypovolemic[R-5; 91]
    (hypovolemic animals can have increased susceptibility to
    renal
    toxicity and should be rehydrated prior to treatment with
    aminoglycosides;[R-91] however, clinicians may administer the
    first dose of aminoglycoside to treat life-threatening
    infections while rehydration is in progress[R-262])
»   Hypersensitivity to aminoglycosides[R-7; 92; 93]
    (a previous reaction to one aminoglycoside may
    contraindicate use of the same or other aminoglycosides due
    to cross-sensitivity)
»   Renal dysfunction[R-91]
    (alternative antimicrobials should be considered in animals
    with
    severe renal compromise and/or renal azotemia;[R-5] because
    they lack the ability to compensate, even dogs with
    subclinical
    renal dysfunction can develop nonreversible acute renal
    failure
    from a dose that produces only mild polyuria in dogs with
    healthy kidneys;[R-213; 214] if an aminoglycoside must be given,
    increasing the dosing interval is more effective in preventing
    toxicity than decreasing the dose[R-217])

***Risk-benefit should be considered when the following medical
    problems exist:***
Cardiac dysfunction
    (gentamicin may exacerbate a decreasing heart rate or
    depression
    of blood pressure)[R-5]
Endotoxemia
    (even a low serum concentration of endotoxin may increase
    the
    toxicity of the aminoglycosides by increasing their
    concentration
    in the kidneys;[R-184] the administration of an aminoglycoside
    to treat gram-negative bacterial infections may also increase

the
amount of endotoxin released;[R-184] see the *Veterinary Dosing Information* section)

Hypocalcemia
(although the clinical impact is not clear, aminoglycosides, including dihydrostreptomycin and neomycin, have been shown to decrease the total blood calcium concentration in cattle by decreasing the protein-bound calcium;[R-187] this effect caused signs of hypocalcemia in 77% of lactating cows treated with 4.5 mg of intravenous neomycin per kg of body weight[R-187])

Potential risk factors for acute renal failure,[R-185; 215] other, including
Acidosis
Advanced age
Diabetes mellitus
Dirofilarial infection[R-91]
Electrolyte imbalances
Fever
Hepatic dysfunction
Hyperviscosity syndromes
Hypoalbuminemia
Hypotension
Sepsis
Septicemia
Trauma, severe
(level of risk of nephrotoxicity with administration of aminoglycosides can be difficult to assess, but caution is indicated in animals with one or several factors associated with increased risk, such as those affecting renal perfusion)
Pyelonephritis
(rats with infected kidneys are more susceptible to gentamicin toxicity than healthy rats)[R-226]

Patient monitoring
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Aminoglycoside, serum concentration
(because of the risk of nephrotoxicity and the wide variability in drug disposition, it is recommended that, whenever possible, serum aminoglycoside concentration should be monitored in animals receiving repeated doses, and dosage adjustments made;[R-55; 56] when multiple dosing is done in a 24-hour period, peak and trough concentrations have been considered the most helpful with the least number of tests.[R-57] With once-daily dosing, serum concentrations are more typically measured at 1 and 2 hours or 2 and 4 hours after the daily dose.[R-266] Many sources recommend serum concentrations be allowed to drop below 1 mcg/mL for gentamicin and below 2.5 to 5 mcg/mL for amikacin for an extended period within a dosing interval to reduce the risk of toxicity.[R-47; 51; 63; 148; 185; 209; 230])

Renal function tests[R-91]
(serial urinalyses may be the most sensitive tests for renal toxicosis in spite of the fact that no early urinary test has been developed that can consistently warn clinicians when serious renal toxicity occurs; serial urinalyses may be monitored for decreased specific gravity in the absence of fluid therapy or appearance of casts, protein, albumin, glucose, or blood in the absence of leukocytes and bacteria;[R-208] proteinuria may be seen within 24 hours with extremely high toxic doses;[R-206] early indication of nephrotoxicity may be possible with the ratio of urinary gamma glutamyltranspeptidase to urinary creatinine excretion [UGGT/U_{Cr}]; this enzyme concentraton ratio is increased to three times the baseline within 2 to 3 days of a nephrotoxic gentamicin dose of 30 mg/kg;[R-206; 209; 210; 211] however, because even a single dose of gentamicin can cause some renal tubule changes, elevations in the UGGT/U_{Cr} ratio may occur without subsequent severe kidney damage; therefore, some clinicians believe that other tests may be needed to decide if gentamicin therapy must be discontinued;[R-210; 220; 221] serum creatinine, creatinine clearance tests, specific gravity, blood urea nitrogen and/or clinical signs of nephrotoxicity may not be diagnostic of severe kidney damage for at least 7 days[R-206; 210; 216])

Side/Adverse Effects
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention
Incidence more frequent
All species
Nephrotoxicity;[R-7; 212] *ototoxicity, auditory; ototoxicity, vestibular*

Note: Evidence of physiological effects on the kidneys has been demonstrated with a single dose of gentamicin at 15 mg per kg of body weight (mg/kg) in 5-month-old beagles, although clinical disease is not necessarily produced.[R-209; 212] It is assumed that renal damage associated with aminoglycoside administration runs a range from mild, subclinical changes to more severe *nephrotoxicity,* to acute renal failure.[R-209; 212] The animal's ability to recover most likely depends on the type of medication exposure and the amount of healthy renal tissue remaining to compensate.[R-213] Neomycin is considered the most nephrotoxic aminoglycoside, dihydrostreptomycin and streptomycin the least nephrotoxic, and the other common aminoglycosides included in this monograph are considered somewhere between those three drugs in their toxicity.[R-254] Aminoglycoside administration is, as a rule, immediately withdrawn when evidence of renal damage is found; however, many signs of toxicity may be delayed for some time after significant damage has occurred.

Although renal toxicity is dependent on the concentration of aminoglycoside in the renal cortex, many variables can affect how much of the medication reaches the cortex and how serious the effects will be, making it difficult to consistently predict which animal is likely to develop clinical toxicity with a particular therapeutic dosage regimen.

Aminoglycosides cause nephrotoxicity by accumulating in the proximal tubular cells and, once there, interfering with cellular metabolism and transport processes.[R-218; 225] The tubular changes can progress to proximal tubular necrosis with increasing exposure to the drug. Fairly late in the process, glomerular filtration rate is affected and azotemia appears.[R-225] These changes may simultaneously occur at different rates in different parts of the renal cortex, making it possible to have both reabsorption defects and glomerular filtration rate reduction at the same time.[R-225]

The toxic renal changes caused by gentamicin and other aminoglycosides will decrease elimination of the antibiotic and increase serum antibiotic concentrations, thereby increasing the potential toxicity.[R-57; 209] Elimination half-lives of 24 to 45 hours have been reported in the horse with renal toxicity, prolonging the toxic exposure to the drug.[R-57] While peritoneal dialysis is useful in lowering creatinine and blood urea nitrates, it may not be effective in significantly speeding the elimination of the accumulating aminoglycoside.[R-57] If there is enough healthy tissue remaining in the kidneys, acute renal failure may be reversible by regeneration and hypertrophy of remaining tissue.[R-193; 213] Dogs with subclinical renal dysfunction are more sensitive to the toxicity of gentamicin; they develop oliguria and acute renal failure that may not be reversible from a high gentamicin dose that produces only mild polyuria in dogs with healthy kidneys.[R-213; 214] Therefore, merely adjusting dosage regimens to compensate for renal dysfunction may not be sufficient to avoid toxicity. Careful selection of candidates for aminoglycoside therapy and a dosage regimen designed to minimize risk of nephrotoxicity is recommended.

Some aminoglycosides are more likely to cause *auditory ototoxicity* and others are more likely to cause *vestibular ototoxicity*.[R-7] This may be due to the distribution characteristics of each drug and its ability to concentrate in each sensory organ.[R-183] As demonstrated in studies on guinea pigs,[R-183; 190] amikacin and dihydrostreptomycin are more toxic to the cochlea than to vestibular organs.[R-183; 190; 191; 233] Neomycin causes severe cochlear toxicity.[R-233] Studies in guinea pigs have shown that auditory toxicity is often delayed,[R-189] requiring at least 4 days after administration of a toxic dose for hearing loss to be measurable.[R-189] This period of delay may shorten with higher doses.[R-189] Vestibular toxicity is more often seen than auditory toxicity with streptomycin.[R-233]

Incidence less frequent or rare
All species
   Neuromuscular blockade[R-7]
   Note: *Neuromuscular paralysis*[R-7] is considered rare compared with the nephrotoxic and ototoxic effects of aminoglycosides.[R-232] The neuromuscular blocking effects of dihydrostreptomycin, gentamicin, neomycin, and streptomycin at a dose of 14 to 43 mg/kg have been demonstrated during pentobarbital anesthesia (28 to 32 mg/kg) in nonhuman primates.[R-186] However, respiratory depression and apnea occurred only at the highest antibiotic dosages.[R-186] Neuromuscular blockade and respiratory paralysis have been reported in response to high doses of gentamicin (40 mg/kg) in the cat.[R-7] The postsynaptic blocking component of this effect can be reversed by a cholinesterase inhibitor, such as neostigmine, and the apparent presynapic effect can be antagonized by the administration of calcium.[R-186]

Those indicating need for medical attention only if they continue or are bothersome
Incidence more frequent
Birds
   Local tissue trauma, mild—at site of injection[R-86]
Incidence rare
Dogs
   Diarrhea—with amikacin;[R-91] *vomiting*—with amikacin[R-91]
Incidence unknown
Calves and *pigs*
   Diarrhea—seen in animals given oral doses of apramycin or neomycin that are higher than the label dose[R-96; 241]
Cats, and *dogs*
   Local tissue trauma, mild—at site of injection, with amikacin or gen-tamicin[R-5; 91; 93; 139]

Human side/adverse effects[R-255]
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph *Aminoglycosides (Systemic)* in *USP DI Volume I*; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of aminoglycosides in the treatment of animals:
Incidence more frequent
   Nephrotoxicity; neurotoxicity; ototoxicity, auditory; ototoxicity, vestibular; peripheral neuritis—only with streptomycin
 Incidence less frequent
   Hypersensitivity; optic neuritis—only with streptomycin
Incidence rare
   Endotoxin-like reaction—gentamicin only; ***neuromuscular blockade***
   Note: Neuromuscular blockade, respiratory paralysis, ototoxicity, and nephrotoxicity may occur following local irrigation or topical application of aminoglycosides during surgery. Because of its potential toxicity, use of parenteral neomycin is not recommended.

