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**

Uses/Indications

Xylazine is approved for use in dogs, cats, horses, deer, and elk. It is indicated in dogs, cats, and horses to produce a state of sedation with a shorter period of analgesia, and as a preanesthetic before local or general anesthesia. Because of the emetic action of xylazine in cats, it is occasionally used to induce vomiting after ingesting toxins.

Pharmacology/Actions

A potent alpha$_2$-adrenergic agonist, xylazine is classified as a sedative/analgesic with muscle relaxant properties. Although xylazine possesses several of the same pharmacologic actions as morphine, it does not cause CNS excitation in cats, horses or cattle, but causes sedation and CNS depression. In horses, the visceral analgesia produced has been demonstrated to be superior to that produced by meperidine, butorphanol or pentazocine.

Xylazine causes skeletal muscle relaxation through central mediated pathways. Emesis is often seen in cats, and occasionally in dogs receiving xylazine. While thought to be centrally mediated, neither dopaminergic blockers (*e.g.*, phenothiazines) nor alpha-blockers (yohimbine, tolazoline) block the emetic effect. Xylazine does not cause emesis in horses, cattle, sheep or goats. Xylazine depresses thermoregulatory mechanisms and either hypothermia or hyperthermia is a possibility depending on ambient air temperatures.

Effects on the cardiovascular system include an initial increase in total peripheral resistance with increased blood pressure followed by a longer period of lowered blood pressures (below baseline). A bradycardic effect can be seen with some animals developing a second-degree heart block or other arrhythmias. An overall decrease in cardiac output of up to 30% may be seen. Xylazine has been demonstrated to enhance the arrhythmogenic effects of epinephrine in dogs with or without concurrent halothane.

Xylazine's effects on respiratory function are usually clinically insignificant, but at high dosages it can cause respiratory depression with decreased tidal volumes and respiratory rates, and an overall decreased minute volume. Brachycephalic dogs and horses with upper airway disease may develop dyspnea.

Xylazine can increase blood glucose secondary to decreased serum levels of insulin; in non-diabetic animals, there appears to be little clinical significance associated with this effect.

In horses, sedatory signs include a lowering of the head with relaxed facial muscles and drooping of the lower lip. The retractor muscle is relaxed in male horses, but unlike acepromazine, no reports of permanent penile paralysis have been reported. Although, the animal may appear to be thoroughly sedated, auditory stimuli may provoke arousal with kicking and avoidance responses.

With regard to the sensitivity of species to xylazine, definite differences are seen. Ruminants are extremely sensitive to xylazine when compared with horses, dogs, or cats. Ruminants generally require approximately 1/10th the dosage that is required for horses to exhibit the same effect. In cattle (and occasionally cats and horses), polyuria is seen following xylazine administration, probably because of decreased production of vasopressin (anti-diuretic hormone, ADH). Bradycardia and hypersalivation are also seen in cattle and diminished by pretreating with atropine. Because swine require 20–30 times the ruminant dose, it is not routinely used.

Pharmacokinetics

Absorption is rapid following IM injection, but bioavailabilities are incomplete and variable. Bioavailabilities of 40–48% in horses, 17–73% in sheep, and 52–90% in dogs have been reported after IM administration.

In horses, the onset of action following IV dosage occurs within 1–2 minutes with a maximum effect 3–10 minutes after injection. The duration of effect is dose dependent but may last for approximately 1.5 hours. The serum half-life after a single dose of xylazine is approximately 50 minutes in the horse; recovery times generally take from 2–3 hours.

In dogs and cats, the onset of action following an IM or SC dose is approximately 10–15 minutes, and 3–5 minutes following an IV dose. The analgesic effects may persist for only 15–30 minutes, but the sedative actions may last for 1–2 hours depending on the dose given. The serum half-live of xylazine in dogs has been reported as averaging 30 minutes. Complete recovery after dosing may take 2–4 hours in dogs and cats.

Xylazine is not detected in milk of lactating dairy cattle at 5 and 21 hours post-dose, but the FDA has not approved its use in dairy cattle and no meat or milk withdrawal times have been specified.

Contraindications/Precautions/Warnings

Xylazine is contraindicated in animals receiving epinephrine or having active ventricular arrhythmias. It should be used with extreme caution in animals with preexisting cardiac dysfunction, hypotension or shock, respiratory dysfunction, severe hepatic or renal insufficiency, preexisting seizure disorders, or if severely debilitated. Because it may induce premature parturition, it should generally not be used in the last trimester of pregnancy, particularly in cattle.

Be certain of product concentration when drawing up into syringe, especially if treating ruminants. Do not give to ruminants that are dehydrated, debilitated, or with urinary tract obstruction. It is not approved for any species to be consumed for food purposes.

