Storage/Stability/Compatibility

Voriconazole tablets should be stored at 15–30°C.

The unreconstituted powder for oral suspension should be stored in the refrigerator (2–8°C); it has a shelf-life of approximately 18 months. Once reconstituted, it should be stored in tightly closed containers at room temperature (15–30°C); do not refrigerate or freeze. After reconstitution, the suspension is stable for 14 days. The suspension should be shaken well for 10 seconds prior to each administered dose.

The powder for injection should be stored at room temperature (15–30°C). After reconstituting with 19 mL of sterile water for injection, the manufacturer recommends using immediately; however, chemical and physical stability remain for up to 24 hours if stored in the refrigerator (2–8°C). Discard solution if it is not clear or particles are visible.

The injectable solution must be further diluted to a concentration of 5mg/mL or less for administration over 1–2 hours. Suitable diluents for IV infusion include (partial list): NS, LRS, D5LRS, and D5W. Voriconazole is **not compatible** with simultaneous infusion with blood products.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Voriconazole Tablets: 50 mg, 200 mg; *Vfend*® (Pfizer); (Rx)

Voriconazole Powder for Oral Suspension: 45 g (40 mg/mL after reconstitution; orange flavor in 100 mL bottles; *Vfend*® (Pfizer); (Rx)

Voriconazole Powder for Injection, Lyophilized: 200 mg/vial (single use); *Vfend I.V.*® (Pfizer); (Rx). Also contains 3200 mg of sulfobutyl ether beta-cyclodextrin sodium (SBECD) per vial (See Warnings) to solubolize the drug for IV administration.

WARFARIN SODIUM

(***war***-far-in) Coumadin®

ANTICOAGULANT

Prescriber Highlights

- Coumarin derivative anticoagulant used primarily for long-term treatment (or prevention of recurrence) of thrombotic conditions, primarily in cats, dogs, or horses
- Contraindications: Preexistent hemorrhage, pregnancy, those undergoing or contemplating eye or CNS surgery, major regional lumbar block anesthesia, surgery of large, open surfaces, active bleeding from the GI, respiratory, or GU tract; aneurysm, acute nephritis, cerebrovascular hemorrhage, blood dyscrasias, uncontrolled or malignant hypertension, hepatic insufficiency, pericardial effusion, & visceral carcinomas
- Adverse Effects: Dose-related hemorrhage
- Teratogenic; contraindicated in pregnancy
- Must actively monitor coagulation status
- Drug Interactions

Uses/Indications

In veterinary medicine, warfarin is used primarily for the oral, long-term treatment (or prevention of recurrence) of thrombotic conditions, primarily in cats, dogs, or horses. Use of warfarin in veterinary species is somewhat controversial and due to unproven benefit in reducing mortality, increased expense associated with monitoring, and potential for serious effects (bleeding), many do not recommend its use.

Pharmacology/Actions

Warfarin acts indirectly as an anticoagulant (it has no direct anticoagulant effect) by interfering with the action of vitamin K_1 in the synthesis of the coagulation factors II, VII, IX, and X. Sufficient amounts of vitamin K_1 can override this effect. Warfarin is administered as a racemic mixture of S (+) and R (-) warfarin. The S enantiomer is a significantly more potent vitamin K antagonist than the R enantiomer in species studied.

Pharmacokinetics

Warfarin is administered as a racemic mixture of S (+) and R (-) warfarin. Warfarin is rapidly and completely absorbed in humans after oral administration. In cats, warfarin is also rapidly absorbed after oral administration.

After absorption, warfarin is highly bound to plasma proteins in humans, with approximately 99% of the drug bound. In cats, more than 96% of the drug is protein bound. It is reported that there are wide species variations with regard to protein binding; horses have a higher free (unbound) fraction of the drug than do rats, sheep or swine. Only free (unbound) warfarin is active. While other coumarin and indanedione anticoagulants are distributed in milk, warfarin does not enter milk in humans.

Warfarin is principally metabolized in the liver to inactive metabolites that are excreted in urine and bile (and then reabsorbed and excreted in the urine). The plasma half-life of warfarin may be several hours to several days, depending on the patient (and species?). In cats, the terminal half-life of the S enantiomer is approximately 23–28 hours and the R enantiomer approximately 11–18 hours.

Contraindications/Precautions/Warnings

Warfarin is contraindicated in patients with preexistent hemorrhagic tendencies or diseases, those undergoing or contemplating eye or CNS surgery, major regional lumbar block anesthesia, or surgery of large, open surfaces. It should not be used in patients with active bleeding from the GI, respiratory, or GU tract. Other contraindications include: aneurysm, acute nephritis, cerebrovascular hemorrhage, blood dyscrasias, uncontrolled or malignant hypertension, hepatic insufficiency, pericardial effusion, pregnancy, and visceral carcinomas.

Adverse Effects

The principal adverse effect of warfarin use is dose-related hemorrhage, which may manifest with clinical signs of anemia, thrombocytopenia, weakness, hematomas and ecchymoses, epistaxis, hematemesis, hematuria, melena, hematochezia, hemathrosis, hemothorax, intracranial and/or pericardial hemorrhage, and death.

