PHENYLBUTAZONE Veterinary—Systemic

Some commonly used brand names for veterinary-labeled products are: *Butaject; Butapaste; Butasone 400; Butasone 1000; Butasone Conc; Butatabs-D; Butatabs-E; Butatron Tablets; Butequine; Buzone Concentrate Powder; Equi-Phar Phenylbutazone 1 Gram Tablets; Equi-Phar Phenylbutazone Injection 20%; Equiphen Paste; Phenylbute Injection 20%; Phenylbute Paste; Phenylbute Tablets 1 Gram; Phenylbute Tablets 100 Mg; Phenylbute Tablets 200 Mg; Phenylzone Paste; Pributazone Tablets; Pro-Bute Injection;* and *Pro-Bute Tablets.*

Some commonly used *brand names* for human-labeled products are *Apo-Phenylbutazone* and *Butazolidin*.

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

Category: Anti-inflammatory, nonsteroidal; analgesic; antipyretic.

Indications

Note: Bracketed information in the *Indications* section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

Accepted

Note: Relief of inflammatory conditions associated with the musculoskeletal system is a common labeled indication for the use of phenylbutazone in dogs and horses. For the purpose of this resource, the USP Veterinary Medicine Committee has interpreted this to mean the following unbracketed indications are labeled uses.

Inflammation, musculoskeletal (treatment); or

Pain (treatment)—*Dogs, horses,* and [*cattle*][1]: Phenylbutazone is indicated for the relief of musculoskeletal inflammation and mild to moderate somatic or [visceral][1] pain. It seems especially of value for the treatment of pain of musculoskeletal and inflammatory origin in dogs, horses, and [cattle][1]. Such conditions commonly include arthritis and laminitis.{R-2} See also the *Regulatory Considerations* section below.

[Fever (treatment)][1]; or

[Inflammation, general (treatment)][1]—Although they are not labeled indications, phenylbutazone, as a nonsteroidal anti-inflammatory drug, would be expected to lower fever and suppress inflammation other than musculoskeletal inflammation in those species where information exists for proper dosing.

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[1]Not included in Canadian product labeling or product not commercially available in Canada.

Regulatory Considerations

U.S.—

The extra-label use of phenylbutazone in female dairy cattle 20 months of age or older is **prohibited** by the United States Food and Drug Administration.{R-34} Although other extra-label uses in food-producing animals, as stated in Animal Medicinal Drug Use Clarification Act (AMDUCA) guidelines, are legal at this writing, the practitioner should check current statutes to be sure restrictions on the use of phenylbutazone in food-producing animals have not been broadened.

The Food and Drug Administration has not approved the use of phenylbutazone in food-producing animals; therefore, there are no established withdrawal times on product labeling for food-producing species. Phenylbutazone is not permitted at any concentration (zero tolerance) in meat, milk, or eggs intended for human consumption. (See also the *Dosage Forms* section of this monograph.)

Federal law restricts phenylbutazone to use by or on the order of a

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licensed veterinarian.

Canada—

Phenylbutazone is not labeled for use in food-producing animals; therefore, there are no established withdrawal times on product labeling for food-producing species. Phenylbutazone is not permitted at any concentration (zero tolerance) in meat, milk, or eggs intended for human consumption. (See suggested withdrawals for extra-label use in the *Dosage Forms* section of this monograph.)

Federal law restricts phenylbutazone to use by or on the order of a licensed veterinarian.

Chemistry

Chemical group: Pyrazolone derivative.{R-3}

Chemical name: 3,5-Pyrazolidinedione, 4-butyl-1,2-diphenyl-.{R-32}

Molecular formula: $C_{19}H_{20}N_2O_2$.{R-32}

Molecular weight: 308.37.{R-32}

Description: Phenylbutazone USP—White to off-white, odorless, crystalline powder.{R-4}

pKa: 4.5 (in water).{R-5}

pH of aqueous solution: 8.2.{R-5}

Solubility: Phenylbutazone USP—Very slightly soluble in water; freely soluble in acetone and in ether; soluble in alcohol.{R-4}

Pharmacology/Pharmacokinetics

Note: See also *Table 1. Pharmacology/Pharmacokinetics,* at the end of this monograph.

