ANTISEDAN® is administered intramuscularly (IM) for reversal of sedation and analgesia. While atipamezole does reverse the clinical signs associated with medetomidine or dexmedetomidine sedation, complete physiologic return to pretreatment status may not be immediate or may be temporarily delayed. Dogs should be monitored closely for persistent hypothermia, bradycardia, and depressed respiration, until signs of recovery persist.

1. Handling: ANTISEDAN can produce an abrupt reversal of sedation; therefore, dogs that have recently received ANTISEDAN should be handled with caution. The potential for apprehensive or aggressive behavior should be considered in the handling of dogs emerging from sedation, especially in dogs predisposed to nervousness or fright. Also, sudden movements where the dog might be startled should be avoided. Do not handle dogs that have received an alpha,-agonist by the IV route, compared to dogs that are sedated using the IM route. Animals should be monitored closely for persistent hypothermia, bradycardia, and depressed respiration, until signs of recovery persist.

2. Sedation relapse: While atipamezole does reverse the clinical signs associated with medetomidine or dexmedetomidine sedation, complete physiologic return to pretreatment status may not be immediate or may be temporarily delayed. Dogs should be monitored closely for persistent hypothermia, bradycardia, and depressed respiration, until signs of recovery persist.

3. Analgesia reversal: Atipamezole reverses analgesic effects as well as sedative effects. Additional procedures for the control of pain may be required.

4. Debilitated dogs: The safety of atipamezole has not been evaluated in dogs with compromised health. Generally, debilitated dogs may be more sensitive to the effects of alpha,-antagonists and may experience adverse reactions associated with the administration of alpha,-antagonists (as well as alpha,-agonists). Dogs with abnormalities associated with the cardiovascular system are especially at risk.

5. Breeding dogs: ANTISEDAN has not been evaluated in breeding dogs; therefore, the drug is not recommended for use in pregnant or lactating dogs, or in dogs intended for breeding.

6. Minimum age and weight: ANTISEDAN has not been evaluated in dogs less than four months of age or in dogs weighing less than 4.4 lb (2 kg).

ADVERSE REACTIONS: Occasional vomiting may occur. At times, a period of excitement or apprehensiveness may be seen in dogs treated with atipamezole. Other effects of atipamezole include hypersalivation, diarrhea, and tachycardia.

CLINICAL PHARMACOLOGY: Atipamezole is a potent alpha,-antagonist which selectively and competitively inhibits alpha,-adrenergic receptors. The result of atipamezole administration in the dog is the rapid recovery from the sedative and analgesic effects produced by the alpha,-adrenergic agonists dexmedetomidine or medetomidine. Atipamezole does not reverse the effects of other classes of sedatives, anesthetics, or analgesics.

Atipamezole is rapidly absorbed following intramuscular injection; maximum serum concentration is reached in approximately 10 minutes. Onset of action is usually apparent within 5 to 10 minutes of injection, depending on the depth and duration of dexmedetomidine- or medetomidine-induced sedation. Elimination half-life from serum is less than 3 hours. Atipamezole undergoes extensive hepatic biotransformation, with excretion of metabolites primarily in urine.

Dexmedetomidine or medetomidine activation of peripheral and central alpha,-adrenergic receptors induces a pattern of pharmacological responses that include sedation, reduction of anxiety, analgesia, and bradycardia. Blood pressure is initially increased due to peripheral vasconstriction and thereafter drops to normal or slightly below normal levels. A transient decrease in systolic blood pressure occurs immediately after administration of atipamezole to dexmedetomidine- or medetomidine-sedated dogs, followed by a transient increase in arterial pressure with 10 minutes compared to pre-atipamezole levels.

This is the opposite of the response to alpha,-agonist treatment, and is probably due to atipamezole-induced peripheral vasodilation. Atipamezole administration rapidly abolishes dexmedetomidine- or medetomidine-induced bradycardia, usually within 3 minutes. The magnitude of the effect of atipamezole on heart rate is greater when dexmedetomidine is administered intravenously compared to intramuscularly. Dogs receiving medetomidine or IM dexmedetomidine may not return to pre-sedative heart rates after atipamezole administration and some dogs briefly show heart rate elevations above baseline. Respiratory rate increases following atipamezole injection.