Horses have been known to kick after a stimulatory event (usually auditory); use caution. The addition of opioids (*e.g.*, butorphanol) may help temper this effect, but may cause increased risks for hypotension or ileus development. Avoid intra-arterial injection; may cause severe seizures and collapse. The manufacturers warn against using xylazine in conjunction with other tranquilizers. Because this drug may inhibit gastrointestinal motility, use with caution in patients treated for intestinal impactions. Use cautiously in horses during the vasoconstrictive development phase of laminitis as xylazine has been shown to reduce digital flow of blood for about 8 hours after administration.

Adverse Effects

Emesis is generally seen within 3–5 minutes after xylazine administration in cats and occasionally in dogs. To prevent aspiration, do not induce further anesthesia until this time has lapsed. Other adverse effects listed in the package insert (*Gemini*®, Butler) for dogs and cats include: muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, and increased urination in cats.

Dogs may develop bloat from aerophagia that may require decompression. Because of gaseous distention of the stomach, xylazine's use before radiography can make test interpretation difficult.

Adverse effects listed in the package insert (*AnaSed*®, Lloyd) for horses include: muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, and sweating (rarely profuse). Additionally, horses may develop increased intracranial pressure or decreased mucociliary clearance rates when xylazine is used.

Adverse reactions reported in cattle include: salivation, ruminal atony, bloating and regurgitation, hypothermia, diarrhea, and bradycardia. Hypersalivation and bradycardia may be alleviated by pretreating with atropine.

Large animals may become ataxic following dosing and caution should be observed.

Reproductive/Nursing Safety

Limited information was located on the safety of xylazine in pregnancy; apparently, there are no reports of teratogenicity in animals. Xylazine may induce premature parturition in cattle.

Xylazine does not appear to be excreted in detectable quantities in cows' milk.

Overdosage/Acute Toxicity

In the event of an accidental overdosage, cardiac arrhythmias, hypotension, and profound CNS and respiratory depression may occur. Seizures have also been reported after overdoses. There has been much interest in using alpha-blocking agents as antidotes or reversal agents to xylazine. Yohimbine, atipamezole, and tolazoline have been suggested for use alone and in combination to reverse the effects of xylazine or speed recovery times. Separate monographs for yohimbine and atipamezole are available with suggested doses, etc.

To treat the respiratory depressant effects of xylazine toxicity, mechanical respiratory support with respiratory stimulants (*e.g.*, doxapram) have been recommended for use.

Drug Interactions

The manufacturers warn against using xylazine in conjunction with **other tranquilizers**.

- **ACEPROMAZINE**: The combination use of acepromazine with xylazine is generally considered safe, but there is potential for additive hypotensive effects and this combination should be used cautiously in animals susceptible to hemodynamic complications.
- **CNS DEPRESSANT AGENTS, OTHER** (**barbiturates, narcotics, anesthetics, phenothiazines**, etc.): May cause additive CNS depression if used with xylazine. Dosages of these agents may need to be reduced.
- **EPINEPHRINE**: The use of epinephrine with or without the concurrent use of halothane with xylazine may induce the development of ventricular arrhythmias.
- **RESERPINE**: A case of a horse developing colic-like clinical signs after reserpine and xylazine has been reported. Until more is known about this potential interaction, use of these two agents together should be avoided.

Doses

- **DOGS:**
  a) 1.1 mg/kg IV, 1.1–2.2 mg/kg IM or SC (Package Insert; *Rompun*®—Miles)
  b) 0.6 mg/kg IV, IM as a sedative (Morgan 1988)
  c) To treat a hypoglycemic crises (with IV dextrose): 1.1 mg/kg IM (Schall 1985)
  d) For epidural injection: 0.02–0.25 mg/kg; dilute with sufficient quantity of sterile saline to a volume of 0.26 mL/kg. Onset of action 20–30 minutes; 2–5 hour duration.

  Xylazine 0.02 mg/kg with morphine 0.1 mg/kg; dilute with sufficient quantity of sterile saline to a volume of 0.26 mL/kg. Onset of action 30–60 minutes; 10–20 hour duration.

  As an analgesic: 0.1–1 mg/kg IV, IM or SC. For post-operative anxiety: 0.1–0.5 mg/kg IV, IM or SC (Carroll 1999)
- **CATS:**
  a) 1.1 mg/kg IV, 1.1–2.2 mg/kg IM or SC (Package Insert; *Rompun*®—Miles)
  b) As an emetic: 0.44 mg/kg IM (Morgan 1988), (Riviere 1985)
  c) As an analgesic: 0.1–1 mg/kg IV, IM or SC. For post-operative anxiety: 0.1–0.5 mg/kg IV, IM or SC (Carroll 1999)
  d) 0.55 mg/kg IM (Mandsager 1988)
- **RABBITS, RODENTS, SMALL MAMMALS:**
  a) Rabbits: For minimally invasive procedures lasting less than 30–45 minutes: 5 mg/kg once SC or IM in combination with ketamine (35 mg/kg).