Mechanism of action/Effect: Inhibition of the arachidonic acid cascade at the level of prostaglandin H synthase and prostacyclin synthase results in decreased production of prostaglandins and thromboxane. Phenylbutazone also inhibits urate crystal phagocytosis by synoviocytes.{R-6}

Other actions: Phenylbutazone reversibly inhibits platelet aggregation. It induces hepatic microsomal enzyme activity. This drug also has uricosuric activity.{R-1}

Absorption:

Cattle—Average oral bioavailability ranged from 54 to 69% in one study.{R-7; 8}

Horses—Approximately 70%. Feed, especially hay, delays time to peak effect and decreases peak plasma concentrations.

Distribution: Phenylbutazone is distributed mainly into plasma and extracellular fluid, as indicated by the relatively small volume of distribution. This low volume of distribution is also indicative of only nominal tissue binding.{R-9}

Protein binding:

Cattle—93 to 98%.{R-9}

Horses—Greater than 98%.

Other species—Protein binding is thought to be very high in other species as well.

Biotransformation: Hepatic. Rate may differ significantly among species and breeds. Phenylbutazone is known to induce hepatic microsomal enzyme activity. Paradoxically, however, mixed function oxidase activity may become saturated, leading to decreasing metabolic rates.

Time to peak plasma concentration:

Cattle—Peak plasma concentration is reached in 8.9 to 10.5 hours in cattle following oral administration.{R-8; 9}

Human data—Peak plasma concentration is reached in about 2 hours after oral administration and 6 to 10 hours after intramuscular

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injection in humans.{R-12}

Peak plasma concentration:

Dogs—A peak plasma phenylbutazone concentration of 49 to 75 mcg/mL occurred following a dose of 15 mg per kg of body weight (mg/kg) given orally to greyhounds.

Human data—A mean peak plasma concentration of 33 mcg/mL was reached 3 hours after oral administration of 300 mg to 6 healthy subjects.{R-13}

Serum concentration: *Cattle*—The mean minimum concentration at steady state in cows given 5 mg per kg of body weight (mg/kg) twice a day for 8 days was 100.4 ± 7.3 mcg/mL.{R-10} Six bulls given a loading dose of 12 mg/kg followed by an oral maintenance dose of 6 mg/kg for 7 additional days had a mean minimum plasma concentration of 75.06 mcg/mL. A minimal plasma drug concentration (minimum effective concentration, MEC) of 50 to 100 mcg/mL of phenylbutazone has been suggested for analgesia in cattle and humans.{R-9}

Peak tissue concentration: *Rabbits*—After an intra-arterial dose of 8 mg/kg in rabbits, concentrations in muscle ranged from 0.16 to 1.3 mcg/gram with detectable levels present up to 7 hours post-administration. Concentrations in the cortex of the kidney ranged from 0.21 to 14.5 mcg/gram with detectable levels present at the end of the study, 22.25 hours post-administration. Levels in the renal medulla ranged from 0.085 to 5.1 mcg/gram and were also present at the end of the study, 22.25 hours post-administration.{R-14}

Liver concentrations: *Rabbits*—After intra-arterial administration of 8 mg/kg, concentrations ranged from 12.4 mcg/gram at 40 minutes to 0.15 mcg/gram 18 hours after administration.{R-14}

Milk concentrations: *Cattle*—Concentrations in milk do not exceed 1% of plasma concentrations.{R-10} The lowest detected concentration of phenylbutazone in milk appeared 5 days after the last dose in a regimen of 5 mg/kg twice a day for eight days, and was found to be 0.05 ± 0.01 mcg/mL.{R-10} The total amount of phenylbutazone excreted into milk during plasma steady state was 0.35 ± 0.07% of the amount administered during the same period.{R-10; 37}

Elimination: It is important to note that phenylbutazone follows zero-order (dose-dependent) kinetics in dogs and horses. Whether this occurs in other species is unknown. Drugs with zero-order elimination typically have longer elimination half-lives as the dose increases. As such, it is important that the recommended doses not be exceeded.

