PENICILLIN G (Veterinary—Systemic)

Some commonly used *brand names* are:

For veterinary-labeled products—*Agri-cillin; Aquacillin; Combi-Pen 48; Depocillin; Derapen SQ/LA; Dual-Cillin; Duplocillin LA; Durapen; Hi-Pencin 300; Longisil; PenAqua Sol-G; Pen-Aqueous; Pen BP-48; Pen-G; Pen G Injection; Penmed; Penpro; Pen Vet 300; Pot-Pen; Procillin; Pro-Pen-G; Propen LA; R-Pen; Twin-pen; UltraPen;* and *UltraPen B.*

For human-labeled products—*Pfizerpen.*

Category: Antibacterial (systemic).

Indications

Note: The text between [EL-US] and [EL] describes uses that are 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 the *Dosage Forms* section of this monograph to confirm availability.

General considerations

The spectrum of activity of penicillin G includes many aerobic and anaerobic gram-positive organisms. Aerobes susceptible to penicillin G include most beta-hemolytic streptococci, beta-lactamase-negative staphylococci, *Actinomyces* species, some *Bacillus anthracis, Corynebacterium* species, and *Erysipelothrix rhusiopathiae.* Most species of anaerobes, including *Clostridium* species, but excluding beta-lactamase-producing *Bacteroides* species, are also susceptible to penicillin G. Penicillin G is easily inactivated by beta-lactamases and has little efficacy against organisms that can produce these enzymes. In addition, penicillin G is ineffective against those bacteria that are resistant by other mechanisms, such as having a relatively impermeable cell wall. Therefore, penicillin G has little activity against many staphylococci and most gram-negative bacteria.{R-3; 4}

Accepted

Blackleg (treatment)—*Cattle* and [EL-US]*sheep*[EL]: Penicillin G is indicated in the treatment of blackleg caused by susceptible organisms such as *Clostridium chauvoei* in cattle and sheep.{R-5; 6}

Erysipelas (treatment)—*Pigs* and *turkeys:* Penicillin G is indicated in the treatment of infections caused by *Erysipelothrix rhusiopathiae (insidiosa)* in pigs and turkeys.{R-6-9}

Pharyngitis (treatment); or

Rhinitis (treatment)—*Cattle:* Penicillin G is indicated in the treatment of bacterial rhinitis or pharyngitis caused by susceptible organisms such as *Actinomyces pyogenes*.{R-5}

Pneumonia, bacterial (treatment)—*Cattle,*{R-6; 7} *sheep,*{R-6; 7} [EL-US]*horses*[EL],{R-6} and [EL-US]*pigs*[EL]:{R-10} Penicillin G is indicated in the treatment of bacterial pneumonia caused by susceptible organisms in cattle, sheep, [EL-US]horses[EL], and [EL-US]pigs[EL]; however, for bacterial pneumonia in cattle, sheep, and pigs, penicillin G is not considered the drug of first choice pending culture and sensitivity results.{R-85; 87}

Strangles (treatment)—*Horses:* Penicillin G is indicated in the treatment of strangles caused by *Streptococcus equi*;{R-7} however, it may be effective only during the acute phase of the infection.{R-13}

[EL-US]Actinomycosis (treatment)[EL]—*Cattle:* Penicillin G is indicated in the treatment of actinomycosis, and may be most effective in infections in which pathogens other than *Actinomyces* species are not yet involved.{R-6; 14}

[EL-US]Arthritis, septic (treatment)[EL]—*Cattle, horses, pigs,* and *sheep:* Penicillin G is indicated in the treatment of septic arthritis caused by susceptible bacteria in cattle, horses, pigs, and sheep.{R-6; 15; 16}

[EL-US]Leptospirosis (treatment)[EL]—*Cattle,*{R-6} *dogs,*{R-6; 17} [EL-CAN]*horses*[EL],{R-18} and *pigs:*{R-6} Penicillin G is indicated in the treatment of acute leptospirosis in cattle, dogs, horses, and pigs. The chronic shedding stage of leptospirosis is often treated with tetracycline; penicillin G administered alone will not clear the carrier state.{R-73; 85}

[EL-US]Malignant edema (treatment)[EL]—*Cattle:* Penicillin G is indicated in the treatment of malignant edema caused by susceptible *Clostridium septicum* in cattle.{R-6}

[EL-US]Metritis (treatment)[EL]—*Cattle, horses, pigs,* and *sheep:* Penicillin G is indicated in the treatment of metritis caused by susceptible organisms in cattle, horses, pigs, and sheep;{R-6; 20; 21} however, therapeutic regimens often emphasize evacuation of uterine contents as the primary treatment.{R-85}

[EL-US]Pyelonephritis (treatment)[EL]—*Cattle:* Penicillin G is indicated in the treatment of pyelonephritis caused by susceptible organisms such as *Corynebacterium renale* in cattle.{R-6; 22; 23}

[EL-US]Skin and soft tissue infections (treatment)[EL]—

Cattle: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with calf diphtheria, foot rot, umbilical infections, and wounds.{R-10}

