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## SEDIVET® 1% INJECTION



Boehringer Ingelheim

(romifidine hydrochloride)

NADA 141-229, Approved by FDA

### **Sedative and analgesic drug for intravenous use in horses only**

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

**Description:** Sedivet 1.0% Injection (romifidine hydrochloride) is an  $\alpha_2$ -adrenoceptor agonist with sedative and analgesic properties. The chemical name is 2-bromo-6-fluoro-2-imidazolidinyliden-benzamine-monohydrochloride. It is a crystalline, white, odorless, water soluble substance with a molecular formula of  $C_9H_9BrFN_3.HCl$ , and a molecular weight of 294.56. Each mL contains 10 mg romifidine hydrochloride, 6.5 mg sodium chloride, 2 mg chlorocresol, and water for injection.

**Indications:** Sedivet 1.0% Injection is indicated for use as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures in adult horses. Sedivet 1.0% Injection is also indicated as a preanesthetic prior to the induction of general anesthesia in adult horses.

**Dosage and Administration: Sedation and Analgesia Dose:** Administer slowly as a single IV injection using a dosage range of 40 - 120 µg/kg (0.4 - 1.2 mL/100 kg body weight) depending on the depth and duration of sedation that is required. The onset of action occurs in 30 seconds to 5 minutes, and gradually subsides during the next 2 to 4 hours. Degree of sedation and analgesia is dose-and time-dependent; therefore, more profound analgesia will occur with larger doses, as well as closer to the time of injection.

**Note:** The animal should be allowed to rest quietly for several minutes prior to and following injection.

**Note:** The duration of analgesia is shorter than the duration of sedation.

| Sedation Dose                | Onset of Sedation* | Duration of Sedation | Onset of Analgesia | Duration of Analgesia |
|------------------------------|--------------------|----------------------|--------------------|-----------------------|
| 40 µg/kg<br>(0.4 mL/100 kg)  | 2-4 minutes        | 75 minutes           | 5 minutes          | 30 minutes            |
| 120 µg/kg<br>(1.2 mL/100 kg) | 2-4 minutes        | 3 hours              | 5 minutes          | 150 minutes           |

\* Times reported are from the sedation dose confirmation study (see Effectiveness).

**Preanesthesia Dose:** A single IV injection using a dose of 100 µg/kg (1.0 mL/100 kg body weight) was shown to be effective in the preanesthesia dose confirmation study (see Effectiveness). Anesthesia should be induced after maximum sedation is achieved. The administration of  $\alpha_2$ -agonists results in anesthetic sparing effects<sup>1,2</sup>; therefore, anesthetic doses should be reduced to avoid overdose.

Mild to moderate sedation occurs within 2-4 minutes. Following induction, lateral recumbency occurs within 4 minutes, followed by complete anesthesia within 6-16 minutes. During recovery from anesthesia, sternal recumbency occurs within 12-83 minutes, followed by standing in 17-84 minutes. Recovery time is primarily determined by the choice of induction anesthetic and/or the duration of anesthesia.

**Contraindications:** Sedivet 1.0% Injection is contraindicated in horses with known hypersensitivity to romifidine.

Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal cardiac dysrhythmias may occur.<sup>3</sup>

**Warnings:** Not for human use. Keep this and all drugs out of the reach of children.

Not for horses intended for human consumption.

Although apparently deeply sedated, some horses may still respond to external stimuli with defensive movements (for example, kicking). Sedated horses are frequently ataxic. Routine safety measures should be used to protect practitioners and handlers.

Romifidine 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. In case of accidental oral exposure or injection, seek

medical attention. If irritation or other adverse reaction occurs (for example, sedation, hypotension, bradycardia), seek medical attention.

As with all injectable drugs causing profound physiological effects, precautions should be taken by practitioners to prevent accidental self-injection when handling and using filled syringes. Users receiving treatment for blood pressure abnormalities should take special precaution to avoid exposure to this product.

*Note to Physician:* This product contains an  $\alpha_2$ -adrenoceptor agonist and can be absorbed by oral and dermal routes.