  Mice/Rats: General anesthesia 13 mg/kg once IP in combination with ketamine (87 mg/kg).

  Hamsters/Guinea pigs: General anesthesia 8–10 mg/kg once IP in combination with ketamine (200 mg/kg for hamsters and 60 mg/kg for Guinea pigs) (Huerkamp 1995)
- **FERRETS:**
  a) As a sedative/analgesic: Xylazine: 0.5–2 mg/kg IM or SC. Usually combined with atropine (0.05 mg/kg) or glycopyrrolate (0.01 mg/kg IM) or Butorphanol/Xylazine: Butorphanol 0.2 mg/kg plus Xylazine (2 mg/kg) IM (Finkler 1999)
  b) Xylazine (2 mg/kg) plus butorphanol (0.2 mg/kg) IM;

  Telazol (1.5 mg/kg) plus xylazine (1.5 mg/kg) IM; may reverse xylazine with yohimbine (0.05 mg/kg IM)

  Telazol (1.5 mg/kg) plus xylazine (1.5 mg/kg) plus butorphanol (0.2 mg/kg) IM; may reverse xylazine with yohimbine (0.05 mg/kg IM) (Williams 2000)
- **BIRDS:**
  a) As a sedative/analgesic: 1–4 mg/kg IM, provides sedation for ketamine anesthesia. Has been used at dosages of up to 10 mg/kg in small psittacines (Clyde and Paul-Murphy 2000)
- **CATTLE:**

  Caution: Cattle are extremely sensitive to xylazine's effects; be certain of dose and dosage form. Pretreatment with atropine can decrease bradycardia and hypersalivation.
  a) 0.05–0.15 mg/kg IV; 0.10–0.33 mg/kg IM. If administering IM use an 18 or 20 gauge needle at least 1.5 inches long. Intravenous route may stress cardiovascular function. (Thurmon and Benson 1986)
  b) 0.044–0.11 mg/kg IV; 0.22 mg/kg IM (Mandsager 1988)
  c) 0.1–0.3 mg/kg IM; 0.05–0.15 mg/kg IV; 0.05–0.07 mg/kg epidurally. When used IV/IM, analgesia can be very short-lived (1/2 hour). (Walz 2006b)
- **HORSES:** (**Note:** ARCI UCGFS Class 3 Drug)
  a) 1.1 mg/kg IV; 2.2 mg/kg IM. Allow animal to rest quietly until full effect is reached. (Package Insert; *Rompun*®—Bayer)
  b) Sedative/analgesic for colic: 0.2–0.5 mg/kg IV (will provide analgesia for 20–30 minutes); or 0.6–1 mg/kg IM (effects for 1–2 hours). Evaluate heart rate prior to therapy. (Moore 1999)
  c) For sedation/analgesia: Xylazine 0.5–1 mg/kg IV or IM with or without butorphanol (0.02–0.03 mg/kg) (Taylor 1999)
  d) Prior to guaifenesin/thiobarbiturate anesthesia: 0.55 mg/kg IV; Prior to ketamine induction: 1.1 mg/kg IV; In combination with opioid/tranquilizers (all IV doses): **1**) Xylazine 0.66 mg/kg and meperidine 1.1 mg/kg; **2**) Xylazine 1.1 mg/kg and butorphanol 0.01–0.02 mg/kg; **3**) Xylazine 0.6 mg/kg; and acepromazine 0.02 mg/kg. **Note**: The manufacturers state that xylazine should not be used in conjunction with tranquilizers (Thurmon and Benson 1987)
  e) For field anesthesia: Sedate with xylazine (1 mg/kg IV; 2 mg/kg IM) given 5–10 minutes (longer for IM route) before induction of anesthesia with ketamine (2 mg/kg IV). Horse must be adequately sedated (head to the knees) before giving the ketamine (ketamine can cause muscle rigidity and seizures). If adequate sedation does not occur, either: **1**) Redose xylazine: up to half the original dose, **2**) Add butorphanol (0.02–.04 mg/kg IV). Butorphanol can be given with the

original xylazine if you suspect that the horse will be difficult to tranquilize (*e.g.*, high-strung Thoroughbreds) or added before the ketamine. This combination will improve induction, increase analgesia and increase recumbency time by about 5–10 minutes. **3**) Diazepam (0.03 mg/kg IV). Mix the diazepam with the ketamine. This combination will improve induction when sedation is marginal, improve muscle relaxation during anesthesia and prolong anesthesia by about 5–10 minutes. **4**) Guaifenesin (5% solution administered IV to effect) can also be used to increase sedation and muscle relaxation. (Mathews 1999)

