SEDATOR VETERINARY Medetomidine hydrochloride 1.0 mg/ml

PACKAGE LEAFLET

The format of this leaflet was determined by the Ministry of Health, and its content was checked and approved by the Ministry of Health.

Veterinary Physician's Prescribing Information

1. Trade name of medicinal product:
SEDATOR VETERINARY

2. Qualitative and quantitative composition:
Active ingredient: Medetomidine hydrochloride 1.0 mg/ml
For a full list of excipients, see Section 6.1.

3. Pharmaceutical form: Solution for Injection.

4. Clinical particulars:
4.1 Target Species: Dogs and Cats.

4.2 Indications for Use, Specifying the Target Species:
With dogs and cats: Sedation to facilitate manageability. Premedication prior to general anaesthesia.
With cats: In combination with ketamine for general anaesthesia in case of minor surgical intervention of short duration.

4.3 Contraindications:
Medetomidine should not be used in conjunction with sympathomimetic amines. Care should be taken with the use of medetomidine in animals with cardiovascular disease or in poor general health. Before using any combinations consult the contraindications and warnings that appear on the other product's data sheet. Medetomidine should not be used with thiopentone or propofol in animals with cardiac or respiratory disease (also see section 4.10).

4.4 Special warnings for each target species:
Medetomidine with ketamine in cats: Medetomidine and ketamine are metabolised in the liver and excreted mainly via the kidneys, therefore any pre-existing hepatic or renal pathology must be carefully evaluated before considering this method of anaesthesia. Vomiting prior to onset of anaesthesia occurs in approximately 10 % of cases. Laryngeal and pharyngeal reflexes are retained during anaesthesia. The combination is reported to elicit a pain response in some cats when administered intramuscularly. Heart rates will generally fall to approximately 50 % of pre-anaesthetic levels and in some cats very slow respiratory rates are observed (4-6 breaths per minute). Where procedures are prolonged it may be helpful to apply an eye preparation at regular intervals to lubricate the cornea. During and after anaesthesia, treated animals should be kept in a warm and even temperature. Medetomidine must not be mixed with other ketamine products.

Medetomidine as a premedicant before thiopentone in dogs: Anaesthesia being maintained with halothane (with or without nitrous oxide). This regime should not be used in animals with cardiovascular or respiratory disease. Medetomidine and thiopentone are metabolised in the liver and excreted via the kidneys; any pre-existing hepatic or renal pathology must be carefully evaluated before considering this method of anaesthesia.
Medetomidine has marked anaesthetic sparing effects. Therefore, it should be ensured that the dose of thiopentone and halothane is reduced accordingly and is administered with care to minimise the possibility of inadvertent overdosage. Respiratory rates may fall by up 30% of pre-dose values following administration of medetomidine. Heart rates will fall following the administration of medetomidine and they will not return to presedation levels following induction. Occasionally there will be a transient rise in heart rate associated with induction followed by bradycardia. During and after anaesthesia, treated animals should be kept in a warm and even temperature.

Medetomidine as a premedicant before propofol in dogs: This regime should not be used in animals with cardiovascular or respiratory disease. Medetomidine and propofol are metabolised in the liver and excreted via the kidneys; any pre-existing hepatic or renal pathology must be carefully evaluated before considering this method of anaesthesia. Medetomidine has marked anaesthetic sparing effects, therefore it should be ensured that the dose of propofol is reduced accordingly and is administered with care to minimise the possibility of inadvertent overdosage. Transient apnoea and movement of the forelegs may occur during induction of anaesthesia and in some cases at higher dosages, a decline in arterial oxygen tension may occur. When using this regime dogs should be intubated and oxygen administered during anaesthesia. During and after anaesthesia, treated animals should be kept in a warm and even temperature.

4.5 Special precautions for use:
Special precautions for use in animals: Care should be taken with the use of medetomidine in animals with cardiovascular disease or in poor general health. Medetomidine, ketamine and thiopentone are metabolised in the liver and excreted mainly via the kidneys. Pre-existing liver or kidney pathology should be carefully evaluated prior to using these products (see also section 4.7 and 4.10). An appropriately graduated syringe must be used to allow accurate administration of the required dose volume. This is particularly important when injecting small volumes.