Overdose
For more information on the management of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer.**

General considerations
When systemically absorbed, the aminoglycosides have the potential to cause nephrotoxicity, neurotoxicity, or ototoxicity.[R-91] This includes absorption through irrigation of tissues in surgery and sometimes from topical application.[R-91] Because of the narrow therapeutic index, the margin between therapeutic concentrations and toxic concentrations, for aminoglycosides used in animals, toxicity is a potential risk in the best of circumstances. The minimum gentamicin dose required to produce nephrotoxicity is variable between species and between animals[R-212] and the data listed in this section cannot clearly define the dose that will produce serious toxicity in a particular animal.
Toxic dose—Information about toxicity of the aminoglycosides has been drawn primarily from human therapeutic literature. It has been reported that minimum serum concentrations within a dosing interval of greater than 2 mcg/mL for gentamicin and greater than 2.5 to 5 mcg/mL for amikacin significantly increase the risk of toxicity.[R-148; 185; 209] Persistant peak serum concentrations of gentamicin greater than 10 to 12 mcg/mL or of amikacin greater than 30 to 40 mcg/mL are also considered to increase the risk of toxicity.[R-230]
  Amikacin:
    Dogs—Renal toxicity: Minimal to mild renal changes are seen with a dose of 45 mg per kg of body weight (mg/kg) a day for 2 weeks[R-91] or 30 mg/kg a day for 90 days.[R-91]
    Guinea pigs: Auditory and vestibular ototoxicity—
      Marked hearing loss—150 to 225 mg/kg a day in divided doses every 8 hours for 1 week.[R-190; 191]
      Hearing loss, less pronounced—When the 150 mg/kg dose was administered every 24 hours for 7 to 21 days, there was a significant decrease in vestibular and auditory damage.[R-190; 191]
  Apramycin:
    Chickens—
      No effect: With a dose of 50 mg per kg of feed, fed as the only ration, no toxic signs are noted.[R-195]
      With a dose of 150 to 250 mg per kg of feed, a reduction in serum hemoglobin and erythrocytes may be noted, as well as dystrophic changes in the internal organs.[R-195]
    Dogs—No effect: Chronic administration yielded no toxicity with 50 parts per million (ppm) fed to dogs for 1 year.[R-96]
    Pigs—
      No effect: With a dose of up to 300 mg per liter of drinking water for 15 days, no signs of toxicity were noted.
      With a dose of 500 to 1000 mg per liter of drinking water (5 to 10 times the label dose) for more than 15 days, some animals developed a drop in the percentage of neutrophils and an increase in lymphocyte percentage in the complete blood count.[R-194]
    Rats—No effect: Chronic administration yielded no toxicity with 10,000 ppm fed to rats for 2 years.[R-96]
  Gentamicin: Renal—
    Cats:
      No significant effect—A dose of 4.4 mg/kg every 12 hours for 12 days produced no significant effects.[R-228]
      Toxic effect—Only mild nephritis was produced by 20 mg/kg a day administered subcutaneously for 70 days.[R-227]

Dogs: Toxic effect—A parenteral dose of 30 mg/kg a day for 10 days (or 10 mg/kg every 8 hours for 8 days) produced evidence of renal toxicity, including elevated serum urea nitrogen concentration, elevated serum creatinine, proteinuria, decreased urine specific gravity, decreased exogenous creatinine clearance, decreased glomerular filtration rate, and histological evidence of renal toxicity.[R-95; 175]

Foals: Toxic effect—Nephrotoxicity occurred in one of twelve foals given 17.6 mg/kg every 12 hours and one of twelve given 8.8 mg/kg every 12 hours for 15 days.[R-218]

Hawks, red tailed: Toxic effect—An intravenous dose of 10 mg/ kg every 12 hours for 4 days caused significantly increased serum uric acid concentrations.[R-87]

Lambs: Toxic effect—An intravenous dose of 80 mg/kg a day for up to 20 days produced renal tubular necrosis and dilation.[R-206] Serum creatinine concentrations of up to 132 micromoles per liter were measured beginning 14 days, on average, after initiation of therapy.[R-206]

Streptomycin: *Cats*—
No effect: A dose of 25 mg/kg a day, administered for 9 to 28 days, did not cause signs of toxicity.[R-246]

Toxic effect: An intramuscular dose of 50 mg/kg a day, divided into doses administered every 8 hours for 9 to 28 days, produced nonreversible hearing loss in most cats.[R-246] A dose of 200 mg/kg produced both permanent hearing loss and vestibular impairment.[R-246]

Lethal dose—
Note: These doses have been reported as lethal but are not necessarily the minimum lethal dose in a particular animal. No effect is listed if the research was intended to define a lethal dose.

Amikacin: LD$_{50}$—*Dogs:* Intramuscular or intravenous, > 250 mg/kg.[R-91]

Apramycin:
Chickens and *dogs*—No effect: No mortality was observed with 520 mg/kg as a single dose in chickens and dogs.[R-96]

Mice—In mice, greater than 5200 mg/kg as a single dose produced no mortality.[R-96]

Gentamicin:
Cats—40 to 70 mg/kg a day administered subcutaneously caused renal necrosis and death within 10 days.[R-227]

Hawks, red-tailed—An intravenous dose of 20 mg/kg every 12 hours was lethal for all five birds in 2 to 6 days; predominant signs were indicative of neuromuscular blockade.[R-87]

Clinical effects of overdose
The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:
Note: The following overdose effects mirror the side/adverse effects listed in this monograph because of the small therapeutic index for aminoglycosides. These effects may occur in some animals with therapeutic doses so that most animals treated should be monitored for adverse effects. These are also dose-related effects, however, with risk increasing as the dose rises above recommended levels.[R-7]
All species
Nephrotoxicity;[R-7; 212] *neuromuscular blockade; ototoxicity, auditory; ototoxicity, vestibular*

Treatment of overdose
Recommended treatment consists of the following:
Note: Some experts suggest that administration of a beta-lactam antibiotic that binds an aminoglycoside (ticarcillin, for example) will decrease the toxicity after accidental overdose of aminoglycosides.[R-266]
For neuromuscular blockade
• Administration of edrophonium, 0.5 mg/kg, will reverse

neuromuscular blocking effects.[R-200; 201] Administration of calcium chloride at 10 to 20 mg/kg, calcium gluconate at 30 to 60 mg/kg, or neostigmine at a dose of 100 to 200 mcg per kg of body weight can also reverse muscle response depression and associated dyspnea.[R-186]
For renal toxicity
• Aminoglycoside administration should be immediately discontinued.[R-208]
• Polyionic electrolyte fluid therapy should be initiated to stimulate diuresis.[R-208]
Note: Three or more weeks of therapy may be required for recovery in animals with sufficient remaining renal tissue to compensate.[R-215] Oliguria may be a poor prognostic sign.[R-215]

Client Consultation
There are reports that aminoglycosides, such as neomycin or streptomycin, can cause contact dermatitis in human beings.[R-236] Direct contact with skin should be avoided by people handling these products.[R-236]

General Dosing Information
Resistance: Reports of antimicrobial resistance support recommendations to culture pathogens to be sure the use of an aminoglycoside is warranted. There is also some evidence that limiting the use of aminglycosides and, in particular, limiting administration at subtherapeutic concentrations to a population of animals may limit the increase in *E. coli* resistance that is seen with more intense antimicrobial use.[R-234]

For parenteral dosage forms only
Systemic aminoglycosides are generally dosed to achieve a high peak serum concentration followed by a period of subtherapeutic serum concentration. This strategy is built on several factors:
1) Aminoglycosides kill bacteria by a concentration-dependent mechanism[R-80] rather than dependence on the length of time the organism is exposed to the antibiotic.[R-160] A spike in concentration[R-80; 232] or, in some situations, a plateau[R-155; 157] above the minimum inhibitory concentration is neccessary for effective bacterial killing.
2) A high peak of antibiotic will cause the most killing of bacteria and will also cause the most prolonged postantibiotic effect (PAE), in which pathogen growth is inhibited after the serum concentration falls below minimum inhibitory concentrations.[R-80] The PAE has been shown to occur when amikacin or gentamicin is administered to treat gram-negative infections.[R-174] Postantibiotic effect may be evidence that exposure to a high concentration of antimicrobial causes cellular changes in the pathogen that will inevitably cause death after drug concentrations have dropped below the MIC.[R-158] The PAE may be shortened in neutropenic animals but prolonged in animals with renal impairment.[R-174]
3) An extended period of serum drug concentrations below a minimum amount is expected to decrease the risk of aminoglycoside toxicity.
Dosing is usually designed to produce peaks above the MIC and troughs below a minimum concentration to prevent adverse effects, regardless of the frequency of dosing within a 24-hour period. Many sources recommend serum concentrations be allowed to drop below 2 mcg/mL for gentamicin and to less than 2.5 to 5 mcg/mL for amikacin for an extended period within a dosing interval to reduce the risk of toxicity.[R-47; 51; 63; 148; 185; 209; 230] A plasma or serum concentration of at least 8 to 10 times the MIC of the organism has been recommended for aminoglycoside antibiotics to be effective.[R-155]
Individualized dosing/Patient monitoring: Even within the same species, individual animals can differ widely in the serum concentrations produced from the same dosage regimen.[R-83; 89; 213;

230} When this relative unpredictability is combined with the often small difference between therapeutic and toxic serum concentrations of aminoglycosides, the determination of serum concentrations in a particular animal becomes very valuable. When it is economically possible to measure plasma or serum concentrations during aminoglycoside therapy, the information can be used to maximize efficacy and minimize toxicity.[R-130-132]

Note: There can be up to a fourfold difference between avian species in the elimination of gentamicin.[R-85] It is recommended that species-specific pharmacokinetic data be used to develop dosing for birds, if at all possible.[R-148]

Once daily dosing: The continuing effort to maximize therapeutic effect and minimize toxic effect of aminoglycosides has led to ongoing research on the efficacy of a 24-hour dosing interval.[R-160; 232; 252] Dosing once a day is considered by some clinicians to be a rational use of aminoglycosides in specific situations.[R-232] The supporting arguments include that use of the highest safe single dose has been linked to increased efficacy in human studies, greater bacterial killing and a longer postantibiotic effect are expected with a higher peak concentration, and once-a-day dosing allows for the longest period of low serum concentration to minimize toxicity.[R-160; 232; 252]

Concern has been expressed that dosing once every 24 hours may be less effective than repeated daily dosing in some situations, such as in immunocompromised patients.[R-158] Studies with guinea pigs have demonstrated no significant difference in bacterial killing between gentamicin administered subcutaneously at 6 mg/kg every 24 hours versus 2 mg/kg every 8 hours.[R-80] However, once-a-day dosing has been less effective in treating some infections in neutropenic animals.[R-158; 232] Some researchers have demonstrated a potential for development of resistance with dosing once a day;[R-232] but others have described an adaptive resistance to aminoglycosides in *Pseudomonas* species that occurs with doses repeated within 16 hours in animal models but that is reduced by longer dosing intervals in the first 3 days.[R-160] Some clinicians have expressed reservations about once-daily dosing when intestinal damage allows continued exposure to bacteria that may replicate during the prolonged periods of subtherapeutic aminoglycoside concentration.[R-263]