Reproductive/Nursing Safety

Warfarin is embryotoxic, can cause congenital malformations and considered contraindicated during pregnancy. If anticoagulant therapy is required during pregnancy, most clinicians recommend using low-dose heparin. In humans, the FDA categorizes this drug as category ***X*** for use during pregnancy (*Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly*

outweighs any possible benefit.) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***D*** (*Contraindicated. These drugs have been shown to cause congenital malformations or embryotoxicity.*)

Based on very limited published data, warfarin has not been detected in the breast milk of humans treated, but there are reports of some breast-fed infants whose mothers were treated having prolonged prothrombin times. Use with caution in nursing patients.

Overdosage/Acute Toxicity

Acute overdosages of warfarin may result in life-threatening hemorrhage. In dogs and cats, single doses of 5–50 mg/kg have been associated with toxicity. It must be remembered that a lag time of 2–5 days may occur before signs of toxicity occur, and animals must be monitored and treated accordingly.

Cumulative toxic doses of warfarin have been reported as 1–5 mg/kg for 5–15 days in dogs and 1 mg/kg for 7 days in cats.

If overdosage is detected early, prevent absorption from the gut using standard protocols. If clinical signs are noted, they should be treated with blood products and vitamin K_1 (phytonadione). Refer to the phytonadione monograph for more information.

Drug Interactions

Drug interactions with warfarin are perhaps the most important in human medicine. The following drug interactions have either been reported or are theoretical in humans or animals receiving warfarin and may be of significance in veterinary patients:

A multitude of drugs have been documented or theorized to interact with warfarin. The following drugs or drug classes may **increase** the **anticoagulant response** of warfarin (not necessarily complete):

- **ACETAMINOPHEN**
- **ALLOPURINOL**
- **AMIODARONE**
- **ANABOLIC STEROIDS**
- **AZITHROMYCIN**
- **CHLORAMPHENICOL**
- **CIMETIDINE**
- **CISAPRIDE**
- **CO-TRIMOXAZOLE** (**trimethoprim/sulfa**)
- **DANAZOL**
- **DIAZOXIDE**
- **ERYTHROMYCIN**
- **ETHACRYNIC ACID**
- **FLUOROQUINOLONES**
- **FLUOXETINE**
- **HEPARIN**
- **METRONIDAZOLE**
- **NSAIDS**
- **PENTOXIFYLLINE**
- **PROPYLTHIOURACIL**
- **QUINIDINE**
- **SALICYLATES**
- **SERTRALINE**
- **SULFONAMIDES**
- **THYROID MEDICATIONS**
- **ZAFIRLUKAST**

The following drugs or drug classes may **decrease** the **anticoagulant response** of warfarin (not necessarily complete):

- **BARBITURATES** (**phenobarbital,** etc.)
- **CORTICOSTEROIDS**
- **ESTROGENS**
- **GRISEOFULVIN**
- **MERCAPTOPURINE**
- **RIFAMPIN**
- **SPIRONOLACTONE**
- **SUCRALFATE**
- **VITAMIN K**

Should concurrent use of any of the above drugs with warfarin be necessary, enhanced monitoring is required. Refer to other references on drug interactions for more specific information.

Laboratory Considerations

- Warfarin may cause falsely decreased **theophylline** values if using the Schack and Waxler ultraviolet method of assay

Doses

- **DOGS:**

  For adjunctive therapy of thromboemboli:

  a) 0.22 mg/kg PO q12h; target dosage to prolong PT by 1.25–1.5 times the pretreatment value (Brooks 2000)

  b) For pulmonary thromboembolism: 0.2 mg/kg PO once daily then 0.05–0.1 mg/kg PO once daily. Adjust dosage to increase PT to 1.5–2.5 times baseline. Heparin may be stopped once appropriate warfarin dosage is established. If PT exceeds 2.5 times baseline, reduce dose. If bleeding develops, stop dose and institute blood or phytonadione therapy as appropriate. (Roudebush 1985)

  c) For prophylactic use in patients with glomerular disease and severe proteinuria: Initially, 0.22 mg/kg, PO once daily. Monitor PT and adjust dose so that PT is maintained at 1.5 times normal. (Grauer and DiBartola 2000)

- **CATS:**

  For adjunctive therapy of thromboembolism:

  a) For feline aortic thromboembolism: 0.06–0.1 mg/kg once daily PO. Evaluate using PT, aPTT, or preferably PIVKA (proteins induced by vitamin K antagonists) daily during initial titration (3 days), then every other day (2 times) and weekly thereafter until stable. New steady state may require one week after dosage adjustments. Long-term therapy should be monitored at least once monthly. (Pion and Kittleson 1989)

  b) For chronic management/prevention of recurrence: 0.1–0.2 mg/kg PO once daily. Adjust dosage to prolong PT to 2–2.5 times normal. Collect blood sample 8 hours after dosing. Requires 48–72 hours to achieve effective anticoagulation. Monitor PT weekly for 1 month, then at monthly intervals. Also determine hematocrit with each PT. (Harpster 1988)

  c) For thromboembolism: 0.5 mg per cat PO once daily; target dosage to prolong PT by 1.25–1.5 times the pretreatment value (Brooks 2000)

  d) For long-term thromboprophylaxis: Initially warfarin at 0.06–0.09 mg/kg per day PO. Due to unequal drug distribution, tablets should be crushed and mixed well. PT, adjusted to international normalized ratio (INR) is used to monitor therapy, but may not be applicable to cats. Overlap heparin and warfarin therapy by at least 4–5 days. Reevaluate anticoagulation status with any change in concurrent drug therapy. (Smith 2004)

e) Initially, 0.25–0.5 mg (total dose) per cat PO once daily. Adjust dosage to prolong PT to twice normal value, or INR to be between 2–3. Overlap therapy with heparin. (Fox 2007a)