Horses: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with umbilical infections and wounds.{R-6}

Pigs: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with umbilical infections.{R-6}

Sheep: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with post-surgical tail docking or castration site infections, and umbilical infections.{R-6; 10}

[EL-US]Streptococcus suis infection (treatment)[EL]—*Pigs:* Penicillin G potassium is indicated in Canadian product labeling for the treatment of infections caused by susceptible *Streptococcus suis*.{R-9}

[EL-US]Tetanus (treatment)[EL]—*Cats, cattle, dogs, horses,* and [EL-CAN]*pigs*[EL]: Penicillin G is indicated in the treatment of *Clostridium tetani* in conjunction with tetanus antitoxin and supportive therapy.{R-6}

Regulatory Considerations

U.S.—

Administration of penicillin G procaine to animals may produce procaine concentrations in the blood and urine that violate equine and greyhound racing commission prohibitions.{R-91; 92}

Penicillin G is not for use in turkeys producing eggs for human consumption or for use in horses intended for food.{R-7; 8}

Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP combination is not labeled for use in lactating cattle or preruminating calves.{R-5}

Some brands of Penicillin G Procaine Injectable Suspension USP are not labeled for use in preruminating calves.{R-53}

Withdrawal times have been established for Penicillin G Potassium For Oral Solution USP, Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP, and Penicillin G Procaine Injectable Suspension USP (see the *Dosage Forms* section).{R-5; 7; 8; 26}

Canada—

Administration of penicillin G procaine to animals may produce procaine concentrations in the blood and urine that violate equine and greyhound racing commission prohibitions.{R-84}

Penicillin G is not labeled for use in turkeys producing eggs for human consumption.{R-9}

Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP combination is not labeled for use in lactating cattle.{R-27; 28}

Withdrawal times have been established for Penicillin G Potassium For Oral Solution USP, Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP, and

Penicillin G Procaine Injectable Suspension USP (see the *Dosage Forms* section).[R-9; 27; 28]

Chemistry

Source: Produced by the mold *Penicillium*.[R-1]

Chemical group: Beta-lactam antibiotics.[R-1; 29]

Chemical name:

Penicillin G benzathine—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, [2*S*-(2α,5α,6β)]-, compd. with *N*,*N*′-bis(phenylmethyl)-1,2-ethanediamine (2:1), tetrahydrate.[R-30]

Penicillin G potassium—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, monopotassium salt, [2*S*-(2α,5α,6β)]-.[R-30]

Penicillin G procaine—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, [2*S*-(2α,5α,6β)]-, compd. with 2-(diethylamino)ethyl 4-aminobenzoate (1:1) monohydrate.[R-30]

Penicillin G sodium—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, [2*S*-(2α,5α,6β)]-, monosodium salt.[R-30]

Molecular formula:

Penicillin G benzathine—$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2 \cdot 4H_2O$.[R-30]

Penicillin G potassium—$C_{16}H_{17}KN_2O_4S$.[R-30]

Penicillin G procaine—$C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2 \cdot H_2O$.[R-30]

Penicillin G sodium—$C_{16}H_{17}N_2NaO_4S$.[R-30]

Molecular weight:

Penicillin G benzathine—981.18.[R-30]

Penicillin G potassium—372.48.[R-30]

Penicillin G procaine—588.72.[R-30]

Penicillin G sodium—356.37.[R-30]

Description:

Penicillin G Benzathine USP—White, odorless, crystalline powder.[R-51]

Penicillin G Potassium USP—Colorless or white crystals, or white, crystalline powder. Is odorless or practically so, and is moderately hygroscopic. Its solutions are dextrorotatory. Its solutions retain substantially full potency for several days at temperatures below 15 ºC, but are rapidly inactivated by acids, by alkali hydroxides, by glycerin, and by oxidizing agents.[R-51]

Penicillin G Procaine USP—White crystals or white, very fine, microcrystalline powder. Is odorless or practically odorless, and is relatively stable in air. Its solutions are dextrorotatory. Is rapidly inactivated by acids, by alkali hydroxides, and by oxidizing agents.[R-51]

Penicillin G Sodium USP—Colorless or white crystals or white to slightly yellow, crystalline powder. Is odorless or practically odorless, and is moderately hygroscopic. Its solutions are dextrorotatory. Is relatively stable in air, but is inactivated by prolonged heating at about 100 ºC, especially in the presence of moisture. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15 ºC. Its solutions are rapidly inactivated by acids, alkali hydroxides, oxidizing agents, and penicillinase.[R-51]

pKa: 2.7.[R-2; 32]

Solubility:

Penicillin G Benzathine USP—Very slightly soluble in water; sparingly soluble in alcohol.[R-51]

Penicillin G Potassium USP—Very soluble in water, in saline TS, and in dextrose solutions; sparingly soluble in alcohol.[R-51]

Penicillin G Procaine USP—Slightly soluble in water; soluble in alcohol and in chloroform.[R-51]

Pharmacology/Pharmacokinetics

See also *Table 1. Pharmacokinetic Parameters* at the end of this monograph.