Desired benefits include reduction of toxicity. If the total daily dose of aminoglycoside is kept constant, less frequent dosing per day is associated with decreasing renal toxicity.[R-232] The same is true for gentamicin ototoxicity in guinea pigs but, while the single daily dose has not been shown to be more toxic for amikacin in guinea pigs, the benefit in reducing ototoxicity is less clear.[R-190; 191; 232]

Renal dysfunction: Treatment with gentamicin every 8 hours is not recommended in patients with subclinical renal disease.[R-72] Because drug clearance may be slowed with gentamicin treatment, the risk of nephrotoxicity may be increased. Trough serum concentrations can be reduced by increasing the dosing interval and decreasing the dose.[R-185] Some clinicians have developed methods to calculate an increased dosing interval based on the creatinine clearance concentration; however, the most prudent course may be to avoid use of aminoglycosides if it is necessary to significantly reduce the aminoglycoside dose because of poor renal function.[R-72]

Endotoxemia: Producing high serum and tissue concentrations of aminoglycoside as early as possible in animals with gram-negative sepsis is important.[R-72] The release of endotoxin by gram-negative organisms may be enhanced by administration of the antibiotic.[R-184] The systemic effects of endotoxemia will also increase the risk of concentrating aminoglycosides in the renal tissue and causing acute renal failure.[R-185]

Diabetes mellitus: It appears that diabetic dogs may have increased clearance of gentamicin and reduced volume of distribution (Vol_{Dss}) of gentamicin, which make them less susceptible to nephrotoxicity at therapeutic doses of the medication;[R-71] however, the possibility of subclinical renal disease should also be considered.

Concurrent fluid administration: In horses, the administration of therapeutic fluids, similar to those that are used in the treatment of colic, does not significantly change the pharmacokinetics of concurrently administered gentamicin.[R-45]

Gastointestinal microflora: Parenterally administered amikacin appears to have minimal effect on gastrointestinal microflora in horses.[R-136]

Gastrointestinal surgery: When gentamicin administration (4 to 6.6 mg/ kg every 24 hours) is begun immediately after abdominal surgery for naturally occurring colic, the pharmacokinetics of the gentamicin has been measured to be within the reference range for normal healthy horses.[R-265]

For oral dosage forms only

Chickens: Because poultry litter may contain bacteria with multiple antibiotic resistance, treatment of litter to prevent contamination before reutilization in soil or bedding is recommended.[R-121]

Diet/Nutrition

Dogs: Dogs with normal renal function consuming a higher protein diet (26%) for 3 weeks before treatment have a faster gentamicin clearance and a larger volume of distribution than dogs fed a medium (13%) or low (9%) protein diet.[R-73]

Horses: Horses fed an alfalfa diet rather than oats alone have a smaller degree of nephrotoxicosis from administration of gentamicin.[R-222]

Likewise, horses administered supplemental calcium gluconate, 20 mg/kg every 12 hours, have a decreased risk of acute renal failure from gentamicin overdose compared with horses not receiving calcium.[R-223]

Sheep: Sheep fed a low protein diet (straw and barley) have a significantly lower total clearance and volume of distribution at steady state than sheep fed a high protein diet (alfalfa and barley). This results in an increased serum concentration of gentamicin in the group fed a low protein diet.[R-38]

AMIKACIN

Summary of Differences

Category: Aminoglycoside

Indications: General considerations—Has the broadest spectrum of activity of the aminoglycosides and is considered effective against strains not susceptible to other aminoglycosides.

Side/adverse effects: Intermediate renal toxicity. More toxic to the cochlea than to vestibular organs. Diarrhea and vomiting in dogs. Mild local tissue trauma in cats and dogs.

Mucosal Dosage Forms

AMIKACIN SULFATE UTERINE SOLUTION

Usual dose: Uterine infections—*Horses:* Intrauterine, 2 grams, administered every twenty-four hours for three days.[R-92; 105; 138] The medication should be mixed with 200 mL of 0.9% sodium chloride injection before administration.[R-92]

Withdrawal times—U.S. and Canada: Product is not labeled for use in horses intended for human consumption.[R-92]

Note: Product labeling recommends that mares not be bred for eight hours after intrauterine treatment with amikacin.[R-92]

Strength(s) usually available:[R-231]

U.S.—

Veterinary-labeled product(s):

250 mg per mL (Rx) [*Amifuse E; Amiglyde-V Intrauterine Solution;*[R-92] *Amikacin E Solution; Equi-Phar EquiGlide;* GENERIC].

Note: These products contain 0.1 mg benzethonium chloride per mL as a preservative.[R-92]

Canada—
Veterinary-labeled product(s):
250 mg per mL (Rx) [*Amiglyde-V*].

Stability: A change from a colorless solution to pale yellow in color does not indicate a decrease in potency of the antimicrobial.[R-92]

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.

USP requirements: Not in USP.[R-19]

Parenteral Dosage Forms
Note: The text between EL US and EL describes uses not included in U.S. product labeling. Text between EL CAN and EL describes uses that are not included in Canadian product labeling.

The EL US or EL CAN designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

AMIKACIN SULFATE INJECTION USP
Note: Intravenous administration—When amikacin is administered by the intramuscular or subcutaneous route, it is rapidly and completely absorbed. Although not always listed on product labeling, this medication is also commonly administered intravenously. An indwelling catheter is used for convenience and to minimize the discomfort of repeated dosing.[R-263] To further decrease the risk of neuromuscular blockade, it is recommended that the drug be diluted in saline or administered slowly.[R-263]

Usual dose:
EL US,CAN Bacteremia EL;
EL US,CAN Bone and joint infections EL;
EL US,CAN Respiratory tract infections EL;
EL US,CAN Septicemia EL;
EL CAN Skin and soft tissue infections EL;
EL CAN Urinary tract infections EL; or
EL US,CAN Uterine infections EL—*Dogs:*
    Intramuscular or subcutaneous, 10 mg per kg of body weight every eight to twelve hours.[R-91; 143]
    Once-daily dosing—Intramuscular or subcutaneous, 15 to 30 mg per kg of body weight every twenty-four hours.[R-266]
EL US,CAN Bacteremia EL;
EL US,CAN Bone and joint infections EL;
EL US,CAN Respiratory tract infections EL;
EL US,CAN Septicemia EL;
EL US,CAN Skin and soft tissue infections EL;
EL US,CAN Urinary tract infections EL; or
EL US,CAN Uterine infections—*Cats:*
    Intramuscular or subcutaneous, 10 mg per kg of body weight every eight hours.[R-139; 140; 264]
    Once-daily dosing—Intramuscular or subcutaneous, 10 to 15 mg per kg of body weight every twenty-four hours.EL[R-266]

Note: EL US,CAN *Calves*—Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations should be considered before the extra-label use of aminoglycosides in food-producing animals: Although the safety and efficacy of amikacin have not been established, a dose of 12 mg per kg of body weight every twelve hours has been suggested for use in the treatment of susceptible *bacterial infections.*EL[R-141; 144]
EL US,CAN *Donkeys* EL and EL US,CAN *ponies*—Although the safety and efficacy of amikacin have not been established, a dose of 6 mg per kg of body weight every six hours, administered intravenously, has been recommended in the treatment of *bacterial infections* in donkeys and ponies.EL[R-136]

EL US,CAN *Foals*, less than 30 days of age—Although the safety and efficacy of amikacin have not been established, a dose of 20 to 25 mg per kg of body weight every twenty-four hours, administered by the intramuscular or intravenous route, has been recommended in the treatment of susceptible *bacterial infections* in foals.EL[R-6; 9; 130-132; 134; 266]

EL US,CAN *Goats*—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy of amikacin have not been established, a subcutaneous dose of 8 mg per kg of body weight every twelve hours has been suggested in the treatment of susceptible *bacterial infections* in goats.[R-151] In one study, this was predicted to provide peak serum concentrations of 32.3 mcg/mL.EL[R-151]

EL US,CAN *Guinea pigs*—Although the safety and efficacy of amikacin have not been established, an intramuscular dose of 15 mg per kg of body weight every twelve hours has been suggested for the treatment of susceptible *bacterial infections* in guinea pigs.EL[R-152]

EL US,CAN *Hawks, red-tailed*—Although the safety and efficacy of amikacin have not been established, a dose of 15 to 20 mg per kg of body weight every twenty-four hours or 7 to 10 mg per kg of body weight every twelve hours, administered intramuscularly, has been suggested for the treatment of susceptible *bacterial infections* in red-tailed hawks.[R-147] This recommendation is based on pharmacokinetic data; it was also noted that larger birds tended to develop lower peak serum drug concentrations than smaller birds in response to the same dose.EL[R-147]

EL US,CAN *Horses* EL and EL US,CAN *foals*, more than 30 days of age—Although the safety and efficacy have not been established, an intramuscular or intravenous dose of 10 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible *bacterial infections,* based on pharmacokinetic data.[R-6] For some infections in horses, dosing more than once a day may still be necessary and, in those cases, an intravenous dose of 6 mg per kg of body weight every eight hours has been recommended.EL[R-136]

EL US,CAN *Parrots,* African gray—Although the safety and efficacy of amikacin have not been established, an intravenous or intramuscular dose of 10 to 20 mg per kg of body weight every eight to twelve hours has been recommended in the treatment of susceptible *bacterial infections,* based on pharmacokinetic data.EL[R-150]

EL US,CAN *Pythons,* ball—Although the safety and efficacy of amikacin have not been established, an intramuscular dose of 3.48 mg per kg of body weight as a single dose has been recommended in the treatment of susceptible *bacterial infections* in ball pythons.EL[R-155]

EL US,CAN *Snakes,* gopher—Although the safety and efficacy of amikacin have not been established, an intramuscular loading dose of 5 mg per kg of body weight, followed by 2.5 mg per kg of body weight every seventy-two hours has been suggested in the treatment of susceptible *bacterial infections* in gopher snakes.[R-154] It has also been recommended that snakes be kept at the high end of their preferred temperature range (37 ºC) to maximize distribution of drug in the body.EL[R-154]

EL US,CAN *Tortoises,* gopher—Although the safety and efficacy of amikacin have not been established, an intramuscular dose of 5 mg per kg of body weight (including shell), administered every forty-eight hours, has been suggested for the treatment of susceptible bacterial infections in gopher tortoises.EL[R-156]

<u>Withdrawal times:</u> This product is not labeled for use in food-producing animals and should not be administered to such animals because of the risk of long-term antibiotic residues.[R-258]

Strength(s) usually available:[R-231]
> U.S.—
>> Veterinary-labeled product(s):
>>> 50 mg per mL (Rx) [*Amiglyde-V Injection;*[R-91] *Amiject D; Amikacin C Injection; Amikacin K-9 Injection; CaniGlide;* GENERIC].
>>> Note: These products contain 0.1 mg benzethonium chloride per mL.[R-92]
> Canada—
>> Veterinary-labeled product(s):
>>> Not commercially available.