Special precautions to be taken by the person administering the veterinary medicinal product to animals: In the case of accidental oral intake or self-injection, seek medical advice immediately and show the package leaflet to the doctor but DO NOT DRIVE as sedation and changes in blood pressure may occur.
Avoid skin, eye or mucosal contact.
Immediately after exposure, wash the exposed skin with large amounts of fresh water. Remove contaminated clothes that are in direct contact with skin.
In the case of accidental contact of the product with eyes, rinse with large amounts of fresh water. If symptoms occur, seek the advice of a doctor.
If pregnant women handle the product, special caution should be observed not to self-inject as uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.

Advice to Doctors: Medetomidine hydrochloride is an alpha2-adrenoreceptor agonist. Symptoms after absorption may involve clinical effects including dose dependent sedation, respiratory depression, bradycardia, hypotension, a dry mouth, and hyperglycaemia. Ventricular arrhythmias have also been reported. Respiratory and haemodynamic symptoms should be treated symptomatically.

4.6 Adverse reactions (frequency and seriousness):
By virtue of this α2-adrenergic activity, medetomidine causes bradycardia and hypothermia. Treated animals should be kept in a warm and even temperature during the procedure and for 12 hours after sedation.
Blood pressure will increase initially and then return to normal or slightly below.
Some dogs and most cats vomit 5-10 minutes after injection.
Some cats may also vomit on recovery.
In some dogs and cats very slow respiratory rates may be seen (see also section 4.10).

4.7 Use during pregnancy, lactation or lay:
The use of medetomidine in pregnancy has not been monitored in a sufficient number of animals. It is therefore not recommended.

4.8 Interaction with other medicinal products and other forms of interaction:
Medetomidine should not be used in conjunction with sympathomimetic amines. The concomitant use of other central nervous system depressants should be expected to potentiate the effect of either product and appropriate dose adjustment should be made.
Medetomidine has marked anaesthetic sparing effects. The dose of compounds such as thiopentone, halothane and propofol should be reduced accordingly.

4.9 Amounts to be administered and administration route:
Intended for injection by intramuscular, intravenous and subcutaneous routes in the dog, and by the intramuscular or subcutaneous route in the cat.

Dosage: The following dose ranges are recommended.

Animal	Dose of medetomidine (µg/kg)	Effect	Quantity of product
Dog	10-30	Slight sedation	0.1 - 0.3 ml/10 kg
	30-80	Moderate to deep sedation and analgesia	0.3 - 0.8 ml/10 kg
	10-20	Pre-anaesthesia	0.1 - 0.2 ml/10 kg
Cat	50-100	Moderate sedation	0.25 - 0.5 ml/5 kg
	100-150	Deep sedation	0.50 - 0.75 ml/5 kg

Maximal effect is obtained within 10-15 minutes. The clinically useful effect is dose-dependent, lasting 30-180 minutes, but may be repeated if necessary.
Animals should be fasted for 12 hours prior to anaesthesia.

Premedication dosing guide: Medetomidine has marked anaesthetic-sparing effects. It is essential to reduce appropriately the dose of anaesthetic induction and maintenance agents in animals that have been given the product.

Dosing guide:

Medetomidine as a premedicant before thiopentone in dogs: Anaesthesia is maintained with halothane, with or without nitrous oxide. Medetomidine is administered at least 20 minutes before thiopentone (induction agent) to allow sedation to develop. Guideline doses of thiopentone are as follows:

Medetomidine dose (µg/kg)	Medetomidine quantity of product (ml/10 kg)	Dose of thiopentone (induction) (mg/kg)
10	0.1	6.9
20	0.2	4.5
40	0.4	2.4

The dose of thiopentone may vary considerably in different animals. The optimum dose of medetomidine is in the range 20-40 µg/kg and is dependent on the temperature of the dog. At higher doses of medetomidine, thiopentone may not be required for intubation.