Note: With the exception of information in *Table 1*, pharmacokinetic data in this section are based on intravenous administration of potassium or sodium penicillin G.

Mechanism of action/Effect: The penicillins produce their bactericidal effect by inhibition of bacterial cell wall synthesis.[R-29] Pencillin G must penetrate the cell wall to attach to specific proteins on the inner surface of the bacterial cell membrane. In actively growing cells, the binding of penicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in an hypo- or iso-osmotic environment.[R-4; 29; 33]

Absorption:

Gastric absorption of penicillin G is poor in many species because it is rapidly hydrolyzed in the acid environment of the stomach or abomasum.[R-4] Only 15 to 30% of penicillin G may be absorbed by the oral route in a fasted animal and that percent decreases when there is food in the stomach.[R-34]

The sodium and potassium salts of penicillin G are the only dosage forms that are suitable for intravenous administration. They are also the most quickly absorbed from intramuscular or subcutaneous sites of administration.[R-4; 34; 35] Procaine penicillin G is more slowly absorbed from intramuscular administration than are the sodium or potassium salts and so produces more sustained but lower plasma concentrations.[R-4; 35] Benzathine penicillin G is the least soluble of the dosage forms and so is the most slowly absorbed; the longest sustained but lowest plasma concentrations of penicillin G are produced.[R-4; 35] The rate of absorption from intramuscular injections of some penicillin dosage forms, such as procaine penicillin G, can vary depending on the injection site; injections into the neck muscle in cattle and horses produce more rapid absorption and higher plasma concentrations than do injections into the gluteal muscle. Also, procaine penicillin G is more completely absorbed in steers when injected intramuscularly than when administered subcutaneously.

Distribution: Volume of distribution—

Dromedaries: 0.34 ± 0.079 liter per kg (L/kg).[R-59]

Horses: 0.72 ± 0.16 L/kg.[R-44]

Sheep: 0.604 ± 0.205 L/kg.[R-59]

Protein binding:

Cattle—28.5%.[R-38; 39]

Dogs—60%.[R-40]

Horses—52–54%.[R-39; 41]

Rabbits—35%.[R-39; 42]

Sheep—30.4%.[R-38; 39]

Half-life: Elimination—

Calves, newborn to 15 days: 26.6 minutes.[R-60]

Dogs: 30 minutes.[R-39]

Dromedaries: 49 minutes.[R-59]

Horses: 48 to 53 minutes.[R-41; 57]

Sheep: 42 minutes.[R-59]

Turkeys: 30 minutes.[R-62]

Elimination: Primarily renal;[R-2; 4] active renal tubular secretion occurs.[R-89] From 60 to 100% of the dose is recoverable from urine following injection of an aqueous solution of penicillin G.[R-43]

Total clearance—

Dromedaries: 4.87 ± 0.63 mL/min/kg.[R-59]

Horses: 8.5 ± 1.33 mL/min/kg.[R-44]

Sheep: 9.17 ± 1.39 mL/min/kg.[R-59]

Calves:

Newborn—2.98 ± 0.52 mL/min/kg.[R-60]

Five days—4.83 ± 1.45 mL/min/kg.[R-60]

Ten days—3.11 ± 1 mL/min/kg.[R-60]

Fifteen days—4.65 ± 1.18 mL/min/kg.[R-60]

Precautions to Consider

Cross-sensitivity and/or related problems

In humans, patients allergic to other penicillins may also be allergic to penicillin G; in addition, patients allergic to cephalosporins may be allergic to penicillin G.[R-52] The incidence of these occurrences in animals is unknown, but it is recommended that penicillin use be avoided in animals that have had a previous severe reaction.[R-2]

Animals allergic to procaine or other ester-type local anesthetics may also be allergic to penicillin G procaine.[R-6; 75]

Pregnancy/Reproduction

Penicillins have been shown to cross the placenta; however, no teratogenic problems have been associated with the use of penicillin G during pregnancy in studies of mice, rabbits, and rats, or during clinical use in many species. No well-controlled studies have been performed for most species.[R-75]

Lactation

Penicillin G is distributed into milk;[R-2] in food animals the distribution is sufficient to cause violative residues. However, the concentrations of penicillin produced in milk are subtherapeutic for most bacteria.[R-85] In sheep, 0.11% of an intramuscular injection of sodium penicillin G was distributed into the milk.[R-31]

Pediatrics

In neonates that have not yet developed full renal function, excretion of penicillin G occurs at a slower rate than it does in a mature animal.[R-60; 75]

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.