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass. A sterile solution of Amikacin Sulfate in Water for Injection, or of Amikacin in Water for Injection prepared with the aid of Sulfuric Acid. Contains an amount of amikacin sulfate equivalent to the labeled amount of amikacin, within −10% to +20%. Meets the requirements for Identification, Bacterial endotoxins, pH (3.5–5.5), and Particulate matter, and for Injections.[R-19]

APRAMYCIN

Summary of Differences
Category: Aminocyclitol.
Indications: General considerations—Apramycin is active against *Staphylococcus aureus*, many gram-negative organisms, and some mycoplasma. It has been reported to be effective *in vitro* against *Escherichia coli* and *Salmonella species*[R-96; 164] that are resistant to streptomycin and neomycin.[R-167; 173]
Side/adverse effects: This medication produces minimal side/adverse effects and toxicity when administered by the oral route.

Oral Dosage Forms
Note: The text between [ELUS]and [EL] describes uses not included in U.S. product labeling. Text between [ELCAN]and [EL] describes uses that are not included in Canadian product labeling.
> The [ELUS] or [ELCAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

APRAMYCIN SULFATE POWDER FOR ORAL SOLUTION
Usual dose: [ELUS]Enteritis, *E. coli*[EL]—*Piglets:* Oral, 12.5 mg per kg of body weight a day for seven days (375 mg per gallon or 100 mg per liter), administered in the only source of water.[R-96]
> Withdrawal times—Canada: Meat—28 days.[R-96]
Note: Water consumption should be monitored closely and adjusted to avoid overdose.

Strength(s) usually available:
> U.S.—
>> Veterinary-labeled product(s):
>>> Not commercially available.
> Canada—
>> Veterinary-labeled product(s):
>>> 48 grams per packet (OTC) [*Apralan*].

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer. Protect from moisture and excessive heat.[R-96]

Preparation of dosage form: Prepare fresh solution daily according to manufacturer's labeling.[R-96]

Incompatibilities: Activity of the medication may be reduced if water delivery system contains rust.[R-96]

USP requirements: Not in USP.[R-19]

DIHYDROSTREPTOMYCIN

Summary of Differences
Category: Aminoglycoside.
Indications: General considerations—Active against mycobacteria, *Leptospira,*[R-243; 244] *Francisella tularensis,* and *Yersinia pestis,* but only some mycoplasma, gram-negative organisms, and *Staphylococcus* species.[R-116] The introduction of newer aminoglycosides has eclipsed the significance of dihydrostreptomycin in the face of increasing bacterial resistance.
Lactation: Irregularly distributed into the milk of cows for 18 hours or more.
Side/adverse effects: Less nephrotoxic than other aminoglycosides. Unlike streptomycin, dihydrostreptomycin is associated with more auditory than vestibular toxicity.[R-233]

Oral Dosage Forms
Note: The text between [ELUS]and [EL] describes uses not included in U.S. product labeling. Text between [ELCAN]and [EL] describes uses that are not included in Canadian product labeling.
> The [ELUS] or [ELCAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

DIHYDROSTREPTOMYCIN INJECTION USP
Usual dose:
> Note: [ELUS]*Cattle*[EL], [ELUS]*dogs*[EL], and [ELUS]*pigs*—Although Canadian product labeling includes a dose of 25 mg per kg of body weight for three to five days in the treatment of *leptospirosis* in cattle, dogs, and pigs, studies have shown that while shedding of leptospires will be halted for at least 2 months, carriers are not necessarily eliminated.[EL]{R-243; 244}
>> Although Canadian product labeling includes the use of dihydrostreptomycin in the treatment of *bacterial pneumonia* in *calves,* there is no published evidence available pertaining to efficacy of this therapy. Such use is not recommended by the USP Veterinary Medicine Advisory Panel due to the lack of efficacy data and the potential for extended tissue withdrawal times.[R-258]
>> Withdrawal times: *Cattle*—Canada: Meat—30 days, Milk—96 hours. *Pigs*—Canada: Meat—30 days.

Strength(s) usually available:
> U.S.—
>> Veterinary-labeled product(s):
>>> Not commercially available.
> Canada—
>> Veterinary-labeled product(s):
>>> 500 mg per mL (OTC) [*Ethamycin*].[R-106]

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.

USP requirements: Preserve in single-dose or in multiple-dose containers. Label it to indicate that it is intended for veterinary use only. Contains an amount of Dihydrostreptomycin Sulfate equivalent to the labeled amount of dihydrostreptomycin, within −

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10% to +20%. Contains one or more suitable preservatives. Meets the requirements for Identification, Bacterial endotoxins, Sterility, and pH (5.0–8.0).[R-19].

GENTAMICIN

Summary of Differences
Category: Aminoglycoside.
Indications: General considerations—Gentamicin has been widely used in the treatment of gram-negative organisms and some gram-positive organisms. As with other aminoglycosides, use is limited by the risk of toxicity.
Side/adverse effects: Intermediate nephrotoxicity. It is considered to be equally toxic to the cochlea and to vestibular organs.

Mucosal Dosage Forms

GENTAMICIN UTERINE INFUSION USP
Usual dose: [ELCAN]Uterine infections, bacterial[EL]—*Horses:*
Intrauterine, 2 to 2.5 grams as a total dose a day for three to five days during estrus.[R-1] Before administration, the dose should be diluted with 200 to 500 mL of sterile physiological saline.[R-1]
Withdrawal times—U.S.: This product is not labeled for use in food-producing animals in the U.S., including horses intended for human consumption.[R-1]

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
100 mg per mL (Rx) [*GentaMax 100; GentaVed 100;*[R-3] *Gentozen;*[R-1] *Legacy;* GENERIC].
Canada—
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store between 2 and 30 ºC (36 and 86 ºF),[R-1] unless otherwise specified by manufacturer.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. A sterile solution of Gentamicin Sulfate in Water for Injection. Label Uterine Infusion to indicate that it is for veterinary use only. The label states that it must be diluted with 0.9% Sodium Chloride Irrigation before aseptic uterine infusion. May contain suitable buffers, preservatives, and sequestering agents. Contains the labeled amount, within –10 to +25%. Meets the requirements for Identification, Sterility, and pH (3.0–5.5).[R-19]

Oral Dosage Forms
Note: The text between [ELUS]and [EL] describes uses not included in U.S. product labeling. Text between [ELCAN]and [EL] describes uses that are not included in Canadian product labeling.

The [ELUS] or [ELCAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

GENTAMICIN ORAL SOLUTION
Usual dose: [ELCAN]Enteritis, *E. coli*[EL]—*Piglets,* 1 to 3 days of age: Oral, 5 mg as a total dose, administered once at the onset of signs.[R-13]
Withdrawal times—US: Meat—14 days.
Note: The above dose is for ''pig pump'' solutions, administered at the strength provided in metered dose packaging;[R-13] see manufacturer's product labeling.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
5 mg per mL (OTC) [*Gentamicin Sulfate Pig Pump Oral Solution*].[R-13]
Canada—
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer. Protect from freezing.

USP requirements: Not in USP.[R-19]

GENTAMICIN POWDER FOR ORAL SOLUTION
Usual dose:
[ELCAN]Enteritis, *E. coli*[EL]—*Piglets:* Oral, 25 mg per gallon of water (approximately 1.1 mg per kg of body weight), administered as the sole source of drinking water for three consecutive days.[R-15]
[ELCAN]Swine dysentery[EL]—*Pigs:* Oral, 50 mg per gallon of water (approximately 2.2 mg per kg of body weight), administered as the sole source of drinking water for three consecutive days.[R-15]
Note: Under extreme hot or cold weather conditions, product labeling recommends that the concentration of medication be adjusted, based on expected changes in water consumption.
Withdrawal times—*Pigs, piglets:* US—Meat: 10 days.[R-15]

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
333.3 mg of gentamicin per gram of powder (OTC) [*Gen-Gard*].[R-15]
Canada—
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer. To avoid degradation of medication, this product should not be stored in rusty containers.[R-15]

Preparation of dosage form: Prepare daily according to manufacturer's recommendation.

USP requirements: Not in USP.[R-19]

Parenteral Dosage Forms
Note: The text between [ELUS]and [EL] describes uses not included in U.S. product labeling. Text between [ELCAN]and [EL] describes uses that are not included in Canadian product labeling.

The [ELUS] or [ELCAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

GENTAMICIN INJECTION USP
Note: Intravenous administration—When gentamicin is administered by the intramuscular or subcutaneous route, it is rapidly and completely absorbed. Although not always listed on product labeling, this medication is also commonly administered intravenously. An indwelling catheter is used for convenience and to minimize the discomfort of repeated dosing.[R-263] To further decrease the risk of neuromuscular blockade, it is recommended that the drug be diluted in saline or administered slowly.[R-263]

Usual dose:
[EL][US]Bacteremia[EL];
[EL][US,CAN]Bone and joint infections[EL];
[EL][US]Respiratory tract infections[EL];
[EL][US]Septicemia[EL];
[EL][US]Skin and soft tissue infections[EL];
Urinary tract infections; or
[EL][US]Uterine infections[EL]—*Dogs:*
> Intramuscular or subcutaneous, 4.4 mg per kg of body weight[R-4; 7] every eight hours.
> Once-daily dosing—Intramuscular or subcutaneous, 10 to 15 mg per kg of body weight every twenty-four hours.[R-266]

[EL][US]Bacteremia[EL];
[EL][US,CAN]Bone and joint infections[EL];
[EL][US]Respiratory tract infections[EL];
[EL][US]Septicemia[EL];
[EL][US]Skin and soft tissue infections[EL];
[EL][US]Urinary tract infections[EL]; or
[EL][US]Uterine infections—*Cats:*
> Intramuscular, intravenous, or subcutaneous, 3 mg per kg of body weight every eight hours.[R-63; 64]
> Once-daily dosing—Intramuscular, intravenous, or subcutaneous, 5 to 8 mg per kg of body weight every twenty-four hours.[EL][R-266]

Note: Authors of a study of *obese cats* considered to be approximately 45% overweight (4.6 to 6.6 kg body weight) recommended an intramuscular, intravenous, or subcutaneous dose of 2.5 mg per kg of body weight every eight hours to compensate for pharmacokinetic differences from normal-weight cats.[R-68]

> Treatment of *urinary tract infections* with aminoglycosides should be reserved for those cases in which resistance exists to safer alternative antimicrobials. Despite label directions to limit treatment duration to 7 days,[R-4] most urinary tract infections will require extended therapy. This is possible with the aminoglycosides, provided careful monitoring is performed (see *Patient monitoring*).