Pigs: Only 0.13% of phenylbutazone and 6.8% of oxyphenylbutazone administered to pigs were excreted renally.{R-21}

Precautions to Consider

Species sensitivity

Cats: Not recommended for use in cats. Phenylbutazone is rapidly converted to the active metabolite oxyphenbutazone; oxyphenbutazone is very slowly eliminated by the cat.{R-11}

Pregnancy/Reproduction

Fetotoxicity, but not teratogenicity, has been demonstrated in animal studies.{R-1}

Lactation

Phenylbutazone is distributed into milk (see *Milk concentrations* above); it may cause blood dyscrasias or other adverse effects in nursing human infants.{R-1}

Geriatrics

Phenylbutazone appears to be eliminated more slowly from the plasma of aged animals, leading to higher plasma levels.

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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):

» Anesthetics
  (respiratory arrest has been observed in cattle pretreated with phenylbutazone when anesthetic induction was the combination of guaifenesin, xylazine, and ketamine; a reinduction of anesthesia has been observed when horses just recovered from barbiturate-glyceryl guaiacolate [guaifenesin] anesthesia were administered phenylbutazone; the mechanism for this interaction is unknown, but may be due to displacement of protein bound anesthetic to its free [active] form by the phenylbutazone)[{R-15}]

» Anti-inflammatory analgesics, nonsteroidal, other, or
  Corticosteroids or
  Dipyrone or
  Salicylates
    (concurrent use with phenylbutazone may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage; also, salicylates may increase the risk of bleeding at sites other than the gastrointestinal tract, due to additive inhibition of platelet aggregation)
  Chloramphenicol
    (the administration of chloramphenicol sodium succinate to mares reduced mean phenylbutazone clearance from 0.6 to 0.34 mg per minute per kg and increased mean half-life from 4.06 to 6.18 hours; the volume of distribution was unchanged)[{R-16}]

» Furosemide
    (premedication with phenylbutazone has been reported to significantly reduce the diurectic and hemodynamic effects of furosemide in horses)[{R-40}]

» Gentamicin
    (repeated administration of phenylbutazone to horses at recommended dosages has been reported to significantly reduce the distribution and elimination of a single intravenous bolus of gentamicin; care should be taken when considering aminoglycoside administration to horses being treated with phenylbutazone)[{R-38}]
  Thyroid hormones
    (concurrent administration with phenylbutazone may inhibit conversion of T_4 to T_3)

» Warfarin or related coumarins
    (phenylbutazone has caused bleeding episodes in animals previously stable on warfarin anticoagulation therapy; this is due to displacement of the warfarin from its protein binding sites by phenylbutazone)

Human drug interactions and/or related problems:[{R-1}]

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 *Anti-inflammatory Drugs, Nonsteroidal (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 phenylbutazone in the treatment of animals:

  Anticoagulants, coumarin- or indanedione-derivative
    (higher risk of bleeding when phenylbutazone is administered with coumarin- or indanedione-derivative anticoagulants than with other nonsteroidal anti-inflammatory drugs [NSAIDs] because phenylbutazone inhibits the anticoagulant's metabolism; concurrent use not recommended)
  Anticonvulsants, hydantoin
    (increased risk of toxicity with hydantoin anticonvulsants, such as phenytoin, because phenylbutazone may displace them from protein-binding sites and inhibit their metabolism)
  Barbiturates or
  Cortisone and possibly other corticosteroids or