Antibacterials, bacteriostatic, such as:
Chloramphenicol or
Tetracycline
(because penicillin G acts only on cells that are actively reproducing, bacteriostatic antibiotics such as chloramphenicol or tetracycline may decrease the efficacy of penicillin G by depressing the activity of target cells;[R-43] however, the clinical significance of this interference is not well documented[R-66])

Phenylbutazone
(the administration of phenylbutazone concurrently with penicillin G may cause higher plasma concentrations of penicillin G, resulting in lower distribution of penicillin G to the tissues)[R-44]

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:

» Hypersensitivity to penicillin
(some reactions, such as hemolytic anemia in horses,[R-49] may be much more likely to occur in an animal that has had a previous reaction to penicillin G)

» Hypersensitivity to procaine[R-6]
(some sources recommend intradermal procaine testing of animals suspected of procaine sensitivity before administering procaine penicillin G)

Risk-benefit should be considered when the following medical problems exist:

Erysipelas in pigs
(administration of procaine penicillin has caused recurrence or exacerbation of signs of erysipelas including abortion, cyanotic ears, fever of 39.5 to 41 ºC, inappetance, lassitude, vomiting, and shivering)[R-50]

Renal function impairment
(because penicillin G is primarily excreted by the kidneys, unnecessary accumulation of medication in the plasma and tissues may occur;[R-45] also, the sodium or potassium content of intravenous penicillin G dosage forms should be considered)

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):

Culture and susceptibility, *in vitro*, and
Minimum inhibitory concentration (MIC)
(*in vitro* cultures and MIC test should be done on samples collected prior to penicillin administration to determine pathogen susceptibility)

Potassium or sodium, serum
(determination of concentrations of serum sodium or potassium may be necessary in animals receiving high doses or long-term therapy with potassium or sodium penicillin G, particularly in those patients with severe renal function impairment, other pre-existing electrolyte imbalance, or congestive heart failure)[R-75]

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 unknown

All species

Allergic reactions, specifically anaphylaxis,[R-6] ***contact dermatitis,***[R-6] ***serum sickness–like syndromes,***[R-6] ***and urticaria;***[R-6] ***overgrowth of nonsusceptible organisms;***[R-7] ***procaine toxicity***—with procaine-containing dosage forms only

Note: Multiple cases of *procaine toxicity* have been reported in pig herds being treated for erysipelas.[R-50; 77] Signs included abortion, cyanotic ears, fever of 39.5 to 41 °C, inappetance, lassitude, vomiting, and shivering.

Horses

Allergic reactions, specifically anaphylaxis (hemorrhagic enterocolitis, progressive respiratory distress from coughing to dyspnea to apnea);[R-6; 48] ***immune-mediated hemolytic anemia*** (icterus, inappetance, listlessness, paleness of mucous membranes, red-brown urine, splenomegaly, tachycardia);[R-49] ***procaine toxicity*** (signs in reported order of occurrence: fright, sudden backing, aimless galloping, loss of coordination, muscle tremors, apnea, cardiac arrest)—with high doses of procaine-containing dosage forms[R-48]

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

All species

Pain at site of injection—with higher doses[R-69]

Human side/adverse effects[R-47]

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 *Penicillins (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 penicillin G in the treatment of animals:

Incidence more frequent

Gastrointestinal reactions; headache; oral candidiasis; vaginal candidiasis

Incidence less frequent

Allergic reactions, specifically anaphylaxis; exfoliative dermatitis; serum sickness–like reactions; skin rash, hives, or itching

Incidence rare

Clostridium difficile colitis; hepatotoxicity; interstitial nephritis; leukopenia or neutropenia; mental disturbances; pain at site of injection; platelet dysfunction or thrombocytopenia; seizures

Note: *Clostridium difficile colitis* may occur up to several weeks after discontinuation of these medications.

Interstitial nephritis is seen primarily with methicillin, and to a lesser degree with nafcillin and oxacillin, but may occur with any penicillin.

Mental disturbances are toxic reactions to the procaine content of penicillin G procaine; this reaction may be seen in patients who receive a large single dose of the medication, as in the treatment of gonorrhea.

Seizures are more likely to occur in patients receiving high doses of a penicillin and/or patients with severe renal function impairment.

Overdose

For information in cases 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 Dosing Information

For parenteral dosage forms only

To prevent procaine toxicity, keeping procaine penicillin at proper storage temperature and following shelf life recommendations are recommended to avoid any degradation of the product.{R-48}

For treatment of adverse effects

Recommended treatment consists of the following:

For anaphylaxis

- Parenteral epinephrine.{R-6}
- Oxygen administration and respiratory support.

For procaine toxicity{R-76}

- If seizures occur, sedation with diazepam{R-48} and/or barbiturates.{R-6}
- Oxygen administration and respiratory support as needed.
- Treatment for cardiovascular collapse if necessary.

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.

PENICILLIN G POTASSIUM FOR ORAL SOLUTION USP

Usual dose: Antibacterial—

Turkeys: Oral, administered as the sole source of drinking water at a concentration of 1,500,000 Units per gallon (395,000 Units per L) for five days.{R-8}

Withdrawal times—US and Canada: Meat—1 day.{R-8; 9; 26}

Not labeled for use in turkeys producing eggs for human consumption.{R-9}

[EL-US]*Pigs*[EL]: Oral, administered as the sole source of drinking water at a concentration of 297,000 Units per liter of water for five days.{R-9}

Withdrawal times—Canada: Meat—1 day.{R-9}

Size(s) usually available:{R-46}

U.S.—{R-8}

Veterinary-labeled product(s):

384,000,000 Units (OTC) [*R-Pen*].