Thiopentone is administered slowly as a dilute solution, intravenously to effect, over a period of 30-45 seconds. Once jaw relaxation is adequate, tracheal intubation can be undertaken. Onset of unconsciousness may be delayed for up to 1 minute following injection of thiopentone, slow intravenous injection is therefore required as indicated above. After intubation, anaesthesia may be maintained with halothane in oxygen (with or without nitrous oxide) administered to effect. Recovery from anaesthesia may take from 20 to more than 60 minutes. For recoveries in excess of 1 hour it is advisable to administer atipamezole (Atipam or Antisedan).

Medetomidine as premedicant before propofol in dogs: Medetomidine is administered either intravenously at least 10 minutes before intravenous propofol (induction agent) or intramuscularly at least 20 minutes before propofol to allow sedation to develop. Medetomidine may be administered at a dose rate of 10, 20 or 40 micrograms/kg. The following table is a guideline for doses.

Medetomidine dose (µg/kg)	Medetomidine quantity of product (ml/10 kg)	Dose of propofol (induction) (mg/kg)
10	0.1	1.5
20	0.2	1.1
40	0.4	1.0

Following premedication with medetomidine, doses of propofol of up to 4 mg/kg administered intravenously have been safely used when a greater depth of anaesthesia is required.

NB: The induction time is increased following premedication, so propofol should be administered by slow intravenous injection and up to 2.5 minutes should be allowed before a further dose is given.

Once jaw relaxation is adequate, tracheal intubation can be undertaken. It is advisable to administer oxygen during anaesthesia.
For maintenance of anaesthesia the dose of propofol is markedly reduced by medetomidine premedication. Infusion doses of 0.06 to 0.35 mg/kg/minute will provide stable anaesthesia for dogs sedated with between 40 and 10 µg/kg medetomidine respectively. For intermittent bolus administration, a dose of 1 mg/kg of propofol at intervals of between 4 and 12 minutes will provide stable anaesthesia. Recovery from anaesthesia may take from 20 to > 60 minutes.
Food should be withheld for 12 hours prior to anaesthesia.
Atipamezole administered in the post-operative phase will hasten the recovery from anaesthesia.

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Medetomidine with butorphanol for canine sedation: Medetomidine and butorphanol can be administered together in the same syringe, by intramuscular or intravenous injection.
Dose rate: Medetomidine 10-25 µg/kg, depending on the degree of sedation required, plus 0.1 mg/kg butorphanol. Allow 20 minutes for sedation to develop before commencing the procedure.
Reversal with an equal volume of Atipam or Antisedan to that of product used results in sternal recumbency approximately 5 minutes later and standing approximately a further 2 minutes later.

Medetomidine with butorphanol followed by thiopentone anaesthesia for canine sedation:
Dose rate: Medetomidine 10 µg/kg and butorphanol 0.1 mg/kg.
Medetomidine and butorphanol can be administered together in the same syringe, by intramuscular or intravenous injection.

Allow 20 minutes for sedation to develop before administering thiopentone.
Atipamezole administered in the post-operative phase will hasten the recovery from anaesthesia.

Canine doses (ml) for mild sedation, or premedication prior to thiopentone:

Weight (kg)	1	3	5	10	15	20	25	30	35	40
(medetomidine hcl 1 mg/ml) (dose of medetomidine 10 µg/kg)	0.01	0.03	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4
Butorphanol 10 mg/ml (dose of butorphanol 0.1 mg/kg)	0.01	0.03	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4

Canine doses (ml) for deep canine sedation:

Weight (kg)	1	3	5	10	15	20	25	30	35	40
(medetomidine hcl 1 mg/ml) (dose of medetomidine 25 µg/kg)	0.03	0.075	0.13	0.25	0.38	0.5	0.63	0.75	0.88	1
Butorphanol 10 mg/ml (dose of butorphanol 0.1 mg/kg)	0.01	0.03	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4

Medetomidine with ketamine in cats: The agents may be given concomitantly in the same syringe, by the intramuscular route. To minimise the risk of cross contamination between vials, insert separate needles into each vial for withdrawal. A dose of 80 µg/kg is recommended for medetomidine, with 2.5 – 7.5 mg/kg ketamine giving onset of anaesthesia in 3-4 minutes and a duration of 30-50 minutes for surgical procedures.
Anaesthesia may be prolonged, if required, with halothane and oxygen, with or without nitrous oxide.
Atropine is not normally necessary when using a medetomidine/ketamine combination.
Food should be withheld for 12 hours prior to anaesthesia.