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Digitalis glycosides or
Estrogen-containing oral contraceptives
(by inducing hepatic microsomal enzymes, phenylbutazone may decrease the effects of these medications)
Cholestyramine
(cholestyramine may decrease absorption of phenylbutazone; administration of phenylbutazone 1 hour before or 4 to 6 hours after cholestyramine is recommended)
Dermatitis-causing medications
(increased risk of severe dermatologic reactions when phenylbutazone is administered concurrently with other dermatitis-causing medications)
Hepatic microsomal enzyme inducers, other
(other hepatic enzyme inducers may increase phenylbutazone metabolism and decrease its half-life)
Methotrexate
(concurrent use with phenylbutazone may increase the risk of agranulocytosis or bone marrow depression)
Penicillamine
(concurrent use with phenylbutazone may increase the risk of serious hematologic and/or renal adverse effects)
Sulfonamides
(concurrent use with phenylbutazone may potentiate the effects of either or both medications)
Other medications, oral
(antacids in buffered phenylbutazone formulations may interfere with absorption of many other medications)

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 diagnostic test results
Thyroid function tests
(phenylbutazone may decrease total and free T_4 concentrations)
Note: A study in *horses* showed that phenylbutazone significantly decreased the baseline total and free thyroxine concentration after five days of treatment. Total T_4 values remained decreased for up to ten days after discontinuation. Free T_4 concentrations returned to baseline by the third day following discontinuation of the drug.[{R-17}]
A study in *dogs* showed that phenylbutazone at a plasma concentration of 50 mcg/mL had no significant effect on the free fraction of thyroxine in plasma.[{R-18}]

With physiology/laboratory test values
Bleeding time
(may be prolonged due to suppressed platelet aggregation)

Human laboratory value alterations[{R-1}]

The following laboratory value alterations have been reported in humans, and are included in the human monograph *Anti-inflammatory Drugs, Nonsteroidal (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 phenylbutazone in the treatment of animals:

With diagnostic test results
Thyroid function tests
(phenylbutazone may interfere with thyroid function tests; specifically, decreasing 24-hour ^{131}I thyroidal uptake or increasing resin or red cell triiodothyronine uptake)
With physiology/laboratory test values
Glucose concentrations
(phenylbutazone may increase blood glucose concentrations)
Uric acid concentrations
(phenylbutazone may decrease serum concentrations and increase urine concentrations of uric acid)

Medical considerations/Contraindications

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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).

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

Blood dyscrasias (or history of) or
Bone marrow suppression or
Gastrointestinal ulcer disease, active or
Hepatic or renal disease, severe
(phenylbutazone is not recommended for use in patients with the problems listed above)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition):

Hydration status
(assure adequate patient hydration)
Monitor for signs of gastrointestinal ulceration
(for example, anorexia, melena, vomiting)

With chronic administration or for patients with a history of renal disease, liver disease, bone marrow suppression, or gastrointestinal ulceration

Complete blood count (CBC) with platelets and
Liver enzymes, including alkaline aminotransferase (ALT [SGPT]) and
Total protein and
Urinalysis
(periodic testing should be considered)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent

Gastroenteropathy or gastrointestinal ulcers—especially in horses;[{R-11}] ***inflammation, severe, with tissue necrosis, abscessation and eventual sloughing of the vein***—with perivascular injection

Incidence less frequent

Blood dyscrasias—in small animals;[{R-11; 19}] ***impaired hepatic function***—may occur at high doses, especially in small animals; ***lesions, oral; necrotizing phlebitis in the portal vein***—in horses receiving high doses over extended periods of time; ***plasma pH, bicarbonate, and total carbon dioxide decrease; renal papillary necrosis; sodium and chloride retention; toxic neutropenia***—especially with restricted water intake

Note: Seven suspected phenylbutazone-induced *blood dyscrasias* in dogs have been reported in the literature. These included pancytopenias with marrow aplasia or hypoplasia, thrombocytopenias, non-regenerative anemias, and neutropenias. Approximately half of these animals recovered with discontinuation of the drug and supportive therapy.[{R-19}]

Human side/adverse effects[{R-1}]

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 *Anti-inflammatory Drugs, Nonsteroidal (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 phenylbutazone in the treatment of animals:

Note: Due to the long list of reported human side/adverse effects, some effects specific to people have not been included in the list below.