500,000,000 Units (OTC) [*R-Pen; PenAqua Sol-G;* GENERIC].

Canada—{R-9}

Veterinary-labeled product(s):

100,000,000 Units (OTC) [*Pot-Pen*].

500,000,000 Units (OTC) [*Pot-Pen;* GENERIC].

15,000,000,000 Units (OTC) [*Pot-Pen;* GENERIC].

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 °C (59 and 86 ºF), unless otherwise specified by the manufacturer. Store in a tight container.

Preparation of dosage form:

U.S.—Dissolve 384,000,000 Units in 256 Gallons (969 L) to produce the final 1,500,000 Units per Gallon (3.8 L) solution.{R-8}

Canada—Dissolve 100,000,000 Units in 88.7 Gallons (337 L) to produce the final 1,128,600 Units per Gallon (3.8 L) solution.{R-9}

Stability: Gravity flow water systems require preparation of fresh solutions every 12 hours. Automatic watering systems require fresh solution preparation every 24 hours.{R-8}

USP requirements: Preserve in tight containers. A dry mixture of Penicillin G Potassium and one or more suitable buffers, colors, diluents, flavors, and preservatives. Contains the labeled number of Penicillin G Units when constituted as directed in the labeling, within –10% to +30%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume (multiple-unit containers), pH (5.5–7.5, in the solution constituted as directed in the labeling), and Water (not more than 1.0%).{R-51}

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.

PENICILLIN G BENZATHINE AND PENICILLIN G PROCAINE INJECTABLE SUSPENSION USP

Note: Penicillin G benzathine and penicillin G procaine combination has been replaced by other more effective medications. Although products containing penicillin G procaine and penicillin G benzathine combined may be effective in the treatment of extremely sensitive organisms, the plasma concentration of penicillin G produced by the administration of recommended doses of penicillin G benzathine drops to such a low level after 12 to 48 hours that it becomes ineffective in the treatment of most systemic infections.{R-78; 79} No dosage of these penicillin G procaine and penicillin G benzathine combinations can be recommended as likely to be effective for many infections caused by penicillin-sensitive organisms.{R-88} Even when administered at label doses, the risk exists for residues, which are 30 to 60 times the maximum limit, to occur at the injection

site.{R-80}

Withdrawal times—US: Meat—30 days.{R-26} US product labeling states that this withdrawal time applies when a dose of 4400 Units of penicillin G benzathine and 4400 Units of penicillin G procaine per kg (2000 Units of each per pound) of body weight is administered subcutaneously to beef cattle every 48 hours for two treatments and is not applicable to higher doses or longer administration.{R-5} Canada: Meat—14 days.{R-27; 28} Canadian product labeling states that this withdrawal time applies when a dose of up to 4444 Units of penicillin G benzathine and 4444 Units of penicillin G procaine per kg of body weight is administered intramuscularly to treated animals and is not applicable to higher doses or longer administration.{R-27; 28; 63} This product is not labeled for use in lactating cows or horses intended for human consumption.{R-28}

Strength(s) usually available:{R-46}

U.S.—

Veterinary-labeled product(s):

150,000 Units of penicillin G benzathine and 150,000 Units of penicillin G procaine per mL (Rx) [*Combi-Pen-48; Dual-Cillin; Durapen; Pen BP-48; Twin-Pen; UltraPen B;* GENERIC].

Canada—

Veterinary-labeled product(s):

150,000 Units of penicillin G benzathine and 150,000 Units of penicillin G procaine per mL (Rx) [*Duplocillin LA; Longisil*].

Packaging and storage: Store between 2 and 8 °C (36 and 46 ºF). Protect from freezing.{R-5}

Preparation of dosage form: The vial should be warmed to room temperature and shaken well to insure a uniform suspension.{R-5}

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass. A sterile suspension of Penicillin G Benzathine and Penicillin G Procaine or when labeled for veterinary use only, of Penicillin G Benzathine and Penicillin G Procaine, in Water for Injection. Where it is intended for veterinary use only, it is so labeled. May contain one or more suitable buffers, preservatives, and suspending agents. Contains the labeled amounts, within –10% to +15%. Meets the requirements for Identification, Crystallinity, pH (5.0–7.5), Limit of soluble penicillin G and procaine (where it is prepared from penicillin G procaine and is labeled for veterinary use only, not more than 1%), and for Bacterial endotoxins, and Sterility under Penicillin G Procaine Suspension, and for Injections.{R-51}

PENICILLIN G POTASSIUM FOR INJECTION USP

Usual dose: EL[US,CAN]Antibacterial[EL]—

Cats and *dogs:* Intravenous or intramuscular, 20,000 to 40,000 Units per kg of body weight every six to eight hours.{R-54}

Horses: Intravenous or intramuscular, 20,000 Units per kg of body weight every six to eight hours.{R-57; 65}

Size(s) usually available:

U.S.—{R-66; 67}

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

1,000,000 Units (Rx) [GENERIC].

5,000,000 Units (Rx) [*Pfizerpen;* GENERIC].