Medetomidine with butorphanol for feline sedation: Medetomidine and butorphanol can be administered together in the same syringe, by intramuscular or subcutaneous injection.
Dose rate: Medetomidine 50 µg/kg, depending on the degree of sedation required, plus 0.4 mg/kg butorphanol. Allow 20 minutes for sedation to develop before commencing the procedure.
Local anaesthetic infiltration should be used for wound suturing.
Reversal with half volume of Atipam or Antisedan to that of product used, results in sternal recumbency approximately 4 minutes later and standing approximately a further 2 minutes later.

Feline doses (ml) for medetomidine / butorphanol sedation:

Weight (kg)	1	1.5	2	2.5	3	3.5	4	4.5	5
(medetomidine hcl 1 mg/ml) (dose of medetomidine 50 µg/kg)	0.05	0.08	0.10	0.13	0.15	0.18	0.20	0.23	0.25
Butorphanol 10 mg/ml (dose of butorphanol 0.4 mg/kg)	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18	0.20

Medetomidine, butorphanol and ketamine for feline anaesthesia:
a) Intramuscular
Dosage: Medetomidine 80 µg/kg, butorphanol 0.4 mg/kg and ketamine 5mg/kg should be given in a single syringe.
Cats become recumbent in 2-3 minutes following injection. Loss of pedal reflex occurs 3 minutes post injection.
Reversal with 200 µg/kg atipamezole results in the return of pedal reflex 2 minutes later, sternal recumbency 6 minutes later and standing 31 minutes later.
Feline doses (ml) for intramuscular medetomidine/butorphanol/ketamine anaesthesia:

Weight (kg)	1	1.5	2	2.5	3	3.5	4	4.5	5
(medetomidine hcl 1 mg/ml) (dose of medetomidine 80 µg/kg)	0.08	0.12	0.16	0.2	0.24	0.28	0.32	0.36	0.40
Butorphanol 10 mg/ml (dose of butorphanol 0.4 mg/kg)	0.04	0.06	0.08	0.1	0.12	0.14	0.16	0.18	0.20
Ketamine 100 mg/ml (dose of ketamine 5 mg/kg)	0.05	0.075	0.1	0.125	0.15	0.175	0.2	0.225	0.25

b) Intravenous
Dosage: Medetomidine 40 µg/kg, butorphanol 0.1 mg/kg and ketamine from 1.25 to 2.5 mg/kg (depending on depth of anaesthesia required).
Reversal with 100 µg/kg of atipamezole results in the return of pedal reflex 4 minutes later, sternal recumbency 7 minutes later and standing 18 minutes later.

Feline doses (ml) for intravenous medetomidine/butorphanol/ketamine anaesthesia:

Weight (kg)		1	1.5	2	2.5	3	3.5	4	4.5	5
(medetomidine hcl 1 mg/ml)	40 µg/kg	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18	0.20
butorphanol 10 mg/ml	0.1 mg/kg	0.01	0.02	0.02	0.03	0.03	0.04	0.04	0.05	0.05
EITHER ketamine 100 mg/ml	1.25 mg/kg	0.01	0.02	0.03	0.03	0.04	0.04	0.05	0.06	0.06
OR ketamine 100 mg/ml	2.5 mg/kg	0.03	0.04	0.05	0.06	0.08	0.09	0.10	0.11	0.13

Approximate time scales in intravenous medetomidine/butorphanol/ketamine anaesthesia:

Ketamine dose	Time to recumbency	Time to loss of pedal reflex	Time to return of pedal reflex	Time to sternal recumbency	Time to standing
1.25 mg/kg	32 secs	62 secs	26 mins	54 mins	74 mins
2.5 mg/kg	22 secs	39 secs	28 mins	62 mins	83 mins

Medetomidine followed by alfaxalone/alfadolone for general anaesthesia:
Dosage: Administer medetomidine 80 µg/kg by intramuscular or subcutaneous injection. 15-60 minutes later administer 2.5 - 5.0 mg/kg alfaxalone/alfadolone intravenously. Anaesthesia may be maintained by further intravenous injections of alfaxalone/alfadolone, or by administration of halothane in oxygen.

