CROPAMEZOLE- atipamezole hydrochloride injection, solution
Cronus Pharma LLC

Cropamezole™
(atipamezole hydrochloride)
Sterile Injectable Solution - 5.0 mg/mL

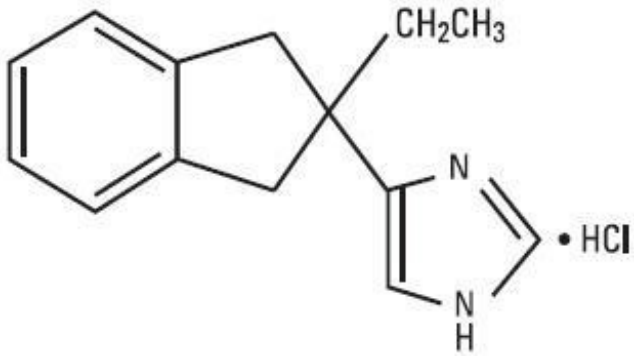
Dexmedetomidine and Medetomidine Reversing Agent
For intramuscular use in dogs only

CAUTION

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

DESCRIPTION

Cropamezole™ (atipamezole hydrochloride) is a synthetic α_2-adrenergic antagonist. The chemical name is 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride. The molecular formula is $C_{14}H_{16}N_2 \bullet HCl$ and structural formula is:



Each mL of Cropamezole™ contains 5.0 mg atipamezole hydrochloride, 1.0 mg methylparaben (NF), 8.5 mg sodium chloride (USP), and water for injection (USP).

INDICATIONS

Cropamezole™ is indicated for the reversal of the sedative and analgesic effects of dexmedetomidine hydrochloride, and medetomidine hydrochloride in dogs.

DOSAGE AND ADMINISTRATION

Cropamezole™ is administered intramuscularly (IM) for reversal of sedation and analgesia regardless of the route used for dexmedetomidine hydrochloride or medetomidine hydrochloride. The atipamezole dose for the reversal of IV dexmedetomidine hydrochloride or medetomidine hydrochloride is 3750 mcg/m^2. The atipamezole dose for the reversal of IM dexmedetomidine hydrochloride or medetomidine hydrochloride is 5000 mcg/m^2.

The dosage of Cropamezole™ is calculated based on body surface area. Use the following tables to determine the correct injection volume or the correct Cropamezole™ dosage on the basis of kilograms of body weight.

Note that the mcg/kg dosage decreases as body weight increases.

Table 1: Atipamezole dosing for reversal of IV dexmedetomidine- or medetomidine-induced sedation/analgesia:

Dose table for Cropamezole (3750 mcg/m^2) when dexmedetomidine or medetomidine is given IV

For # lbs	For # kg	dose = mcg/kg	Volume = mL Cropamezole
4-7	2-3	300	0.1
7-9	3-4	250	0.15
9-11	4-5	230	0.2
11-22	5-10	200	0.3
22-33	10-15	170	0.4
33-44	15-20	150	0.5
44-55	20-25	140	0.6
55-66	25-30	130	0.7
66-81	30-37	120	0.8
81-99	37-45	110	0.9
99-110	45-50	105	1.0
110-132	50-60	100	1.1
132-143	60-65	95	1.2
143-165	65-75	93	1.3
165-176	75-80	91	1.4
>176	>80	90	1.5

Table 2: Atipamezole dosing for reversal of IM dexmedetomidine- or medetomidine-induced sedation/analgesia:

Dose table for Cropamezole™ (5000 mcg/m^2) when dexmedetomidine or medetomidine is given IM

For # lbs	For # kg	dose = mcg/kg	volume = mL Cropamezole™
4-7	2-3	400	0.15
7-9	3-4	350	0.2
9-11	4-5	300	0.3
11-22	5-10	250	0.4
22-29	10-13	230	0.5
29-33	13-15	210	0.6
33-44	15-20	200	0.7
44-55	20-25	180	0.8
55-66	25-30	170	0.9

66-73	30-33	160	1.0
73-81	33-37	150	1.1
81-99	37-45	145	1.2
99-110	45-50	140	1.3
110-121	50-55	135	1.4
121-132	55-60	130	1.5
132-143	60-65	128	1.6
143-154	65-70	125	1.7
154-176	70-80	123	1.8
>176	>80	120	1.9

CONTRAINDICATIONS

Since atipamezole is always used concomitantly with dexmedetomidine or medetomidine, it should not be used in dogs with the following conditions: cardiac disease, respiratory disorders, liver or kidney diseases, dogs in shock, severely debilitated dogs, or dogs stressed due to extreme heat, cold or fatigue.
Administration of atipamezole is contraindicated in dogs with a known hypersensitivity to the drug.