20,000,000 Units (Rx) [*Pfizerpen;* GENERIC].

Canada—{R-68}

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

Not commercially available.

Packaging and storage: Prior to reconstitution, store below 40 ºC (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

Preparation of dosage form:

To prepare initial dilution for intramuscular or intravenous use, see the manufacturer's labeling.

To prepare for further dilution for intravenous use, see the manufacturer's labeling.

Stability: After reconstitution, solutions retain their potency for 24 hours at room temperature or for 7 days if refrigerated.{R-66; 68}

Incompatibilities:

Penicillin G potassium is rapidly inactivated by oxidizing and reducing agents, such as alcohols and glycols.{R-68}

Extemporaneous admixtures of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. Do not mix these antibacterial agents in the same intravenous bag, bottle, or tubing.{R-69}

Additional information:

Human guidelines recommend that daily doses of 10,000,000 Units or more should be administered by slow intravenous infusion or by intermittent piggyback infusion to avoid causing or exacerbating possible electrolyte imbalance.{R-68}

The potassium content and sodium content (derived from sodium citrate buffer) of penicillin G potassium for injection are approximately 1.7 mEq (66.3 mg) and 0.3 mEq (6.9 mg), respectively, per 1,000,000 Units of penicillin G.{R-66}

USP requirements: Preserve in Containers for Sterile Solids. It is sterile Penicillin G Potassium or a sterile, dry mixture of Penicillin G Potassium with not less than 4.0% and not more than 5.0% of Sodium Citrate, of which not more than 0.15% may be replaced by Citric Acid. Has a potency of the labeled number of Penicillin G Units, within –10% to +20%. In addition, where it contains Sodium Citrate it has a potency of not less than 1335 and not more than 1595 Penicillin G Units per mg. Meets the requirements for Constituted solution, Identification, Crystallinity, Bacterial endotoxins, Sterility, pH (6.0–8.5, in a solution containing 60 mg per mL or, where packaged for dispensing, in the solution constituted as directed in the labeling), Loss on drying (not more than 1.5%), and Particulate matter, and for Uniformity of dosage units and Labeling under Injections.{R-51}

PENICILLIN G PROCAINE INJECTABLE SUSPENSION USP

Usual dose: Antibacterial—

EL[US]*Cats*[EL] and EL[US]*dogs*: Intramuscular, 20,000 to 40,000 Units per kg of body weight every twelve to twenty-four hours.[EL]{R-54}

Cattle, pigs, and *sheep:* EL[US,CAN]Intramuscular, 24,000 to 66,000 Units per kg of body weight every twenty-four hours.[EL]{R-36; 79}

Withdrawal times:

U.S.—There are no products in the United States that list the above dosages.

US product type 1 lists a dose of 6600 Units per kg of body weight every twenty-four hours: *Calves*, preruminating—Meat withdrawal: 7 days. *Cattle*—Meat: 4 days, Milk: 48 hours. *Sheep*—Meat: 8 days. *Pigs*—Meat: 6 days.{R-7; 26; 53} Treatment should not exceed the labeled dose for five days in lactating cattle or seven days in nonlactating cattle, pigs, or sheep for these withdrawal times to apply.{R-7; 26}

US product type 2 also lists a dose of 6600 Units per kg of body weight every twenty four hours: *Cattle*—Meat: 10

days, Milk: 48 hours. *Sheep*—Meat: 9 days. *Pigs*—Meat: 7 days.{R-26; 53; 70} Treatment should not excede the labeled dose for four days for these withdrawal times to apply.{R-26; 53; 70} These products are not labeled for use in calves to be processed for veal or horses intended for human consumption.

Canada—

Canadian product type 1 lists a dose of 6670 Units per kg of body weight every twenty-four hours for cattle and 12,000 to 18,000 Units per kg of body weight every twenty-four hours for pigs or sheep: *Cattle*—Meat: 5 days, Milk: 72 hours. *Pigs* and *sheep*—Meat: 5 days.{R-81}

Canadian product type 2 lists a dose of 15,000 Units per kg of body weight every twenty-four hours for pigs and 21,000 Units per kg of body weight every twenty-four hours for cattle and sheep: *Cattle*—Meat: 10 days, Milk: 96 hours. *Pigs*—Meat: 8 days. *Sheep*—Meat: 10 days.{R-93} Treatment should not exceed the labeled dose for five days for withdrawal times to apply.{R-93}

Extra-label withdrawal times—The Canadian Bureau of Veterinary Drugs has published results of tissue residue studies and calculated withdrawal times for use of penicillin G procaine administered at doses that are higher than U.S. label doses.{R-80; 82; 83} Some of these withdrawal times are now listed in the labeling of Canadian products, as shown above, with the exception of the withdrawal calculated for the highest dose.