Feline doses (ml) for medetomidine/alfaxalone/alfadolone anaesthesia:

Weight (kg)		1	1.5	2	2.5	3	3.5	4	4.5	5
(medetomidine hcl 1 mg/ml)	80µg/kg	0.08	0.12	0.16	0.2	0.24	0.28	0.32	0.36	0.40
alfaxalone 9 mg/ml /alfadolone 3 mg/ml	Min. Dose = 2.5 mg/kg	0.21	0.31	0.42	0.52	0.63	0.73	0.83	0.94	1.04
alfaxalone 9 mg/ml /alfadolone 3 mg/ml	Max. dose = 5 mg/kg	0.42	0.63	0.83	1.04	1.25	1.46	1.67	1.88	2.08

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary:
In cases of overdosage, or if the effects of medetomidine become life-threatening, the appropriate dose of atipamezole is recommended provided that reversal of sedation and analgesia is not dangerous to the patient. For example, atipamezole does not reverse the effects of ketamine. If it is imperative to reverse bradycardia but to maintain sedation, atropine may be used.

4.11 Withdrawal Period(s):
Not applicable.

5. Pharmacological properties
Pharmacotherapeutic group: Sedative / Analgesic
ATCvet code: QN05CM91

5.1 Pharmacodynamic properties: The active ingredient of the product is (R,S)-4-[1-(2,3-dimethylphenyl)-ethyl)]-imidazole-hydrochloride (INN: Medetomidine), a sedative compound with analgesic and myorelaxing properties. Medetomidine is a selective, specific and highly efficious alpha-2-receptor agonist. The activation of alpha-2 receptors leads to a decrease in release and turnover of norepinephrine in the central nervous system, leading to sedation, analgesia and bradycardia. In the periphery medetomidine causes vasoconstriction via stimulation of postsynaptic alpha-2 adrenoceptors, leading to a transient arterial hypertension.
Within 1 – 2 hours arterial blood pressure falls back to normotension or slight hypotension. The respiratory rate may be transiently decreased. Depth and duration of sedation and analgesia are dose related. Profound sedation and recumbency, with reduced sensitivity to environmental stimuli (sounds, etc.), are seen with medetomidine. Medetomidine acts synergistically with ketamine and opiates, such as fentanyl, leading to better anaesthesia. The amount of volatile anaesthetics, such as halothane, will be reduced by medetomidine. Beside its sedative, analgesic and myo-relaxing properties, medetomidine also exerts hypothermic and mydriatic effects, inhibits salivation and decreases intestinal motility.

5.2 Pharmacokinetic particulars: After intramuscular administration medetomidine is rapidly and nearly completely absorbed from the injection site and pharmacokinetics is very similar to intravenous administration. Maximal plasma concentrations are reached within 15 and 20 minutes. Plasma half-life is considered to be 1.2 hours in the dog and 1.5 hours in the cat. Medetomidine is mainly oxidized in the liver, a smaller amount undergoes methylation in the kidneys. Metabolites will be excreted mainly via urine.

6. Pharmaceutical particulars
6.1 List of Excipients:
Propyl parahydroxybenzoate, Methyl parahydroxybenzoate, Sodium chloride, Sodium hydroxide, Hydrochloride acid, Water for injection.

6.2 Incompatibilities:
In the absence of incompatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products in the same syringe.

6.3 Shelf Life:
The expiry date of the product is indicated on the label and packaging. Do not use after the expiry date.
Shelf-life after first opening the immediate packaging: 28 days.

6.4 Special Precautions for Storage:
Store below 30°C. Protect from frost.

6.5 Nature and composition of immediate packaging:
Glass vials of 5, 10 and 20 ml. Vials are fitted with a teflon coated halogenated rubber stopper and sealed with an aluminium cap.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products, if appropriate:
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. Israeli Drug Registration Number: 151-02-33761-00

8. Manufacturer:
EUROVET ANIMAL HEALTH B.V.,
HANDELSWEG 25, 5530 AE BLADEL, THE NETHERLANDS

9. Israeli Marketing Authorization Holder & Importer:
ABIC VETERINARY PRODUCTS LTD,
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