HUMAN WARNINGS

Not for human use. Keep out of reach of children.

Atipamezole hydrochloride can be absorbed and may cause irritation following direct exposure to skin, eyes, or mouth. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing.

If irritation or other adverse reaction occurs (for example, increased heart rate, tremor, muscle cramps), seek medical attention.

In case of accidental oral exposure or injection, seek medical attention. Caution should be used while handling and using filled syringes.

Users with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product.

Note to Physician: This product contains an alpha$_2$-adrenergic antagonist.

PRECAUTIONS

1. Handling

Cropamezole™ can produce an abrupt reversal of sedation; therefore, dogs that have recently received Cropamezole™ 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, avoid situations where a dog might fall.

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 temporary, and dogs should be monitored for sedation relapse. Sedation relapse is more likely to occur in dogs that receive an alpha$_2$-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.

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. Geriatric, debilitated, and ill dogs are more likely to experience adverse reactions associated with the administration of alpha$_2$-antagonists (as well as alpha$_2$-agonists). Dogs with abnormalities associated with the cardiovascular system are especially at risk.

5. Breeding dogs
Cropamezole™ 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
Cropamezole™ has not been evaluated in dogs less than four months of age or in dogs weighing less than 4.4 lbs (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 tremors.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

Atipamezole is a potent alpha$_2$-antagonist which selectively and competitively inhibits alpha$_2$-adrenergic receptors. The result of atipamezole administration in the dog is the rapid recovery from the sedative and analgesic effects produced by the alpha$_2$-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 arousal 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$_2$-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 vasoconstriction 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 within 10 minutes compared to pre-atipamezole levels. This is the opposite of the response to alpha$_2$-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 weight was 45.5 lbs (20.7 kg), ranging from 4.8 lbs to 117 lbs (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 evident within 5 minutes after administration of atipamezole (57% could stand). Within 15 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$_2$-agonist (IV dexmedetomidine dogs had heart rates from 60 to 85 bpm, and IV medetomidine dogs from 51 to 67 bpm; IM dexmedetomidine dogs had heart rates from 45 to 73 bpm, and IM medetomidine dogs from 52 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 the 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) or 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$_2$-agonist. Signs were dose-related and included excitement, panting, trembling, vomiting, soft or liquid feces and scleral injection. At 10X the recommended dose, increases in creatine kinase, AST, and ALT were noted. Creatine kinase also increased in 3 (of 6) dogs in the 3X 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 medetomidine or dexmedetomidine exhibited no adverse clinical signs. In additional safety studies, adverse events were absent up to the 3X 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. However, heart rate and cardiac conduction times did not return to predexmedetomidine values. Heart rate increases after atipamezole were closer to baseline values in dogs treated with dexmedetomidine IV (compared to IM).

STORAGE INFORMATION

Store at USP controlled room temperature 20° to 25°C (68 to 77°F), with excursions permitted between 15° to 30°C (59 to 86°F). Protect from light.

Use within 28 days of first puncture and maximum allowable punctures are 16 punctures.

HOW SUPPLIED

Cropamezole™ is supplied in 10-mL, multidose vials containing 5.0 mg of atipamezole hydrochloride per mL.

