Atipamezole, a synthetic drug with an imidazole structure, is a highly selective α₂-adrenergic antagonist.¹² It is used to counteract the sedative, hypnotic, analgesic, and other effects produced by α₂-adrenergic agonists such as imidazole-type drugs (e.g., dexmedetomidine hydrochloride, medetomidine hydrochloride) or xylazine.²⁻⁶ Atipamezole was approved by the FDA in 1996 to reverse the sedative and analgesic effects of medetomidine hydrochloride (Domitor, Pfizer) in dogs.⁷ It is currently approved to reverse the sedative and analgesic effects of medetomidine hydrochloride and dexmedetomidine hydrochloride (Dexdomitor, Pfizer).⁸

**PHARMACOKINETICS**

Atipamezole is a weak lipophilic base.¹ Absorption after intramuscular administration is rapid; a peak plasma level is reached in about 10 minutes in dogs.² Peak concentrations in tissue, including the brain, are two to three times higher than corresponding plasma levels.⁷ Atipamezole rapidly crosses the blood–brain barrier. The drug undergoes extensive hepatic biotransformation, and metabolites are primarily excreted in urine.⁹ The elimination half-life is 1.3 hours in rats and 2.6 hours in dogs.⁹,¹⁰

**PHARMACOLOGY**

Atipamezole is a central and peripheral α₂-adrenergic antagonist.²¹⁰ Adrenergic receptors are membrane-associated proteins through which catecholamines act to alter cell and organ functions.¹¹ They can be divided into α and β types. α-Adrenergic receptors can be subdivided into subtypes (α₁ and α₂) according to their agonist and antagonist affinities.¹² α₂-Adrenergic receptors are located in the central nervous system, sympathetic nervous system, vasculature, and tissue (e.g., gastrointestinal tract, kidney, uterus).¹²,¹³ They exist presynaptically, postsynaptically, and extrasynaptically in the vasculature.¹³

α₂-Adrenergic receptors are divided into three pharmacologically different subtypes: α₂A, α₂B, and α₂C.¹³ In the central nervous system, α₂A is the prevalent subtype; the major noradrenergic nucleus in the brainstem, the locus coeruleus, contains only subtype α₂A receptors.¹³ Several specific functions have been attributed to α₂- adrenergic receptors.¹³ α₂A Receptors mediate sedation, analgesia, hypotension, and bradycardia, while α₂B receptors regulate peripheral vasoconstrictive effects.¹¹ The α₂C receptors mediate hypothermia.¹³ Mydriasis is attributable to activation of postsynaptic α₂-adrenergic receptors.¹⁴
Atipamezole has a high affinity for all three \( \alpha_2 \)-adrenergic receptor subtypes in both humans and rodents.\(^9\) It competitively displaces \( \alpha_2 \)-adrenergic agonist drugs and rapidly blocks or reverses several drug effects. Atipamezole is more potent and selective than other \( \alpha_2 \)-antagonists (e.g., yohimbine, tolazoline). Receptor binding studies in rodents have shown the \( \alpha_2 \)-to-\( \alpha_1 \) selectivity ratio of atipamezole to be 8526 compared with 3240, 1620, 260, and 160 for dexmedetomidine, medetomidine, detomidine, and xylazine, respectively.\(^9,11\) The \( \alpha_2 \)-to-\( \alpha_1 \) selectivity ratio for yohimbine, an indole alkaloid, is 40.\(^9\) Atipamezole is highly selective: studies based on receptor binding and conducted using isolated organ preparations have shown that atipamezole has no affinity for or effects on other receptors (e.g., histaminergic, opiate, muscarinic, serotoninergic, dopaminergic, GABA-ergic, or benzodiazepine receptors). This selectivity minimizes the undesirable effects.\(^16\)

Experimental studies in rats have shown that atipamezole has beneficial effects on functional recovery after traumatic brain lesions and stroke.\(^17\) Repeated treatment with atipamezole (1 mg/kg SC) facilitates sensorimotor recovery after focal cerebral ischemia in rats.\(^9,17,18\) Atipamezole also increases sexual activity in rats and monkeys.\(^18\)

**APPLICATIONS**

Atipamezole is used in the anesthesiology setting as an effective agent to reverse the sedative/analgesic effects of the \( \alpha_2 \)-adrenergic agonist drugs medetomidine, dexmedetomidine, romifidine (Sedivet, Boehringer Ingelheim), and xylazine (Rompun, Bayer; AnaSed, Lloyd; Sedazine, Fort Dodge).\(^2-5\) Atipamezole can also be used to shorten the duration of sedation, mobilize an animal after a noninvasive or minor surgical procedure, and reverse cardiovascular effects of the specific drugs listed above.\(^19,20\) Atipamezole produces a rapid reversal of medetomidine- or dexmedetomidine-induced bradycardia. This effect is of greater magnitude when dexmedetomidine is administered intravenously compared with intramuscular administration.\(^8\) If a patient has received combined anesthesia using ketamine, the clinician should wait at least 30 to 45 minutes after ketamine administration before administering atipamezole to reduce the risk of a rough recovery.\(^19\)