[EL][US]Enteritis, *Escherichia coli*[EL]—*Piglets,* 1- to 3-day-old: Intramuscular, 5 mg as a single total dose.[R-7]
> Withdrawal times—Canada: Meat—42 days.[R-7]

E. coli infection;
Pseudomonas aeruginosa infection; or
Salmonella typhimurium infection—*Chicks,* 1-day-old: Subcutaneous, 0.2 mg as a total single dose.[R-7; 8]
> Withdrawal times—US and Canada: Meat—35 days.[R-7; 8]

Paracolon—*Turkey poults,* 1- to 3-day-old: Subcutaneous, 1 mg as a total single dose.[R-7; 8]
> Withdrawal times—US and Canada: Meat—63 days.[R-4; 7]

[EL][US]Uterine infections, bacterial[EL]—*Horses:* Intrauterine, 2 to 2.5 grams a day for three to five days during estrus.[R-7] Before administration, the dose should be diluted with 200 to 500 mL of sterile physiological saline.[EL][R-7]
> Withdrawal times—This product is not labeled for use in horses intended for human consumption.[R-7]

The administration of gentamicin to cattle in the treatment of uterine infections is included in Canadian product labeling. However, gentamicin is not labeled for use in food-producing animals in the U.S. and the USP Veterinary Medicine Advisory Panel does not recommend use in the treatment of uterine infections in cattle. Therefore, the labeled intrauterine dose and withdrawal time for cattle are not listed in this monograph.

Note: The following recommendations have been suggested based on pharmacokinetic studies:
> [EL][US,CAN]*Baboons*—Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 3 mg per kg of body weight every six to eight hours has been suggested in the treatment of *Pseudomonas aeruginosa* infections in baboons.[EL][R-76]

[EL][US,CAN]*Buffalo calves*—Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 3.25 mg per kg of body weight as an initial dose, followed by 2 to 3 mg per kg of body weight every twelve hours has been recommended in the treatment of susceptible *bacterial infections* in buffalo calves.[EL][R-77; 78]

[EL][US,CAN]*Budgerigars*—Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 5 mg per kg of body weight every eight hours for three days has been suggested in the treatment of susceptible *bacterial infections* in budgerigars.[EL][R-86]

[EL][US,CAN]*Calves,* less than 2 weeks of age—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy have not been established, an intravenous dose of 12 to 15 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible *bacterial infections,* based on pharmacokinetic data.[EL][R-21; 266]

[EL][US,CAN]*Cattle*—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy have not been established, an intramuscular dose of 5 to 6 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible *bacterial infections,* based on pharmacokinetic data.[EL][R-22; 25; 261; 266]

[EL][US,CAN]*Eagles*[EL], [EL][US,CAN]*hawks*[EL], or [EL][US,CAN]*owls*—Although the safety and efficacy of gentamicin have not been established, an intramuscular or intravenous dose of 2.5 mg per kg of body weight every eight hours has been recommended in the treatment of susceptible *bacterial infections* in eagles, hawks, and owls.[R-88] Caution is advised in extrapolating dosage recommendations from one avian species to another, as pharmacokinetics can vary widely.[EL]

[EL][US,CAN]*Goats*—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy of gentamicin have not been established, an intravenous dose of 4 mg per kg of body weight every eight hours has been recommended for use in the treatment of susceptible *bacterial infections* in goats.[EL][R-40]

[EL][US,CAN]*Horse foals*[EL] and [EL][US,CAN]*pony foals,* less than 30 days of age—Although the safety and efficacy of gentamicin have not been established, some researchers have suggested an intramuscular or intravenous dose of 10 to 14 mg per kg of body weight every twenty-four hours for use in the treatment of susceptible *bacterial infections* in horse and pony foals less than 30 days of age.[EL][R-6; 266]

[EL][US,CAN]*Horses*[EL] and [EL][US,CAN]*foals,* more than 30 days of age—Although the safety and efficacy of gentamicin have not been established, an intramuscular or intravenous dose of 4 to 6.8 mg per kg of body weight every twenty-four hours has been suggested for the treatment of susceptible *bacterial infections* in horses and foals more than 30 days of age.[EL][R-6; 46; 50; 52; 53; 55; 252; 265; 266]

[EL][US,CAN]*Llamas*—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy of gentamicin have not been established, a dose of 2.5 mg per kg of body weight every eight hours for six days has been suggested in the treatment of *bacterial infections* in llamas.[EL][R-82]

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Pythons—Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 2.5 mg per kg of body weight as an initial dose, followed by 1.5 mg per kg of body weight at ninety-six–hour intervals has been suggested in the treatment of susceptible *bacterial infections* in pythons.EL[R-89]

Strength(s) usually available:
    U.S.—
        Veterinary-labeled products:
            50 mg per mL (Rx) [*GentaVed 50*].[R-4]
            100 mg per mL (OTC) [*Garasol Injection*].[R-8]
    Canada—
        Veterinary-labeled products:
            100 mg per mL (Rx) [*Gentocin Solution Injectable*].[R-7]

Packaging and storage: Store between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer. Keep from freezing.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. May contain suitable buffers, preservatives, and sequestering agents, unless it is intended for intrathecal use, in which case it contains only suitable tonicity agents. Contains an amount of gentamicin sulfate equivalent to the labeled amount of gentamicin, within –10% to +25%. Meets the requirements for Identification, Bacterial endotoxins, pH (3.0–5.5), and Particulate matter, and for Injections.[R-19]

NEOMYCIN

Summary of Differences
Category: Aminoglycoside.
Indications: General considerations—Effective against many gram-negative organisms and *Staphylococcus aureus*.
Side/adverse effects: High risk of nephrotoxicity and severe cochlear toxicity when parenterally administered.

Oral Dosage Forms
Note: The text between EL US and EL describes uses not included in U.S. product labeling. Text between EL CAN and EL describes uses that are not included in Canadian product labeling.

The EL US or EL CAN designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

NEOMYCIN SULFATE ORAL SOLUTION USP
Usual dose: Enteritis, *E. coli*—*Cattle*, EL CAN*goats*EL, EL US*horses*EL, *pigs*, and *sheep*: Oral, 22 mg per kg of body weight a day, administered in the only source of drinking water for fourteen days.[R-98-100]
Withdrawal times—US: Meat—*Cattle:* 1 day or 30 days, depending on the product; *goats:* 3 days or 30 days, depending on the product; *pigs:* 3 days or 20 days, depending on the product; *sheep:* 2 days or 20 days, depending on the product. Products are not labeled for use in preruminating calves to be processed for veal or for lactating dairy cattle or goats producing milk for human consumption.   Canada: Meat—*Cattle:* 30 days; broiler *chickens:* 7 days; laying *chickens, pigs, sheep,* and *turkeys:* 14 days. This product is not labeled for use in lactating dairy cattle or horses to be slaughtered for human consumption.

Note: For many of these products, individual animal treatment is also possible by dividing the daily dose and administering as a drench with milk or water or by mixing in an individual animal's only water supply.[R-98-100] Consult the manufacturer's product labeling.

    Canadian product labeling lists the dose of neomycin in terms of

mL per liter of drinking water and an incrementally increasing dose from 2 weeks to adult, or 2 weeks to 26 weeks of age, for *chickens* and *turkeys,* respectively.[R-103] See product labeling for specific dosing directions.

Strength(s) usually available:
    U.S.—
        Veterinary-labeled product(s):
            200 mg per mL (OTC) [*Biosol Liquid; Neomycin 200; Neoved 200;* GENERIC].[R-98-100]
    Canada—
        Veterinary-labeled product(s):
            200 mg per mL (OTC) [*Biosol Liquid*].[R-103]

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.

Preparation of dosage form: Prepare solutions daily according to manufacturer's instructions. When administered in the drinking water, adjustments must be made in concentration, based on factors altering water consumption, such as age, disease signs, and environmental factors.[R-98]

USP requirements: Preserve in tight, light-resistant containers, preferably at controlled room temperature. Contains an amount of neomycin sulfate equivalent to the labeled amount of neomycin, within –10 to +25%. Meets the requirements for Identification and pH (5.0–7.5).[R-19]

NEOMYCIN SULFATE POWDER FOR ORAL SOLUTION
Usual dose:
    E. coli infection—*Turkeys,* growing: Oral, 22 mg per kg of body weight a day, administered in the only source of drinking water for five days.[R-2; 97]
        Withdrawal times—US: Meat—*Turkeys,* growing: 0 days.[R-97; 101]   Canada: Meat—*Turkeys:* 14 days.
    Enteritis, *E. coli*—*Cattle,* EL CAN*goats*EL, EL US*horses*EL, *pigs,* and *sheep:* Oral, 22 mg per kg of body weight a day for fourteen days, administered in the only source of drinking water.[R-97; 104]

        Withdrawal times—US: Meat—*Cattle:* 1 day or 30 days, depending on the product; *goats:* 3 days or 30 days, depending on the product; *pigs:* 3 days or 20 days, depending on the product; *sheep:* 2 days or 20 days, depending on the product. Products are not labeled for use in preruminating calves to be processed for veal or for lactating dairy cattle or goats producing milk for human consumption.[R-97; 101]
        Canada: Meat—*Cattle:* 30 days; broiler *chickens:* 7 days; laying *chickens, pigs, sheep,* and *turkeys:* 14 days. Products are not labeled for use in horses intended for human consumption.

Note: For many of these products, individual animal treatment is also possible by dividing the daily dose and administering as a drench with milk or water or by mixing in an individual animal's only water supply.[R-97] Consult manufacturer's product labeling for specific dosing directions.

    Canadian product labeling lists the dose of neomycin in terms of mL per liter of drinking water and an incrementally increasing dose from 2 weeks to adult, or 2 weeks to 26 weeks of age, for *chickens* and *turkeys,* respectively.[R-104] Consult manufacturer's product labeling for specific dosing directions.

Strength(s) usually available:[R-231]
    U.S.—
        Veterinary-labeled product(s):
            715 mg per gram of powder (OTC) [*NeoMed 325;*

Neomix 325;[R-97] *Neomix AG 325; Neomycin 325;*[R-101] *Neo-Sol 50; Neosol Soluble Powder; Neovet 325/100;* GENERIC].

Canada—
    Veterinary-labeled product(s):
        715 mg per gram of powder (OTC) [*Neomix Soluble Powder*].[R-104]
        813 mg per gram of powder (OTC) [*NeoMed 325; Neomycin 325*].