**Precautions:** The use of Sedivet 1.0% Injection with other  $\alpha_2$ -agonists is not recommended since the effects (for example, cardiovascular changes, respiratory depression, ataxia) could be additive.

The adverse effects of Sedivet 1.0% Injection may be potentiated by the administration of other sedatives, tranquilizers, or opioids.

The use of epinephrine should be avoided since epinephrine may potentiate the effects of  $\alpha_2$ -agonists.

Anesthetic doses should be reduced in the presence of Sedivet 1.0% Injection to avoid excessive depression of the central nervous system.

Sedivet 1.0% Injection has not been evaluated in horses with compromised cardiovascular function. The effects of bradycardia, increased vascular resistance, decreased cardiac output, and respiratory depression could be significant in horses with primary myocardial disease, or circulatory shock.

Sedivet 1.0% Injection should not be used in horses with respiratory disease, hepatic or renal disease, dehydration, or other systemic conditions of compromised health.

The effects of Sedivet 1.0% Injection have not been evaluated in horses with colic.

The effects of Sedivet 1.0% Injection have not been evaluated in pregnant mares, in horses intended for breeding, or in foals.

**Adverse Reactions:** As with other drugs of this class, the administration of Sedivet 1.0% Injection causes bradycardia (possibly profound), first and second degree atrioventricular heart block, and hypotension. The frequency and duration of cardiac arrhythmias have been shown to be dose related.

The following commonly occurring adverse reactions have been noted using  $\alpha_2$ -agonists: hypertension, hypotension, bradycardia, ataxia, piloerection, sweating, muscle tremors, salivation, penile relaxation, urination (about an hour after treatment), lowering of head (causing passive congestion and swelling of face, lips, upper airways), stridor, decreased gastrointestinal motility, flatulence, and mild colic.

The potential exists, as with all  $\alpha_2$ -agonists, for isolated incidences of excitation (paradoxical response).

Rare anaphylactic reactions have been reported, including one or more of the following: urticaria, dyspnea, edema of the upper airways and head, trembling, recumbency, and subsequent death.

To report adverse reactions and/or to obtain a copy of the Material Safety Data Sheet (MSDS), call 1-800-821-7467.

**Clinical Pharmacology:** Romifidine is a potent  $\alpha_2$ -adrenoceptor agonist that produces sedation and analgesia. Sedation is induced by stimulation of presynaptic  $\alpha_2$ -receptors in the central nervous system. Administration of romifidine to conscious or anesthetized horses results in a biphasic effect on blood pressure. A transient increase in blood pressure due to peripheral vasoconstriction is followed by a compensatory vagal baroreceptor response resulting in longer lasting hypotension and bradycardia. A transient change in the conductivity of the cardiac muscle may manifest clinically as a partial atrioventricular block. Peripheral vasoconstriction may also lead to a transient

reduction in gastrointestinal motility.

**Effectiveness:** A field study was conducted to evaluate romifidine as a sedative or a preanesthetic. Clinicians selected an appropriate dose, based on the procedure. Sedative doses ranged between 30-100  $\mu\text{g}/\text{kg}$ ; preanesthetic doses ranged between 40-100  $\mu\text{g}/\text{kg}$ . The quality of sedation was rated as “good” or “excellent” in 18 of 23 horses. Of the remaining five horses evaluated for sedation, three were rated as “fair” and two were rated as “poor”. When used for preanesthesia, inductions were rated as “well-controlled” in 16 of 23 horses. Recoveries from anesthesia were evaluated as “satisfactory” or “excellent” in 20 of 23 horses. Two horses required more than three attempts to stand. One horse was euthanized without recovery, due to an unfavorable diagnosis unrelated to drug administration.