Atipamezole has been used off-label in dogs to treat intoxication by imidazoline decongestants (e.g., naphazoline, oxymetazoline, tetrahydrozoline, xylometazoline) used for temporary relief of nasal congestion in humans.\(^21\) Most dogs show signs of poisoning after accidental ingestion of very small quantities of these substances,\(^21\) which are peripheral \( \alpha_2 \)-adrenergic receptor agonists.\(^20\) Atipamezole has been used off-label as an antidote in the treatment of amitraz intoxication in dogs and cats. Amitraz is an insecticide/acaricide that is an \( \alpha_2 \)-adrenergic receptor agonist.\(^10\) Atipamezole has been shown in animal models to improve survival after amitraz intoxication, and its use may be attempted in severe cases of human exposure.\(^22\) In cats, bradycardia, mydriasis, and sedation induced by amitraz were more effectively reversed by atipamezole than by yohimbine, probably because of atipamezole’s higher affinity for \( \alpha_2 \)-adrenergic receptors.\(^7\) Atipamezole is not licensed for use in cats in the United States.

**ACUTE TOXICITY**

The LD\(_{50}\) of atipamezole delivered by the subcutaneous route is 44 mg/kg in female rats.\(^1\) Atipamezole is well tolerated in healthy dogs receiving doses 10 times the recommended dose or repeated doses at one, three, and five times the recommended dose.\(^8,19\) Some localized skeletal muscle injury can occur at the injection site.\(^2,8\) The manufacturer does not recommend the use of the product in debilitated, pregnant, or lactating dogs or in animals intended for breeding.\(^8\) The drug has not been evaluated in dogs younger than 4 months or weighing less than 4.4 lb (2 kg).\(^8\)

**PRECAUTIONS**

Atipamezole can produce an abrupt reversal of sedation and, presumably, analgesia induced by \( \alpha_2 \)-agonist activity. Additional procedures for pain control may be required. The potential for apprehensive or aggressive behavior should be considered when handling dogs emerging from sedation, especially dogs predisposed to nervousness or fright.\(^8\) Staff members should use caution when handling dogs that have recently received atipamezole and should avoid situations in which the animal could fall.\(^8\) Direct exposure of the skin, eyes, or mouth to atipamezole may cause irritation; therefore, practitioners should avoid drug contact with eyes and skin and wear impervious gloves during drug administration.\(^8\) Atipamezole and anticholinergics can both cause dramatic increases in heart rate, so concurrent use of these drugs should be avoided.\(^23\)

**DOSE AND ADMINISTRATION**

When administered IM at doses four to six times the medetomidine dose, atipamezole is highly effective in
reversing medetomidine-induced sedation/analgesia, recumbency, and bradycardia in dogs within 3 to 7 minutes.\textsuperscript{19,24} The commercial preparations of atipamezole, medetomidine, and dexmedetomidine are formulated so that the concentration of atipamezole is five times the concentration of medetomidine and dexmedetomidine in the respective products. Therefore, the injection volume of the recommended dose of atipamezole is identical to the volume of the recommended dose of medetomidine or dexmedetomidine.\textsuperscript{8} Atipamezole dosages based on patient body weight are listed in the product prescribing information. If more than 30 minutes has elapsed since medetomidine administration, the dose of atipamezole should be reduced.\textsuperscript{23} Transient hypotension may still occur. This may not be clinically significant in healthy dogs; however, clinicians should be aware of this effect.\textsuperscript{25} Atipamezole is not approved for the treatment of amitraz poisoning but has been used for this purpose at a published dose of 0.2 mg/kg IM. The injection may need to be repeated, particularly if the animal has ingested an amitraz-containing collar that has not been retrieved from the gastrointestinal tract.\textsuperscript{26,27} Most treated dogs recover in less than 24 hours.\textsuperscript{10,27}

**PREPARATIONS**

Atipamezole is currently approved by the FDA for use only in dogs and for intramuscular injection.\textsuperscript{2,19} It is available in the United States as a veterinary pharmaceutical product (Antisedan, Pfizer) and is supplied as a sterile injectable solution in 10-mL, multidose vials containing 5.0 mg/mL of atipamezole hydrochloride.\textsuperscript{2} Because of the potential for hypotension and tachycardia, atipamezole is not labeled for IV use, although such use has been reported in emergency situations.\textsuperscript{23}

**STORAGE AND HANDLING**

Atipamezole hydrochloride should be stored at room temperature (59°F to 86°F [15°C to 30°C]) and protected from light.\textsuperscript{8}

**REFERENCES**