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.

Preparation of dosage form: Prepare solutions daily according to manufacturer's instructions. When administered in the drinking water, adjustments must be made in concentration, based on factors altering water consumption, such as age, disease signs, and environmental factors.[R-98]

USP requirements: Not in USP.[R-19]

NEOMYCIN SULFATE TYPE A MEDICATED ARTICLE

Usual dose: [EL CAN]Enteritis, *Escherichia coli* (treatment)—*Cattle* and *calves, goats* and *kids, pigs* and *piglets,* and *sheep* and *lambs:* Oral, 22 mg per kg of body weight a day for up to a maximum of fourteen days.[EL][R-16; 94]

Withdrawal times—US: Meat—*Cattle* and ruminating *calves:* 1 day, *goats, kids, pigs* and *piglets:* 3 days, *sheep* and *lambs:* 2 days. Products are not labeled for use in preruminating calves to be processed for veal or for lactating dairy cattle or goats producing milk for human consumption.

Note: This product is labeled for use in the preparation of Type B or Type C medicated feeds; Type C medicated feeds may be either medicated solid feeds or milk replacers. To administer the recommended dosage, adjustments must be made in the concentration of neomycin in feed or milk replacer, based on factors altering consumption, such as age and weight of the animal, disease signs, and environmental factors.[R-94]

Strength(s) usually available:
    U.S.—
        Veterinary-labeled product(s):
            715 grams per kg (OTC) [*Neomix AG 325 Medicated Premix*].
    Canada—
        Veterinary-labeled product(s):
            Not commerically available.

Packaging and storage:
    Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), in a tightly closed container, unless otherwise specified by manufacturer.
    Store in a dry place, securely closing packaging to prevent caking of contents.[R-231]

Preparation of dosage form: Prepare solutions daily according to manufacturer's instructions.

USP requirements: Not in USP.[R-19]

STREPTOMYCIN

Summary of Differences

Category: Aminoglycoside.

Indications: General considerations—First aminoglycoside introduced. Active against *Francisella tularensis, Leptospira,*[R-243; 244] mycobacteria, and *Yersinia pestis,* but only some mycoplasma, gram-negative organisms, and *Staphylococcus* species.[R-116] The introduction of newer aminoglycosides has eclipsed the significance of streptomycin in the face of increasing bacterial resistance.

Side/adverse effects: Less nephrotoxic than other aminoglycosides. Vestibular toxicity is more often seen than auditory toxicity.

Oral Dosage Forms

Note: The text between [EL US]and [EL] describes uses not included in U.S. product labeling. Text between [EL CAN]and [EL] describes uses that are not included in Canadian product labeling.

    The [EL US] or [EL CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

STREPTOMYCIN SULFATE ORAL SOLUTION

Usual dose: [EL CAN]Enteritis, bacterial[EL]—*Calves, chickens,* and *pigs:* Oral, 22 to 33 mg per kg of body weight, administered in the only source of drinking water.[R-181; 182]

Withdrawal times—US: Meat—*Calves:* 2 days, *chickens:* 4 days, *pigs:* 0 days. Product labeling listing the above withdrawal times states that they are not labeled for use in chickens producing eggs for human consumption.

Note: Strength of administered solution may be adjusted to compensate for variations in age or weight, the severity of disease signs, and environmental factors that may affect water consumption.[R-182]

Strength(s) usually available:[R-231]
    U.S.—
        Veterinary-labeled product(s):
            250 mg per mL (OTC) [GENERIC].
    Canada—
        Veterinary-labeled product(s):
            Not commercially available.

Packaging and storage: Store below 40 ºC (104º F), preferably between 15 and 30º C (59 and 86º F), unless otherwise specified by manufacturer.

Preparation of dosage form: Prepare according to manufacturer's instruction.

USP requirements: Not in USP.[R-19]

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Table I. Pharmacology/Pharmacokinetics—Intravenous administration

AMIKACIN

Species	Dose (mg/kg)	Number of doses	Vol$_D$ area (L/kg)	Vol$_D$ steady state (L/kg)	Clearance (mL/min/kg)	Elimination half-life, initial phase	Elimination half-life, gamma phase*

						(hour)	(hour)
Birds							
Chickens[R-146]	10	Single	0.229 ± 0.08	0.193 ± 0.06	1.82 ± 0.28		
Emus[R-149]	7.2	Single	0.18 ± 0.03	0.17 ± 0.07	0.5 ± 0.16	0.87	6.06
Parrots, African grey [R-150]	5	Single	0.289	0.233	3.1	1.06	
	10	Single	0.184	0.122	2.4	0.9	
	20	Single	0.444	0.308	3.8	1.34	
Calves[R-142]	7.5	Single	0.35 ± 0.01		1.5 ± 0.2	2.51 ± 0.58	
Calves[R-141]	10	Single	0.4 ± 0.03	0.27 ± 0.02	1.5 ± 0.03	3.09 ± 0.27	
Cats[R-139]	5	Single		0.17 ± 0.02	1.46 ± 0.26	1.31 ± 0.32	
Cats[R-140]	5	Single	0.134 ± 0.008		1.83 ± 0.26	0.8 to 1.3	
	10	Single	0.141 ± 0.08		2.02 ± 0.38	0.8 to 1.3	
	20	Single	0.184 ± 0.22		2.3 ± 0.04	0.8 to 1.3	
Dogs[R-143]	5	Single	0.258		2.82	1.07	
	10	Single	0.227		2.66	0.98	
	20	Single	0.361		3.57	1.03	
Donkeys[R-136]	6	Single	0.157	0.15	0.97	1.9	
Foals,							
3 days of age†[R-130]	7	Single	0.473 ± 0.067	0.422 ± 0.051	1.92 ± 0.37	2.69	
5 days of age†[R-130]	7	Single			2.22 ± 0.35		
Premature, hypoxic [R-131]	7	Every 8 hours for 2 days	0.60 ± 0.09		1.9 ± 1.13	5.39 ± 3.46	
Neonatal, critically ill [R-131; 132]	7	Every 8 hours for 2 d/6 days	0.56 ± 0.11		2.44 ± 0.73	2.86 ± 0.89	
Neonatal, critically ill, azotemic, and hypoxemic[R-132]	7	Every 8 hours for 6 days	0.43 ± 0.05		1.3 ± 0.3	4 ± 1.11	
Horses[R-137]	4.4	Single	0.198 ± 0.052		1.49 ± 0.39	1.44 2.8	
Horses[R-136]	6	Single	0.215	0.207	0.75	1.57	
Horses[R-137]	6.6	Single	0.174 ± 0.028		1.28 ± 0.19	1.14	
Horses[R-137]	11	Single	0.138 ± 0.018		1.41 ± 0.22		
Ponies[R-136]	6	Single	0.173	0.15	1.5	1.3	
Pythons, ball[R-155]							
25 ºC	3.48; IC	Single	0.46 ± 0.17		0.04 ± 0.01	126	
37 ºC	3.48; IC	Single	0.41 ± 0.11		0.04 ± 0.01	110	
Sheep[R-142]	7.5	Single	0.2 ± 0.03		0.7 ± 0.06	1.93 ± 0.27	

APRAMYCIN

Species	Dose (mg/kg)	Number of doses	Vol$_D$ area (L/kg)	Vol$_D$ steady state (L/kg)	Clearance (mL/min/kg)	Elimination half-life, initial phase (hour)	Elimination half-life, gamma phase* (hour)
Birds							
Chicks, 18-day-old[R-62]	10	Single	0.245 ± 0.01		3.63 ± 0.23	0.8 ± 0.01	
Chickens[R-162]	10	Single	0.182 ± 0.021		1.3 ± 0.17	1.68 ± 0.07	
Chickens[R-165]	75	Single	5.62 ± 0.14	4.82 ± 0.08	31.3 ± 0.83	2.1 ± 0.01	
Pigeons[R-162]	10	Single	0.077 ± 0.001		3.5 ± 0.03	0.25 ± 0	
Quail, Japanese[R-167]	10	Single	0.133 ± 0.007		3.1 ± 0.01	0.5 ± 0.02	
Calves, 3- to 5-week old[R-164]	20	Single		0.708 ± 0.012	3.22 ± 0.44	4.4 ± 1.21	
Cows, lactating[R-163]	20	Single	1.26 ± 0.18		12.16 ± 1.69	2.10 ± 0.24	
Goats, lactating[R-163]	20	Single		1.36 ± 0.11	11.69 ± 2.31	0.47 ± 0.16	
Rabbits[R-162]	10	Single	0.284 ± 0.035		4.3 ± 0.68	0.80 ± 0.14	
Sheep[R-162]	10	Single	0.167 ± 0.08		1.3 ± .07	1.51 ± 0.14	
Ewes, lactating[R-163]	20	Single		1.45 ± 0.10	14.14 ± 1.75	1.84 ± 0.19	

GENTAMICIN

Species	Dose (mg/kg)	Number of doses	Vol$_D$ area (L/kg)	Vol$_D$ steady state (L/kg)	Clearance (mL/min/kg)	Elimination half-life, initial phase (hour)	Elimination half-life, gamma phase* (hour)