US: Because dosages greater than 6600 Units per kg in the treatment of cattle, pigs, and sheep are not included in product labeling in the United States, there are no established withdrawal times for higher dosages. If penicillin G procaine injectable suspension is administered to pigs at a dose of 15,000 Units per kg of body weight, evidence has been compiled by the Food Animal Residue Avoidance Databank (FARAD) that suggests a meat withdrawal interval of 8 days would be sufficient to avoid violative residues.{R-94} If penicillin G procaine injectable suspension is administered to cattle at a dose of 24,000 Units per kg of body weight, evidence has been compiled by FARAD that suggests a meat withdrawal interval of 12 days would be sufficient to avoid violative residues.{R-94} If penicillin G procaine injectable suspension is administered at a dose of 66,000 Units per kg of body weight, evidence has been compiled by FARAD that suggests a meat withdrawal interval of 21 days for cattle and 15 days for pigs would be sufficient to avoid violative residues.{R-94}

Canada: If penicillin G procaine injectable suspension is administered at the extra-label dose of 60,000 Units per kg of body weight every twenty-four hours, there is some evidence to suggest that a withdrawal time of 21 days would be sufficient to avoid violative residues in sheep and nonlactating cattle and that a withdrawal time of 15 days would be sufficient for pigs.

Horses: Intramuscular, ELUS21,000 Units per kg of body weight every twelve to twenty-four hours.EL{R-56; 58; 65; 69; 93}

Withdrawal times—Canada: These products are not labeled for use in horses intended for human consumption.{R-93}

Note: Penicillin G procaine should not be administered subcutaneously at high doses{R-80} because doing so produces significant local inflammation and hemorrhage, as well as medication deposits{R-82} that can contribute to residue problems. The maximum dose per injection site of penicillin G procaine should be 3,000,000 Units (10 mL); injection sites should be different for each succeeding treatment.{R-7; 53} Penicillin G procaine should never be administered intravenously.

Strength(s) usually available:{R-46}

U.S.—

Veterinary-labeled product(s):

300,000 Units per mL (OTC) [*Agri-cillin; Aquacillin; Pen-Aqueous; Pen-G; Pro-Pen-G; UltraPen;* GENERIC].

Canada—

Veterinary-labeled product(s):

300,000 Units per mL (OTC) [*Depocillin; Hi-Pencin 300; Pen-Aqueous; Pen G Injection; Penmed; Penpro; Pen Vet 300; Procillin;* GENERIC].

Packaging and storage: Store between 2 and 8 °C (36 and 46 °F). Protect from freezing.{R-53; 70}

Preparation of dosage form: The vial should be warmed to room temperature and shaken well to insure a uniform suspension.{R-53}

Additional information:

Some animals may develop procaine toxicity, which can result in acute neurologic signs.{R-48}

Administration of penicillin G procaine to racing horses may produce violative procaine concentrations in urine for more than two weeks.{R-91; 92}

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass, in a refrigerator. A sterile suspension of Penicillin G Procaine or, where labeled for veterinary use only, of sterile penicillin G procaine, in Water for Injection and contains one or more suitable buffers, dispersants, or suspending agents, and a suitable preservative. It may contain procaine hydrochloride in a concentration not exceeding 2.0%. Where it is intended for veterinary use, the label so states. Contains an amount of penicillin G procaine equivalent to the labeled amount of penicillin G, within –10% to +15%, the labeled amount being not less than 300,000 Penicillin G Units per mL or per container. Meets the requirements for Identification, Crystallinity, Bacterial endotoxins, Sterility, pH (5.0–7.5), and Penicillin G and procaine contents, and for Injections.{R-51}

PENICILLIN G PROCAINE INJECTABLE OIL SUSPENSION

Note: These Canadian products list their strengths and dosing in terms of milligrams rather than international units (IU);{R-46} procaine penicillin G contains 1009 penicillin G IU per mg.{R-25}

Usual dose: ELUSAntibacterialEL—

Cattle: Intramuscular or subcutaneous, 20 mg per kg of body weight, as a single dose.{R-27}

Pigs: Intramuscular, 20 mg per kg of body weight, as a single dose.{R-27}

Withdrawal times—Canada: *Cattle*—Meat: Intramuscular administration—21 days, Subcutaneous administration—14 days. *Pigs*—Meat: 10 days.{R-27} Canadian product labeling listing the above withdrawal times states that they apply when a single dose of 20 mg per kg of body weight is administered to nonlactating cattle by intramuscular or subcutaneous injection and to pigs by intramuscular injection only. The dose may be repeated in seventy-two hours.{R-27}

Extra-label withdrawal times—For Canadian injectable oil suspensions, there is insufficient information available about drug disposition to recommend extra-label withdrawal intervals. Contact Canadian gFARAD for more information (www.cgfarad.usask.ca).

Note: Penicillin G procaine should not be administered subcutaneously at high doses{R-80} because doing so produces significant local inflammation and hemorrhage, as well as

medication deposits{R-82} that can contribute to residue problems. The maximum dose per injection site of penicillin G procaine should be 15 mL for cattle and 10 mL for pigs; injection sites should be different for each succeeding treatment.{R-27} Penicillin G procaine should never be administered intravenously.

Strength(s) usually available:{R-46}
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Canada—
Veterinary-labeled product(s):
300 mg per mL (OTC) [*Derapen SQ/LA; Propen LA*].