In a sedation dose confirmation study with a crossover design, twenty horses were used to evaluate romifidine at two doses: 40 and 120  $\mu\text{g}/\text{kg}$ . Clinical assessments of depth of sedation, behavioral attitude, stance/posture, head ptosis, ear ptosis, eyelid and lip drooping were evaluated. Depth and duration of sedation were affected in a dose dependent manner. By the response of the horses to thermal noxious stimuli applied to withers and fetlock, the degree and duration of analgesia were also shown to be dose dependent. Transient physiological and clinical effects included decreased respiratory and heart rates, second degree atrioventricular block, sweating, increased salivation, stridor, penile relaxation, and a slight decrease in body temperature. Seventy-five minutes after receiving the 40  $\mu\text{g}/\text{kg}$  dose, one older horse with a preexistent grade IV/VI systolic murmur, experienced ventricular tachycardia that lasted for 11.5 minutes. Another horse was diagnosed with pneumonia three days after receiving the 120  $\mu\text{g}/\text{kg}$  dose of romifidine.

In a separate preanesthesia crossover study, the effectiveness of the 100  $\mu\text{g}/\text{kg}$  preanesthetic romifidine dose was confirmed. Ten horses were induced with either ketamine or thiopental, followed by isoflurane maintenance anesthesia. The quality of induction, the transition to inhalant anesthesia, and the quality of anesthesia were scored as “excellent” for all horses. All horses except one stood on the first attempt (one stood on the third attempt).

**Animal Safety:** A toxicity study was conducted to observe the effects of a single dose of Sedivet 1.0% Injection at 360  $\mu\text{g}/\text{kg}$  (3X the highest recommended dose) and 600  $\mu\text{g}/\text{kg}$  (5X dose), using 3 horses per group. There were no clinically important alterations of blood gas, acid-base, hematological, or clinical chemistry values. The duration of bradycardia and second degree heart block was longer using the higher dose. Occasional periods of apnea (20 to 40 seconds) were followed by several deep successive breaths. Mild respiratory stridor was present, and horses periodically exhaled forcefully (“snorting”) in an apparent effort to clear their upper airways. The duration of sedation was dose dependent.

Horses exhibited signs of deep sedation, but would occasionally respond to environmental stimuli, only to return to deep sedation shortly thereafter. Mild sweating was observed. Urination commenced at 60-90 minutes and occurred frequently through four hours. One horse, which had been given a small amount of hay before full gastrointestinal motility had returned, showed mild abdominal discomfort twelve hours after administration of 600  $\mu\text{g}/\text{kg}$  romifidine. Horses in this study were not necropsied. Toxicity study results for another product in the  $\alpha_2$ -agonist class, showed microscopic foci of myocardial necrosis during histopathological examination in one of eight horses that received ten times the high end of the recommended dose for that product.

In another safety study, Sedivet 1.0% Injection was administered IV at doses of 120 µg/kg (1X the highest recommended dose), 360 µg/kg (3X), and 600 µg/kg (5X) for up to 3 consecutive days (9 horses per group). Sinus bradycardia (<30 bpm) and second degree heart block were most pronounced within 30 seconds to 5 minutes, gradually subsiding over two to four hours. Severe ataxia was observed in the 3X and 5X dose groups. Sweating was noted in all romifidine groups. Horses receiving the 1X dose showed an initial rise in blood pressure, followed by a return to baseline by 20-30 minutes. In the 3X and 5X groups, increases in blood pressure were seen at five minutes; returning toward baseline after 1 hour. Respiratory rates in all groups fell initially, followed by a gradual increase toward baseline values. Body temperature response varied, increasing slightly in the 1X and 3X groups, and decreasing slightly in the 5X group.

**Storage Information:** Store at controlled room temperature, 59-86°F (15-30°C).

**How Supplied:** Sedivet 1.0% Injection is supplied in 20 mL multi-dose vials containing 10 mg romifidine hydrochloride per mL.

**References:**

1. Muir, WM. Anesthesia for the equine patient. World Equine Vet Rev 1998; 3(4):27-29.
2. England, GCW, Clarke, KW. Alpha<sub>2</sub> adrenoceptor agonists in the horse - a review. Br Vet J 1996; 152:641-657.
3. Taylor PM, et al. Possible potentiated sulphonamide and detomidine interactions. Vet Rec 1988; 122:143.

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