	n	Regimen				
Birds						
Eagles[R-88]	10	Single	0.21 ± 0.01		1.01 ± 0.09	2.46 ± 0.32
Hawks, red-tailed[R-88]	10	Single	0.24 ± 0.03		2.09 ± 0.16	1.35 ± 0.18
Owls[R-88]	10	Single	0.23 ± 0.02		1.41 ± 0.1	1.93 ± 0.24
Roosters[R-84]	5	Single	0.23 ± 0.02	0.21 ± 0.01	0.78 ± 0.13	3.38 ± 0.62
Buffalo calves, 3 to 4 months of age (Murrah)[R-77]	5	Single	0.43 ± 0.03		0.91 ± 0.12	5.69 ± 0.54
Camels[R-79]	2	Single	0.32 ± 0.02		1.35 ± 0.11	2.93 ± 0.24
Cats,[R-65]						
with induced endotoxemia	3	Single		0.19 ± 0.02	2.6 ± 0.7	1.1 ± 0.2
without endotoxemia	3	Single		0.2 ± 0.03	2 ± 0.2	1.28 ± 0.21
Cats, obese[R-68]	3	Single		0.12 ± 0.02	1.07 ± 0.25	1.37 ± 0.24
Cats[R-64]	3	Every 8 hours for 5 days				1.79 ± 0.21
Cats[R-63]	5	Single		0.14 ± 0.02	1.38 ± 0.35	1.25 ± 0.3
Calves,[R-21]						
1 day of age	4	Single	0.4 ± 0.04	0.37 ± 0.04	1.92 ± 0.43	2.5 ± 0.6
5 days of age	4	Single	0.4 ± 0.05	0.38 ± 0.04	2.44 ± 0.34	2 ± 0.3
10 days of age	4	Single	0.34 ± 0.02	0.32 ± 0.02	2.02 ± 0.27	2 ± 0.2
15 days of age	4	Single	0.33 ± 0.04	0.31 ± 0.03	2.10 ± 0.32	1.9 ± 0.1
Calves,[R-20] 4 to 5 weeks of age	3	Single	1.95 ± 1.24	0.75 ± 0.2	4.9 ± 1.9	3.9 ± 1.7
Calves,[R-180] 6 weeks of age	5	Single	0.3 ± 0.08		1.68 ± 0.4	2.16 ± 0.25
Cows, adult[R-21]	4	Single	0.14 ± 0.02	0.13 ± 0.02	1.29 ± 0.26	1.3 ± 0.2
Cows, adult[R-26]	4.4	Single	0.25		1.12	1.9
Cows, lactating[R-22]	5	Single	0.19 ± 0.04	0.16 ± 0.03	1.32 ± 0.17	1.83 ± 0.18
Puppies, 5 months of age (beagles)[R-70]	10	Single	0.35 ± 0.04		4.08 ± 0.62	
Dogs (mixed breed)[R-69]	3	Single		0.17 ± 0.03	2.29 ± 0.48	0.91 ± 0.26
Dogs,[R-71]						
with diabetes mellitus	4.4	Single	0.32 ± 0.13	0.2 ± 0.05	2.84 ± 0.95	1.1
without diabetes	4.4	Single	0.23 ± 0.08	0.18 ± 0.03	2.27 ± 0.41	1.08
Donkeys[R-43]	2.2	Single		0.2 ± 0.06	1.67 ± 0.48	1.87
Goats[R-39]	5	Single	0.26 ± 0.04		3.10 ± 0.27	0.96 ± 0.09
Goats[R-40]	5	Single	0.24	0.2	1.7	1.73
Horse foals,[R-47]						
1 day of age	4	Single	0.32 ± 0.03	0.3 ± 0.03	1.75 ± 0.47	2.12 ± 0.39
5 days of age	4	Single	0.38 ± 0.08	0.35 ± 0.06	2.98 ± 1.48	1.51 ± 0.53
10 days of age	4	Single	0.4 ± 0.13	0.34 ± 0.1	2.60 ± 0.96	1.69 ± 0.55
15 days of age	4	Single	0.35 ± 0.05	0.33 ± 0.05	2.4 ± 0.87	1.77 ± 0.55
30 days of age	4	Single	0.32 ± 0.05	0.28 ± 0.03	3.66 ± 1.93	1.01 ± 0.52
Horses[R-47]	4	Single	0.17 ± 0.03	0.16 ± 0.22	1.69 ± 0.65	1.09 ± 0.92
Horses[R-61]	2.2	Single	0.3 ± 0.05		2.18 ± 0.5	1.52 ± 0.32
Horses[R-45]	2.2	Single	0.18 ± 0.02	0.15 ± 0.01	1.04 ± 0.13	1.96
Horses[R-50]	2.2	Every 8 hours for 24 hours	0.46 ± 0.05			0.83
	2.2	Every 8 hours for 10 days	0.18 ± 0.02			1.06
Horses,[R-54]						
with induced endotoxemia	3	Single	0.15 ± 0.04	0.14 ± 0.04	1.17 ± 0.35	1.54 ± 0.15
without endotoxemia	3	Single	0.2 ± 0.03	0.17 ± 0.01	1.41 ± 0.19	1.66 ± 0.06
Horses[R-46]	3.3	Single		0.12 ± 0.02	1.4 ± 0.2	1.2 ± 0.3
	3.3	Every 12 hours for 2.5 days		0.18 ± 0.01	1.4 ± 0.2	1.2 ± 0.2
Horses,[R-204]						
without halothane	4	Single	0.26 ± 0.02		1.54 ± 0.27	2.01 ± 0.35
with halothane anesthesia	4	Single	0.26 ± 0.03		0.81 ± 0.32	4.03 ± 1.69
Horses[R-44]	5	Single	0.25 ± 0.03	0.24 ± 0.03	1.15 ± 0.12	2.54 ± 0.33
Horses[R-252]	6.6	Single		0.14 ± 0.06	3.44 ± 0.44	3 ± 2.8

Species	Dose (mg/kg)	Number of doses	Vol_D area (L/kg)	Vol_D steady state (L/kg)	Clearance (mL/min/kg)	Elimination half-life, initial phase (hour)	Elimination half-life, gamma phase* (hour)
Horses[R-50]	6.6	Every 8 hours for 24 hours	0.12 ± 0.04			0.78	
	6.6	Every 8 hours for 10 days	0.21 ± 0.01			1.08	
Llamas[R-82]	2.5	Single	0.22 ± 0.06		0.97 ± 0.13	2.75 ± 0.67	
	5	Single	0.25 ± 0.03		1.1 ± 0.14	2.77 ± 0.34	
Llamas[R-81]	4	Single	0.12		0.51	3.03	
Piglets,[R-41]							
newborn	5	Single	0.59 ± 0.11	0.79 ± 0.04	2 ± 0.17	5.19 ± 0.3	
42 days of age	5	Single	0.43 ± 0.06	0.47 ± 0.03	2.8 ± 0.17	3.5 ± 0.23	
Pigs[R-42]	2	Every 8 hours for 7 days	0.32 ± 0.32	0.24 ± 0.03	1.66 ± 0.12	1. 9	20.2
Rabbits[R-75]	3	Single	0.14 ± 0.01		1.69 ± 0.07	0.94 ± 0.04	
Rabbits,[R-76]							
with induced endotoxemia	3	Single				0.77 ± 0.08	
without endotoxemia	3	Single				1.5 ± 0.029	
Rabbits[R-74]	3.5	Single	0.11 ± 0.02		2.82 ± 0.97	0.74 ± 0.25	
Sheep[R-31]	2.2	Single	0.19 ± 0.06		1.56 ± 0.40	1.4 ± 0.08	
Sheep[R-35]	3	Single	0.16 ± 0.01	0.15 ± 0.01	1.15 ± 0.08	1.68 ± 0.28	
Sheep[R-36; 37]	3	Single		0.41 ± 0.2	0.66 ± 0.26		41.9 ± 18.5
Sheep[R-36]	3	Every 8 hours for 7 days					57.5 ± 26.2
Sheep[R-33]	4	Single	0.16		1.03	1.75	
Sheep[R-32]	10	Single		0.24 ± 0.03	1.03 ± 0.15	2.4 ± 0.5	30.4 ± 18.9
Sheep[R-36; 37]	10	Single		0.38 ± 0.2	0.81 ± 0.32		88.9 ± 19.8
Sheep[R-36; 37]	20	Single		0.71 ± 0.75	0.88 ± 0.34		167.2 ± 42.7

NEOMYCIN

Species	Dose (mg/kg)	Number of doses	Vol_D area (L/kg)	Vol_D steady state (L/kg)	Clearance (mL/min/kg)	Elimination half-life, initial phase (hour)	Elimination half-life, gamma phase* (hour)
Calves,[R-180]							
2 days of age	10	Single	0.356 ± 0.042		2.26 ± 0.61	2.12 ± 0.39	
1 week of age	10	Single	0.472 ± 0.085		3.62 ± 0.58	1.5 ± 0.03	
2 weeks of age	10	Single	0.322 ± 0.056		2.31 ± 0.31	1.59 ± 0.08	
4 weeks of age	10	Single	0.462 ± 0.065		2.63 ± 0.24	1.9 ± 0.01	
>8 months of age	10	Single	0.355 ± 0.075		2.03 ± 0.54	2.04 ± 0.19	
Calves, 3 months of age[R-237]	12	Single		1.17 ± 0.23	4.16 ± 0.67	1.4 ± 0.47	7.48 ± 2.02
Horses[R-176]	10	Single	0.232 ± 0.06		1.38 ± 0.39	2.1 ± 0.97	
Sheep[R-248]	10	Single	0.304 ± 0.08		1.52 ± 0.33	1.98 ± 0.5	

STREPTOMYCIN

Species	Dose (mg/kg)	Number of doses	Vol_D area (L/kg)	Vol_D steady state (L/kg)	Clearance (mL/min/kg)	Elimination half-life, initial phase (hour)	Elimination half-life, gamma phase* (hour)
Horses[R-176]	10	Single	0.231 ± 0.04		0.79 ± 0.13	3.40 ± 0.42	

* Researchers have described a dose-dependent slow elimination phase (gamma) many times longer than the initial elimination phase.[R-32] It is postulated that gentamicin is bound to tissues by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound to tissue by another process is more gradually eliminated.[R-25; 32; 34; 36]

† Clearance was the only pharmacokinetic value that differed with statistical significance for amikacin between 3 and 5 days of age.[R-130] Another study showed no pharmacokinetic differences for amikacin between foals 1 and 7 days of age.[R-133]