Approved by FDA under ANADA # 200-753

Cropamezole™ is the trademark of Cronus Pharma LLC

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)
Made in India
July 2023

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 69043-039-10

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5.0 mg/mL
Sterile Injectable Solution

Dexmedetomidine and
Medetomidine Reversing
Agent

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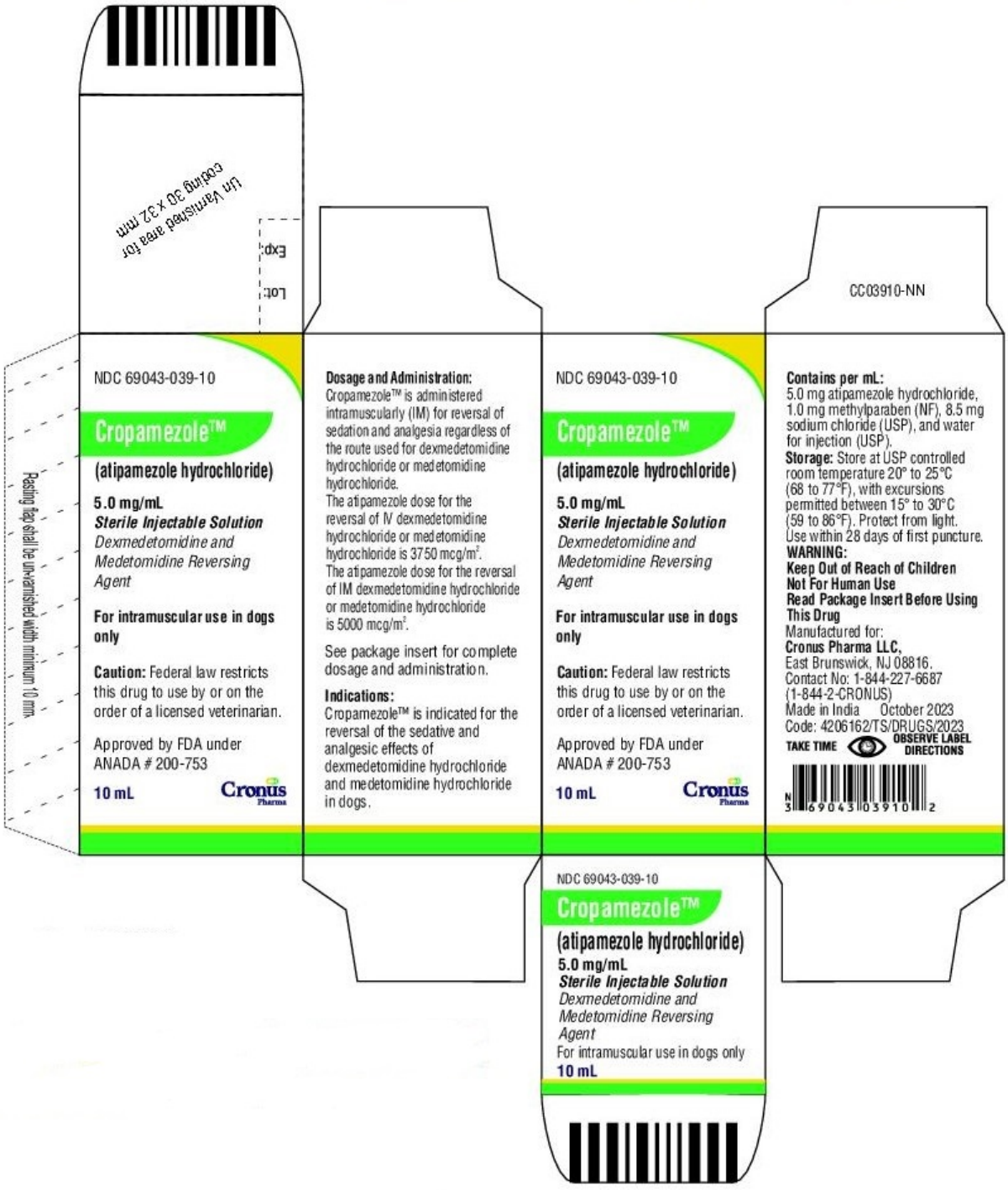
10 mL



CROPAMEZOLE

atipamezole hydrochloride injection, solution

Product Information			
Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:69043-039
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATIPAMEZOLE HYDROCHLORIDE (UNII: 2W4279571X) (ATIPAMEZOLE - UNII:03N9U5JAF6)	ATIPAMEZOLE HYDROCHLORIDE	5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69043-039-10	10 mL in 1 VIAL, GLASS		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANADA	ANADA200753	10/01/2023	

Labeler - Cronus Pharma LLC (079421067)

Revised: 12/2023 Cronus Pharma LLC