■ **HORSES:** (**Note:** ARCI UCGFS Class 5 Drug)

As an anticoagulant:

a) For adjunctive treatment of laminitis: 0.0198 mg/kg PO once daily; monitor OSPT (one-step prothrombin time) until prolonged 2–4 seconds beyond baseline (Brumbaugh, Lopez et al. 1999)

b) Initially, 0.018 mg/kg PO once daily and increase dose by 20% every day until baseline PT is doubled. Final dose rates may be from 0.012 mg/kg to 0.57 mg/kg daily. (Vrins, Carlson, and Feldman 1983)

Monitoring

Note: The frequency of monitoring is controversial, and is dependent on several factors including dose, patient's condition, concomitant problems, etc. See the Dosage section above for more information.

- While Prothrombin Times (PT) or International Normalized Ratio (INR) are most commonly used to monitor warfarin, PIVKA (proteins induced by vitamin K antagonists) has been suggested as being more sensitive. PT's are usually recommended to be 1.5–2X normal and INR's to be between 2–3.
- Platelet counts and hematocrit (PCV) should be done periodically
- Occult blood in stool and urine; other observations for bleeding
- Clinical efficacy

Client Information

- Clients must be counseled on both the importance of administering the drug as directed
- Immediately report any signs or symptoms of bleeding

Chemistry/Synonyms

A coumarin derivative, warfarin sodium occurs as a slightly bitter tasting, white, amorphous or crystalline powder. It is very soluble in water and freely soluble in alcohol. The commercially available products contain a racemic mixture of the two optical isomers.

Warfarin Sodium may also be known as: sodium warfarin, warfarinum natricum, *Coumadin®, Jantoven®, or Panwarfin®*; there are many other trade names internationally.

Storage/Stability

Warfarin sodium tablets should be stored in tight, light-resistant containers at temperatures less than 40°C, preferably at room temperature. Warfarin sodium powder for injection should be protected from light and used immediately after reconstituting.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 5 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Warfarin Sodium Tablets (scored): 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg & 10 mg; *Coumadin®* (Bristol-Myers Squibb), *Jantoven®* (Upsher-Smith), generic; (Rx)

Warfarin Sodium Powder for Injection, lyophilized: 5.4 mg (2 mg/mL when reconstituted) preservative-free in 5 mg vials; *Coumadin®* (Bristol-Myers Squibb); (Rx)

A method of suspending warfarin tablets in an oral suspension has been described (Enos 1989). To make 30 mL of a 0.25 mg/mL suspension: Crush three 2.5 mg tablets with a mortar and pestle. Add 10 mL glycerin to form a paste; then 10 mL of water; add sufficient amount of dark corn syrup (*Karo®*) to obtain a final volume of 30 mL. Warm gently; shake well and use within 30 days.

XYLAZINE HCL

(*zye*-la-zeen) Rompun®

ALPHA$_2$-ADRENERGIC AGONIST

Prescriber Highlights

- **Alpha$_2$-adrenergic agonist used for its sedative & analgesic in a variety of species; sometimes used as an emetic in cats**
- **Contraindications: Animals receiving epinephrine or having active ventricular arrhythmias. Extreme caution: preexisting cardiac dysfunction, hypotension or shock, respiratory dysfunction, severe hepatic or renal insufficiency, preexisting seizure disorders, or if severely debilitated. Should generally not be used in the last trimester of pregnancy, particularly in cattle. Do not give to ruminants that are debilitated, dehydrated, or with urinary tract obstruction. Horses may kick after a stimulatory event (usually auditory); use caution. Avoid intra-arterial injection; may cause severe seizures & collapse. Caution in patients treated for intestinal impactions. Use cautiously in horses during the vasoconstrictive development phase of laminitis.**
- **Adverse Effects: CATS: emesis, muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, & increased urination.**
- **Adverse Effects: DOGS: Muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, emesis, bloat from aerophagia which may require decompression.**
- **Adverse Effects: HORSES: Muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, sweating, increased intracranial pressure, or decreased mucociliary clearance.**
- **Adverse Effects: CATTLE: Salivation, ruminal atony, bloating, regurgitation, hypothermia, diarrhea, bradycardia, premature parturition, & ataxia.**
- **Yohimbine, atipamezole, & tolazoline may be used alone or in combination to reverse effects or speed recovery times**
- **Dosages between species can be very different; be certain of product concentration when drawing up into syringe, especially if treating ruminants**
- **Drug Interactions**