EFFECTIVENESS: One hundred and nine dogs received atipamezole in the field study (55 dogs received the reversal agent following dexmedetomidine: 54 following medetomidine). The mean age was 5.9 years and ranged between 17 weeks and 16 years. The mean body weight was 45.6 lb (20.7 kg), ranging from 4.8 lb to 117.2 lb (2.2 kg to 53.2 kg). Atipamezole was administered by the IM route of administration, within a range of 39-57 minutes after administration of either dexmedetomidine (IV and IM) or medetomidine (IV and IM).

Atipamezole reversed the effects of dexmedetomidine and medetomidine in all cases. In dexmedetomidine treated dogs, the onset of reversal was noted at 5 minutes after administration of atipamezole, 5%/100%/500 mcg/kg IV. Within 5 minutes, 96% of dexmedetomidine treated dogs were standing, 92% responded normally to sound, 86% had a normal muscle tone of jaw, and >90% had a normal pedal reflex response. Responses in dogs treated with medetomidine were similar or slightly later.

Following atipamezole, heart rate increased between 0 and 5 minutes following either alpha,-agonist (IV dexmedetomidine dogs had heart rates from 60 to 85 bpm, and IM dexmedetomidine dogs from 51 to 76 bpm). IM dexmedetomidine dogs had lower heart rates after atipamezole treatment (from 45 to 72 bpm, and IM medetomidine dogs from 40 to 79 bpm). Bradycardia resolved more slowly in the IM treatment groups. The body temperature remained at the same level during the 120 minutes of follow-up after atipamezole administration. Respiratory rates increased toward normal between 0 and 5 minutes after administration of atipamezole in all treatment groups. Mucous membranes were described as normal after 5 minutes in 91% of dexmedetomidine dogs (IV or IM). By 120 minutes, 96% were normal (after IV dexmedetomidine) and 100% were normal (after IM dexmedetomidine). Many physiological responses were slightly slower to return toward normal when dogs were treated with medetomidine IV or IM.

No adverse events were reported in the atipamezole treated dogs.

ANIMAL SAFETY: Atipamezole was tolerated in healthy dogs receiving 10X the recommended dose and in dogs receiving repeated doses at 1, 3, and 5X the recommended dose, in the absence of an alpha,-agonist. Signs were dose-related and included excitement, panting, trembling, vomiting, soft or liquid feces and scleral injection. With the recommended dose, increases in creatine kinase, AST, and ALT were noted. Creatine kinase also increased in 3 (of 6) dogs in the 5X treatment group. Localized skeletal muscle injury was seen at the injection site but no associated clinical signs or complications were observed. Dogs receiving the recommended atipamezole dose in the absence of a medetomidine or dexmedetomidine exhibited no adverse clinical signs. In additional safety studies, adverse events were absent up to the 2X dose of atipamezole when its administration followed medetomidine or dexmedetomidine sedation.

In a separate safety study using a crossover design, 5 dogs received atipamezole after dexmedetomidine (IV and IM). Dexmedetomidine's effects on blood pressure, heart rate, respiratory rate, and cardiac conduction times were reversed by atipamezole. Heart rate and cardiac conduction times did not return to pretreatment values. Heart rate increases after atipamezole were closer to baseline values in dogs treated with dexmedetomidine than in those treated with medetomidine. However, heart rate and cardiac conduction times did not return to pretreatment values. Heart rate increases after atipamezole were closer to baseline values in dogs treated with dexmedetomidine than in those treated with medetomidine. However, heart rate and cardiac conduction times did not return to pretreatment values. Heart rate increases after atipamezole were closer to baseline values in dogs treated with dexmedetomidine than in those treated with medetomidine. However, heart rate and cardiac conduction times did not return to pretreatment values. Heart rate increases after atipamezole were closer to baseline values in dogs treated with dexmedetomidine than in those treated with medetomidine. However, heart rate and cardiac conduction times did not return to pretreatment values.

STORAGE INFORMATION: Store protected from light at controlled room temperature 15°C–30°C (59°F–86°F).

HOW SUPPLIED: ANTISEDAN is supplied in 10-mL multidose vials containing 5.0 mg of atipamezole hydrochloride per mL.

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