IC = Intracardiac

Table II.   Pharmacology/Pharmacokinetics—Other systemic data

AMIKACIN

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)
Birds								
Chickens[R-157]	10; IM	Single		19.9	0.25		2.3	
	20; IM	Single		30.8	0.25		2.9	
Chickens[R-146]	20; IM	Single	0.48 ± 0.158	50.79 ± 4.05	0.5 ± 0.258	91	1.43 ± 0.34	
	20; IM	Every 8 hours for 10 doses		38.58 ± 6.96	0.79 ± 0.37		1.86 ± 0.42	
Cockatiels[R-148]	15; IM	Every 12 hours for 3 days		27.3 ± 6.89	1		1.29	
Hawks, red tailed[R-147]	20; IM	Single	0.16 ± 0.05	56 ± 8.8	0.64 ± 0.16		2.02 ± 0.63	
Parrots, African gray[R-150]	5; IM	Single		10.8 ± 0.63	1	98	1.08	
	10; IM	Single		21.1 ± 1.77	0.75	61	1.04	
	20; IM	Single		32.7 ± 1.23	0.75	106	0.97	
Calves[R-142]	7.5; IM	Single		23.5 ± 2.4	0.83 ± 0.14	99	1.94 ± 0.34	
Calves[R-144]	10; IM	Single		30 ± 3.7	0.05		2.2	
	25; IM	Single		57.7 ± 3.6	0.05			
Cats[R-139]	5; IM	Single		16.41 ± 1.98	0.75 ± 0.2	95		
	5; SC	Single		22.61 ± 4.29	0.67 ± 0.12	123		
Cats[R-140]	5; IM	Single		18.45	0.5	94		
	5; SC	Single		23.17	0.75	100		
	10; IM	Single		38.51	0.5	94		
	10; SC	Single		39.55	0.75	100		
	20; IM	Single		65.57	0.5	94		
	20; SC	Single		67.88	0.75	100		
Dogs[R-143]	10; IM	Single			1		1	
	10; SC	Single		14 (from graph)	1		1.5	
Goats[R-151]	10; IM	Single	0.24	27.63 ± 1.61	0.75	102		
	10; SC	Single	0.21	38.93 ± 3.06	0.5	107		
Guinea pigs[R-152]	3.75; IM	Single	0.03 ± 0	12.2 ± 0.4	0.14 ± 0.03		0.98 ± 0.07	
	7.5; IM	Single	0.11 ± 0.06	20.5 ± 1.1	0.3 ± 0.09		1.25 ± 0.07	
	15; IM	Single	0.14 ± 0.05	41.6 ± 1.5	0.4 ± 0.07		1.17 ± 0.75	
Horse foals, 3- to 5-day old†[R-130]	7; IO	Single		34.17 ± 3.54	0.05	98		
Horses[R-137]	4.4; IM	Single		13.3 ± 1.6	1			
	6.6; IM	Single		23 ± 0.6	1			
	11; IM	Single		29.8 ± 3.2	1			
Pony foals, 2- to 11-day old[R-135]	7; IM	Single		14.7 ± 1.14	0.5		3 ± 0.29	
Pythons, ball[R-155]								
25 °C	3.48; IM	Single	1.31	11.94 ± 1.67	1.47 ± 0.72	109		
37 °C	3.48; IM	Single	2.27	13.87 ± 2.61	1.27 ± 0.6	109		
Sheep[R-139]	7.5; IM	Single		34.4 ± 6.5	1.26 ± 0.34	87	1.96 ± 0.38	
Snakes, gopher[R-154]								
25 °C‡	5; IM	Single	5.58 ± 2.77				71.9 ± 10	
37 °C‡	5; IM	Single	5.69 ± 1.11				75.4 ± 30.1	
Tortoises, gopher[R-156]	5; IM	Single		25 (from graph)	0.5			

APRAMYCIN

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)
Calves, 3- to 5-week old[R-164]	10; IM	Single		18.6	0.5			
	20; IM	Single		40.8	1			
	30; IM	Single		1.49	1			
	40; IM	Single		1.84	1			
Cows, lactating[R-163]	20; IM	Single		42.52 ± 4.79	0.5 ± 0	60	4.42 ± 0.63	
Birds								
Chickens[R-165]	75; IM	Single	0.19 ± 0	11.06 ± 0.31	0.76 ± 0.03	58	2.31 ± 0.02	
	75; PO	Single	0.1 ± 0	0.79 ± 0.02	0.2 ± 0.01	2	1.22 ± 0.01	
Quail, Japanese[R-167]	50; PO	Single		0.84 ± 0.24	0.53 ± 0.09	56	2.31 ± 0.38	
Ewes, lactating[R-163]	10; IM	Single		31.04 ± 3.67	0.5 ± 0	70	2.42 ± 0.29	

DIHYDROSTREPTOMYCIN

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)
Cattle[R-247]	11; IM	Single		44.7 ± 25.6	1			
	16.5; IM	Single		65				
	25; IM	Single		78	1.5			
Cattle[R-249]								
Pigs[R-249]	25; IM	Single		87	2.5			

GENTAMICIN

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)
Baboons[R-76]	3; IM	Single					1.58	
Birds								
Budgerigars[R-86]	5; IM	Single		17.3	0.25		0.53	
	10; IM	Single		37	0.25		0.53	
Cockatiels[R-148]	5; IM	Every 12 hours for 3 days		4.66 ± 1.45	1		1.29	
Cranes[R-85]	5 to 20; IM	Single					2.75 ± 0.62	
Galahs[R-205] (cockatoos)	5; IM	Single		20.55 ± 1.3	0.5		1.23	
Eagles[R-88]	10; IM	Single				70		
Hawks[R-88]	10; IM	Single				95		
Macaws[R-205]	5; IM	Single		20.62 ± 2.45	0.5		1.17	
	5; IM	Every 12 hours For 7 days		14.15 ± 1.75	0.5			
Owls[R-88]	10; IM	Single				95		
Quail[R-85]	5 to 20; IM	Single					0.7 ± 0.2	
Pheasants[R-85]	5 to 20; IM	Single					1.25 ± 0.25	
Buffalo calves, 3 to 4 months of age[R-78]	10; IM	Single	0.43 ± 0.08	39.4 ± 9.6	0.75		3.79 ± 0.23	

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)
Camels,[R-79]								
normal hydration	2; IM	Single		5.4 ± 0.4	1.09 ± 0.21	135		
dehydrated	2; IM	Single		3 ± 0.36	1.83 ± 0.48	54		
Cats,[R-62]	2.5; IM	Single		9.1 ± 0.8	0.5			
	5; IM	Single		23.1 ± 2.1	0.5			
Cats,[R-65]								
with endotoxemia	3; IM	Single		12.53 ± 3.57	0.54 ± 0.16		1.0 ± 0.23	
	3; SC	Single		12.43 ± 2.05	0.42 ± 0.12		1.08 ± 0.23	
without endotoxemia	3; IM	Single		13.79 ± 3.15	0.43 ± 0.11		1.0 ± 0.17	
	3; SC	Single		15.25 ± 1.49	0.54 ± 0.17		1.24 ± 0.1	
Cats[R-68]	3; SC	Single	0.11 ± 0.16	17 ± 2	0.58 ± 0.13	84	1.24 ± 0.22	
Cats[R-63]	5; IM	Single		21.6 ± 1.96	0.67 ± 0.12	68	1.27 ± 0.27	
	5; SC	Single		23.5 ± 3.57	0.25	76	1.14 ± 0.11	
Cows[R-29]	5; IM	Single	0.28 ± 0.02	40.46 ± 1.05	0.98 ± 0.05		2.52 ± 0.1	
Cows[R-29]	5; IM	Every 8 hours for 3 days	0.23 ± 0.01	32.56 ± 2.39	0.98 ± 0.09	70	2.65 ± 0.27	
Cows, lactating[R-22]	5; IM	Single	0.63 ± 0.28	15.39 ± 6.19	0.75	92		
Cows, lactating[R-22]	5; IM	Every 8 hours for 10 days						44.91 ± 9.38
Cows, with endometritis[R-29]	5; IM	Single	0.21 ± 0.02	19.36 ± 1.56	0.84 ± 0.06		2.71 ± 0.35	
Dogs, (mixed-breed)[R-69]	3; IM	Single	0.16	10.7	0.52	96		
	3; SC	Single	0.26	10.2	0.69	94		
Goats[R-39]	5; IM	Single		33.9 ± 4.37	0.67 ± 0	96	2.37 ± 0.47	
Goats[R-39]	5; SC	Single		28 ± 3.84	0.66 ± 0	77	3.56 ± 0.39	
Horse foals[R-48]								
1 month of age	2; IM	Single	0.19 ± 0.08	18.2 ± 5.3	0.5		4.28 ± 2.23	
	4; IM	Single	0.22 ± 0.09	52	0.5		3.07 ± 0.68	
3 months of age	2; IM	Single	0.21 ± 0.11	18.2 ± 5.3	0.5		3.68 ± 0.71	
	4; IM	Single	0.15 ± 0.03	66	0.5		2.87 ± 0.82	
Horses[R-46]	3.3; IM	Single		11.7 ± 1.7	0.8 ± 0.3		2.5 ± 0.9	
	3.3; IM	Every 12 hours for 2.5 days		12.2 ± 2.8	0.8 ± 0.1		3.5 ± 0.6	
Horses[R-57]	4.4; IM	Single		16.8	0.5			
Horses[R-252]	6.6; IM	Single		22 ± 4.9	1.3 ± 0.5	100		
Pony foals[R-49]	2; IM	Single		6.85	0.25		2.81 ± 0.28	
Ponies[R-53]	5; IM	Every 8 hours for 7 days	0.25 ± 0.06	12.74 ± 1.94	1		2.13 ± 0.48	
Pythons, blood[R-89]	2.5; IM	Single		5.76			50.9	
Rabbits[R-74]	3.5; IM	Single		14.5 ± 1.7	0.48 ± 0.25	132	0.83 ± 0.14	
	3.5; SC	Single		11.5	0.57 ± 0.16	113	0.78 ± 0.15	
Sheep[R-32]	4; IM	Single				99	1.82	
Sheep[R-33]	3; IM	Every 8 hours for 7 days		13.7				82.1 ± 17.8

NEOMYCIN

Species	Dose (mg/kg); Route	Number of doses	Absorption half-life (hour)	Peak serum concentration (mcg/mL)	Time to peak concentration (hour)	Bioavailability (%)	Terminal half-life, initial phase (hours)	Terminal half-life, gamma phase* (hours)
Calves, 3 months of age[R-237]	24; IM	Single		31.7 ± 11.8	1.38 ± 0.95	127	11.5 ± 3.8	
	96; PO	Every 12 hours for 15.5 days		0.26 ± 0.37	2.6 ± 2.9	0.45		
Horses[R-176]	10; IM	Single	0.16 ± 0.05	2.43 ± 9.9		74	2.58 ± 0.69	
	10; IM	Every 12 hours for 7 doses	0.21 ± 0.08	25.6 ± 8.8		66	2.67 ± 0.69	
Sheep[R-248]	10; IM	Single	0.31 ± 0.13	17.63 ± 2.27	1.33 ± 0.41	75	2.68 ± 0.29	
	10; SC	Single	0.35 ± 0.14	18.66 ± 3.05	1 ± 0.32	85	2.82 ± 0.51	

STREPTOMYCIN

	Absorption	Peak serum	Time to peak	Bioavailability	Terminal	Terminal

Species	Dose (mg/kg); Route	Number of doses	half-life (hour)	concentration (mcg/mL)	concentration (hour)	(%)	half-life, initial phase (hours)	half-life, gamma phase* (hours)
Horses[R-176]	10; IM	Single	0.34 ± 0.15	43.4 ± 21.4	1	83	3.83 ± 0.3	
	10; IM	Every 12 hours for 7 doses	0.32 ± 0.14	44.5 ± 2.7	1	98	3.84 ± 1.18	

* Researchers have described a slow elimination phase (gamma) many times longer than the initial elimination phase.[R-32] It is postulated that gentamicin is bound to tissues by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound to tissue by another process is more gradually eliminated.[R-25; 32; 34; 36]

† The major pharmacokinetic values for intraosseus administration of amikacin did not significantly differ from those measured for intravenous administration.[R-130]

‡ Although the half-lives of absorption and elimination were similar at different temperatures, the estimated volume of distribution and clearance were significantly higher at the warmer temperature.[R-154]

IM = intramuscular, IO = intraosseous, SC = subcutaneous

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