Packaging and storage: Store below 25 °C (77 °F). Protect from freezing.{R-27}

Preparation of dosage form: The vial should be warmed to room temperature and shaken well to insure a uniform suspension.{R-53}

Additional information:
Some animals may develop procaine toxicity, which can result in acute neurologic signs.{R-48}
Administration of penicillin G procaine to racing horses may produce violative procaine concentrations in urine for more than two weeks.{R-91; 92}

USP requirements: Not in USP.{R-51}

PENICILLIN G SODIUM FOR INJECTION USP
Usual dose: EL,US,CAN Antibacterial EL—See *Penicillin G Potassium for Injection USP*.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
5,000,000 Units (Rx) [GENERIC].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
1,000,000 Units (Rx) [GENERIC].
5,000,000 Units (Rx) [GENERIC].
10,000,000 Units (Rx) [GENERIC].

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

Preparation of dosage form: To prepare initial dilution for intramuscular or intravenous use, see manufacturer's labeling for instructions.

Stability: After reconstitution, solutions retain their potency for 24 hours at room temperature or for 7 days if refrigerated.{R-68}

Incompatibilities:
Penicillin G sodium is rapidly inactivated by acids, alkalies, and oxidizing agents and in carbohydrate solutions at alkaline pH.
Extemporaneous admixtures of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. Do not mix these antibacterials in the same intravenous bag, bottle, or tubing.{R-29; 71}

Additional information:{R-68}
Human guidelines recommend that daily doses of 10,000,000 Units or more should be administered by slow intravenous infusion to avoid causing or exacerbating electrolyte imbalance.
The sodium content is approximately 2 mEq (2 mmol) per 1,000,000 Units of penicillin G. This should be considered in patients on a restricted sodium intake.

USP requirements: Preserve in Containers for Sterile Solids. It is sterile Penicillin G Sodium or a sterile mixture of penicillin G sodium and not less than 4.0% and not more than 5.0% of Sodium Citrate, of which not more than 0.15% may be replaced by Citric Acid. Contains the labeled amount of Penicillin G, within –10% to +20%, and where it contains Sodium Citrate it has a potency of not less than 1420 and not more than 1667 Penicillin G Units per mg. Meets the requirements for Constituted solution, Identification, Crystallinity, Bacterial endotoxins, Sterility, pH (6.0–7.5, in a solution containing 60 mg per mL), Loss on drying (not more than 1.5%), and Particulate matter, and for Uniformity of dosage units and Labeling under Injections.{R-51}

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Interim revision: 07/19/95; 07/11/96; 7/15/98; 11/5/99; 09/30/02; 04/05/03; 06/30/07

Table 1. Pharmacokinetic Parameters

Species	Penicillin G Dosage Form	Dose (Units/kg)	Route/Site Of Administration*	C_{max} (mcg/mL)	T_{max} (hours)	Duration† Of Action (hours)	Target† Minimum Serum Conc. (mcg/mL)	Disappearance Rate Constant (hour $^{-1}$)
Calves (6–9 mo.)	Potassium{R-55}	10,000	IM/Neck	4.71 ± 3.86	1 to 1.5	—	—	—
	Procaine{R-55}	30,000	IM/Neck	1.55 ± 0.33	1.5 to 6	—	—	—
Cattle	Procaine{R-36}	66,000	IM/Neck	4.24 ± 1.08	6.00 ± 0.00	—	—	0.08 ± 0.03
		66,000	SC/Neck	1.85 ± 0.27	5.33 ± 0.67	—	—	0.04 ± 0.01
After 5-day administration	Procaine{R-36}	24,000	IM/Gluteal	0.99 ± 0.04	5.33 ± 0.67	—	—	0.04 ± 0.01
		66,000	IM/Gluteal	2.63 ± 0.27	6.00 ± 0.00	—	—	0.04 ± 0.00
During 7-day administration:	Benzathine with Procaine{R-69}‡	11,000	IM/Not stated	0.72	2			
Foals (0—7 days)	Procaine{R-58}	22,000	IM/Semimembranosus	2.17 ± 0.27	2			

Horses	Sodium[{R-57}]	10,000	IV/Jugular			1.68	0.5
		20,000	IV/Jugular			2.92	0.5
		40,000	IV/Jugular			3.90	0.5
	Procaine[{R-57}]	10,000	IM/Gluteal			4.90	0.5
		20,000	IM/Gluteal			18.75	0.5
		40,000	IM/Gluteal			>24	0.5
	Procaine[{R-56}]	22,000	IM/Gluteal	1.42 ± 0.22	3		

*Legend: IM = intramuscular; IV = intravenous; SC = subcutaneous.
†The durations of action in this study were based on a specific minimum target serum concentration considered by that researcher to be a value high enough to treat penicillin-susceptible organisms.
‡This study gave the stated dose once every 24 hours and monitored serum concentrations for 7 days. The C_{max} shown here was the highest measured; values stayed below 0.31 after the first day and went as low as 0.12 mcg/mL.

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