Incidence more frequent

Abdominal or stomach cramps; fluid retention/edema

Incidence less frequent or rare

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Abdominal distension; agranulocytosis; amblyopia, toxic, or retinal or macular disturbances; anaphylaxis or anaphylactoid reactions; anemia, hemolytic; angioedema; blood in urine; blurred vision or double vision; bronchospastic allergic reaction; change in hearing; cholestatic hepatitis or jaundice; colitis or regional enteritis; congestive heart failure or exacerbation of; constipation; crystalluria, renal calculi, or ureteral obstruction; dermatitis, allergic; dermatitis, exfoliative; diarrhea; dizziness; drowsiness; dry irritated or swollen eyes; erythema multiforme; erythema nodosum; esophagitis; fever; gastritis; gastrointestinal hemorrhage or ulceration; glomerulonephritis; headache; hepatitis; increased blood pressure; muscle cramps or pain; nephritis, interstitial; nephrotic syndrome; nervousness or irritability; neuropathy, peripheral; neutropenia; oliguria/anuria; pancreatitis, acute; pancytopenia; pericarditis; petechiae; proteinuria; regional enteritis or exacerbation of; renal impairment or failure; renal papillary or tubular necrosis; retinal hemorrhage; ringing or buzzing in ears; scotomata; serum sickness–like reaction; Stevens-Johnson syndrome; stomatitis, aphthous; systemic lupus erythematosus [SLE]–like syndrome; thrombocytopenia with or without purpura; toxic epidermal necrolysis; trembling; troubled breathing; unusual weakness; vasculitis; vomiting

Incidence unknown

Anxiety; bladder pain; bleeding from vagina; cardiac arrhythmias; colitis or exacerbation of; conjunctivitis; convulsions; corneal opacity; cystitis, urethritis, or urinary tract infection; decreased appetite or loss of appetite; desquamation; disseminated intravascular coagulation; dry, irritated, or swollen eyes; dysphagia; dysuria; ecchymosis/bruising; enterocolitis; eosinophilia; eosinophilic pneumonitis; erythema or other skin discoloration; fast heartbeat; gastroenteritis; gastrointestinal perforation; gingival ulceration; glossitis; hemoptysis; hyperkalemia; hypocoagulability; incontinence; increased sweating; irritation, dryness, or soreness of mouth; laryngeal edema; lightheadedness/vertigo; loosening or splitting of fingernails; lymphadenopathy; meningitis, aseptic; muscle weakness; nephrosis; nosebleeds, unexplained; photophobia; photosensitivity reactions resembling porphyria cutanea tarda and epidermyolysis bullosa; polyuria; pounding heartbeat; rhinitis, allergic; strong-smelling urine; swelling of the lips and tongue; syncope; taste change; thirst, continuing; weight loss, unexplained

Note: The risk of *anaphylaxis* may be increased when previously discontinued therapy with a nonsteroidal anti-inflammatory medication is reinstituted.

Patients 40 years of age and older may be more susceptible to the toxic effects of phenylbutazone. In patients 60 years of age and older, there is an increased risk of severe, possibly fatal, toxic reactions.

Laboratory findings in overdose may reveal respiratory or metabolic acidosis or alkalosis, other electrolyte disturbances, impaired hepatic or renal function, and abnormalities of formed blood elements.