- **SHEEP & GOATS:**

Note: Use xylazine with extreme caution in these species.

a) 0.05–0.1 mg/kg IV; 0.1–0.22 mg/kg IM (Thurmon and Benson 1986)

b) 0.044–0.11 mg/kg IV; 0.22 mg/kg IM (Mandsager 1988)

- **EXOTICS:**

a) An extensive list of suggested dosages can be found on page 359 of Veterinary Pharmacology and Therapeutics, 6th Ed., Booth, NH and McDonald, LE, Eds. 1988; Iowa State University Press; Ames, Iowa

Monitoring

- Level of anesthesia/analgesia
- Respiratory function; cardiovascular status (rate, rhythm, BP if possible)
- Hydration status if polyuria present

Client Information

- Xylazine should only be used by individuals familiar with its use

Chemistry/Synonyms

Xylazine HCl is a alpha$_2$-adrenergic agonist structurally related to clonidine. The pH of the commercially prepared injections is approximately 5.5. Dosages and bottle concentrations are expressed in terms of the base.

Xylazine HCl may also be known as Bay-Va-1470, *Rompun*®, *AnaSed*®, *Sedazine*®, *X-Ject*®, or *Xyla-Ject*®.

Storage/Stability/Compatibility

Do not store above 30°C (86°F). Xylazine is reportedly physically **compatible** in the same syringe with several compounds, including: acepromazine, buprenorphine, butorphanol, chloral hydrate, and meperidine.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Xylazine Injection: 20 mg/mL in 20 mL vials or 100 mg/mL in 50 mL vials: *AnaSed*® (Lloyd); *X-Ject*® (Butler); *Xyla-Ject*® (Phoenix); *Sedazine*® (Fort Dodge); *TranquiVed*® (Vedco); generic; (Rx); Approved for use (depending on strength and product) in dogs, cats, horses, deer, and elk.

While xylazine is not approved for use in cattle in the USA, at labeled doses in Canada it reportedly has been assigned withdrawal times of 3 days for meat and 48 hours for milk. FARAD has reportedly suggested a withdrawal of 7 days for meat and 72 hours for milk for extra-label use.

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS: None

YOHIMBINE HCL

(yo-*him*-been) Yobine®, Antagonil®

ALPHA$_2$-ADRENERGIC ANTAGONIST

Prescriber Highlights

- Alpha$_2$-adrenergic antagonist used to reverse xylazine & potentially amitraz; may be used prophylactically before amitraz dips
- Contraindications: Hypersensitivity to it. Caution: Renal disease, seizure disorders
- Adverse Effects: Transient apprehension or CNS excitement, muscle tremors, salivation, increased respiratory rates, & hyperemic mucous membranes; more likely in small animals
- Drug interactions

Uses/Indications

Yohimbine is indicated to reverse the effects of xylazine in dogs, but it is being used clinically in several other species as well.

Yohimbine may be efficacious in reversing some of the toxic effects associated with other agents (*e.g.*, amitraz) and can be used prophylactically before amitraz dips.

Pharmacology/Actions

Yohimbine is an alpha$_2$-adrenergic antagonist that can antagonize the effects of xylazine. Alone, yohimbine increases heart rate, blood pressure, causes CNS stimulation and antidiuresis, and has hyperinsulinemic effects.

By blocking central alpha$_2$-receptors, yohimbine causes sympathetic outflow (norepinephrine) to be enhanced. Peripheral alpha$_2$-receptors are also found in the cardiovascular system, genitourinary system, GI tract, platelets, and adipose tissue.

Pharmacokinetics

The pharmacokinetics of this drug have been reported in steers, dogs, and horses (Jernigan et al. 1988). The apparent volume of distribution (steady-state) is approximately 5 L/kg in steers, 2–5 L/kg in horses, and 4.5 L/kg in dogs. The total body clearance is approximately 70 mL/min/kg in steers, 35 mL/min/kg in horses, and 30 mL/min/kg in dogs. The half-life of the drug is approximately 0.5–1 hours in steers, 0.5–1.5 hours in horses, and 1.5–2 hours in dogs.

Yohimbine is believed to penetrate the CNS quite readily and, when used to reverse the effects of xylazine, onset of action generally occurs within 3 minutes. The metabolic fate of the drug is not known.

Contraindications/Precautions/Warnings

Yohimbine is contraindicated in patients hypersensitive to it. In humans, yohimbine is contraindicated in patients with renal disease.

Yohimbine should be used cautiously in patients with seizure disorders. When used to reverse the effects xylazine, normal pain perception may result.

Adverse Effects

Yohimbine may cause transient apprehension or CNS excitement, muscle tremors, salivation, increased respiratory rates, and hyperemic mucous membranes. Adverse effects appear to be more probable in small animals than in large animals.