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.**

Signs of overdose

Anorexia; depression; diarrhea or soft feces; edema, ventral abdominal; ulceration, oral

Client Consultation

In providing consultation, consider emphasizing the following selected

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information:
Returning patients for periodic rechecks while they are on medication
Keeping water readily available during the treatment period to avoid dehydration
Never exceeding the recommended daily amount without veterinary consultation
Familiarizing clients with signs that an adverse reaction may be occurring and instructing them to contact their veterinarian and discontinue treatment if a reaction is suspected
Not administering nonsteroidal anti-inflammatory drugs labeled for human use to animals without guidance from a veterinarian; human dosages may be toxic or fatal for animals

Oral Dosage Forms

Note: Bracketed information in the *Dosage Forms* section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

PHENYLBUTAZONE ORAL PASTE

Usual dose:

Inflammation; or
Pain—

Horses: Oral, 4.4 mg per kg of body weight every twelve hours initially, followed by 2.2 mg per kg of body weight every twelve hours.{R-20} For maintenance, use the lowest dose required to produce the desired clinical response.

[*Cattle*][1]: Oral, 10 mg per kg of body weight as a loading dose, followed by 5 mg per kg of body weight every forty-eight hours. In severely painful conditions, a maintenance dose of 3 mg per kg of body weight every twenty-four hours may be necessary to prevent breakthrough pain.{R-15} For maintenance, use the lowest dose required to produce the desired clinical response. (See also the *Withdrawal times* section below.)

Strength(s) usually available:{R-2}

U.S.—
Veterinary-labeled product(s):
200 mg per cc (200 mg per gram; 20% paste) (Rx) [*Butapaste; Equiphen Paste, Phenylbute Paste; Phenylzone Paste*].

Canada—
Veterinary-labeled product(s):
333 mg per mL (Rx) [*Butequine*].

Additional information: Higher blood levels of phenylbutazone have been reported with the paste formulation.

Withdrawal times: There are no established withdrawal times for food-producing animals in the United States or Canada because phenylbutazone is not approved for use in those species. Phenylbutazone residues are not permitted at any concentration (zero tolerance) in meat, milk, or eggs for human consumption.

U.S—The extra-label use of phenylbutazone in female dairy cattle 20 months of age or older is **prohibited** by the United States Food and Drug Administration.{R-34} Although other extra-label uses in food-producing animals, as stated in Animal Medicinal Drug Use Clarification Act (AMDUCA) guidelines, are legal at this writing, the practitioner should check current statutes to be sure restrictions on the use of phenylbutazone in food-producing animals have not been broadened.

Because phenylbutazone is prohibited from use in adult dairy cattle and use in other food animals is highly discouraged, the Food Animal Residue Avoidance Databank (FARAD) in the United States does not make recommendations for phenylbutazone residue withdrawals with extra-label use in food-producing species.{R-27}

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Canada—If phenylbutazone is administered orally to cattle at the dose of 10 mg per kg of body weight as a single loading dose followed by 5 mg per kg of body weight every forty-eight hours or, if necessary, administered at the dose of 3 mg per kg of body weight every twenty-four hours, evidence has been compiled by the Canadian gFARAD that suggests a meat withdrawal time of 60 days and a milk withholding time of 10 days would be sufficient to avoid residues.{R-42}

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

USP requirements: Not in USP.{R-4}

PHENYLBUTAZONE ORAL POWDER

Usual dose: See *Phenylbutazone Oral Paste.*

Strength(s) usually available:{R-2}

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Canada—

Veterinary-labeled product(s):

67 mg per gram of powder (Rx) [GENERIC].

100 mg per gram of powder (Rx) [*Butasone 400*].

267 mg per gram of powder (Rx) [*Butasone Conc; Buzone Concentrate Powder*].

Withdrawal times: See *Phenylbutazone Oral Paste*.

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

USP requirements: Not in USP.{R-4}

PHENYLBUTAZONE TABLETS USP

Usual dose:

Inflammation; or

Pain—

Dogs[1]: Oral, 15 mg per kg of body weight every eight hours, up to a maximum total daily dose of 800 mg, regardless of weight. For maintenance, the lowest dose required to produce the desired clinical response is used.

Horses: Oral, 4.4 mg per kg of body weight every twelve hours initially followed by 2.2 mg per kg of body weight every twelve hours.{R-20} For maintenance, the lowest dose required to produce the desired clinical response is used.

[*Cattle*][1]: Oral, 10 mg per kg of body weight as a loading dose, followed by 5 mg per kg of body weight every forty-eight hours. In severely painful conditions, a maintenance dose of 3 mg per kg of body weight every twenty-four hours may be necessary to prevent breakthrough pain.{R-15} For maintenance, use the lowest dose required to produce the desired clinical response. (See also the *Withdrawal times* section below.)

Strength(s) usually available:{R-1; 2}

U.S.—

Veterinary-labeled product(s):

100 mg (Rx) [*Butatabs-D; Butatron Tablets; Phenylbute Tablets 100 Mg;* GENERIC].

200 mg (Rx) [*Phenylbute Tablets 200 Mg;* GENERIC].

1 gram (Rx) [*Butatabs-E; Butatron Tablets; Equi-Phar Phenylbutazone 1 Gram Tablets; Phenylbute Tablets 1 Gram; Pributazone Tablets; Pro-Bute Tablets;* GENERIC].

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Human-labeled product(s):
100 mg (Rx) [GENERIC].
Canada—
Veterinary labeled product(s):
1 gram (Rx) [*Butasone 1000;* GENERIC].
Human-labeled product(s):
100 mg (Rx) [*Apo-Phenylbutazone; Butazolidin*].

Withdrawal times: See *Phenylbutazone Oral Paste*.

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

USP requirements: Preserve in tight containers. Contain the labeled amount, within ±7%. Meet the requirements for Identification, Dissolution (70% in 30 minutes in simulated intestinal fluid TS [without the enzyme] in Apparatus 1 at 100 rpm), and Uniformity of dosage units.{R-4}

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[1]Not included in Canadian product labeling or product not available in Canada.

Parenteral Dosage Forms

Note: Bracketed information in the *Dosage Forms* section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

PHENYLBUTAZONE INJECTION USP

Usual dose:

Inflammation; or
Pain—
Horses: Intravenous, 2.2 to 4.4 mg per kg of body weight every twelve hours. The dose is reduced after the first forty-eight to ninety-six hours. Administration should be limited to a maximum of five successive days. Oral administration may follow.
[*Dogs*]: Intravenous, 8 mg per kg of body weight every eight hours, not to exceed 800 mg daily regardless of weight. Intravenous injections should be limited to two successive days. Oral administration may follow.
[*Cattle*][1]: Intravenous, 10 mg per kg of body weight loading dose. Maintenance dose of 5 mg per kg of body weight every forty-eight hours if oral administration is not feasible. (See also the *Withdrawal times* section below.)
Note: Although phenylbutazone injection has been administered intramuscularly in cattle, no residue studies exist to establish appropriate slaughter withdrawals following such administration. Therefore, this route of administration is not recommended.{R-15; 36}

Strength(s) usually available:{R-2}

U.S.—
Veterinary-labeled product(s):
200 mg per mL (Rx) [*Butaject; Equi-Phar Phenylbutazone Injection 20%; Phenylbute Injection 20%; Pro-Bute Injection;* GENERIC]
Canada—
Veterinary-labeled product(s):
200 mg per mL (Rx) [GENERIC].

Withdrawal times: There are no established withdrawal times for food-producing animals in the United States or Canada because phenylbutazone is not approved for use in those species. Phenylbutazone residues are not permitted at any concentration (zero tolerance) in meat, milk, or eggs for human consumption.

U.S.—The extra-label use of phenylbutazone in female dairy cattle 20

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months of age or older is **prohibited** by the United States Food and Drug Administration.{R-34} Although other extra-label uses in food-producing animals, as stated in Animal Medicinal Drug Use Clarification Act (AMDUCA) guidelines, are legal at this writing, the practitioner should check current statutes to be sure restrictions on the use of phenylbutazone in food-producing animals have not been broadened.

Because phenylbutazone is prohibited from use in adult dairy cattle and use in other food animals is highly discouraged, the Food Animal Residue Avoidance Databank (FARAD) does not make recommendations for phenylbutazone residue withdrawals with extra-label use in food-producing species in the United States.{R-27}

Canada—If phenylbutazone is administered to cattle as a single intravenous loading dose of 10 mg per kg of body weight, evidence has been compiled by the Canadian gFARAD that suggests a meat withdrawal time of 60 days and a milk withholding time of 10 days would be sufficient to avoid residues.{R-42}

Packaging and storage: Store between 8 and 15 ºC (46 and 59 ºF). Protect from light.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. Protect from light, and store in a refrigerator. A sterile solution of Phenylbutazone in Sterile Water for Injection. Label Injection to indicate that it is for veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Clarity of solution, Identification, Sterility, Bacterial endotoxins, and pH (9.5–10), and for Injections.{R-4}

[1]Not included in Canadian product labeling or product not commercially available in Canada.

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Table 1. Pharmacology/Pharmacokinetics*

Note: Zero-order (dose-dependent) kinetics, especially for the elimination half-life, have been reported in dogs and horses. Such an occurrence cannot be discounted as possible in other species. For such drugs, larger doses typically lead to longer elimination half-lives.

Species	Protein Binding (%)	Half-life of Elimination (hr)	Volume of Distribution (L/kg)	Clearance (mL/min/kg)	Route; Dose (mg/kg)	T_{max} (hr)	C_{max} (mcg/mL)	F (%)
Baboons{R-22}		5						
Cattle								
Bulls{R-9}		61.6	V_{ss} 0.134	0.025	IV; 10			
		62.6			Oral; 10	8.9	47.13	73
Steers {R-35}		34	V_{ss} 0.14	0.053	IV; 6			
Cows{R-8}					IM; 4.4	7.5	42.3	99
	98	35.9	Vc 0.06	0.046	IV; 4.4			
			V_{area} 0.08					
					Oral; 4.4	10.5	23.9	54
{R-23}		55	Vc 0.052	0.021	IV; 5			
			V_{area} 0.092					
					Oral; 5	8	32†	68
{R-10}		38.6			Oral; 5			
{R-7}	93	42.4	V_{area} 0.097	0.027	IV; 6			
					Oral; 6	12.8	38.2	69
Dogs{R-22}		6						
{R-24}		2.5			Oral; 14.6	1	31.5	
Goats{R-25}	60.3	14.5	Vc 0.28		IV; 33			
{R-30}	99.5	10.4	Vc 0.18	0.217	IV; 10			
			V_{area} 0.28					
			V_{ss} 0.27					
{R-31}		15.3	V_{ss} 0.088	0.074	IV; 4.4			
		22.0			Oral; 4.4	3.47	27.2	61
Horses{R-26}		3.5			IV; 4.4			
					Oral; 8.8	5	21†	
{R-41}		5.5	V_{ss} 0.141	0.3	IV; 4.4			
Humans{R-22}		72						
Llamas{R-28}		2.52**	V_{ss} 0.155	1.11	IV; 5			
			V_{area} 0.190					
					Oral; 5	4.3	4.39	70
Pigs{R-21}	98	3.5	0.18‡	0.65	IV; 20			
Rabbits{R-14}		1.9	0.183§		IA; 8			
Rats{R-22}		6						
Sheep{R-29}		17.92	V_{ss} 0.099	0.076	IV; 4.4			
			V_{area} 0.117					

*Abbreviations: IA = Intra-arterial, IM = Intramuscular, IV = Intravenous, T_{max} = Time to peak serum concentration, C_{max} = Peak serum concentration, F = Bioavailability; percent absorbed

† Estimated from graph

‡ One-compartment model

§ Method of Vd calculation not specified

** For oral administration, a flip-flop model may exist with an absorption half-life of 7.09 hours.

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