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DOMITOR PACKAGE INSERT

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DOMITOR VETERINARY

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Medetomidine hydrochloride 1 mg/ml

Excipients:

Methyl parahydroxybenzoate 1 mg/ml

Propyl parahydroxybenzoate 0.2 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

Dogs: For restraint, sedation and analgesia associated with clinical examinations and procedures, minor surgery and pre-anaesthesia. As a premedicant before halothane general anaesthesia and as a premedicant before general anaesthesia with propofol.

Cats: For restraint and sedation. In combination with ketamine for induction of general anaesthesia prior to surgical procedures.

4.3 Contraindications

Do not use in animals with heart failure, respiratory disease or impaired liver or kidney function, animals in shock, seriously debilitated animals, or animals that are stressed due to extreme heat, cold or fatigue. Do not use in conjunction with sympathomimetic amines.

Do not use in dogs under 12 weeks of age.

4.4 Special warnings for each target species

When Domitor is administered, the animal should be allowed to rest in a maximally quiet place. Before any procedure is started or other drugs are administered, sedation should be allowed to reach its peak effect, which occurs at about 10 to 30 min, depending on route of administration.

In extremely nervous, excited or agitated animals, the levels of endogenous catecholamines may be high. The pharmacological response elicited by alpha-2 agonists (e.g. medetomidine) in such animals is often reduced, with depth and duration of sedative and analgesic effects ranging from slightly diminished to non-existent. Highly agitated animals should therefore be put at ease and allowed to rest quietly prior to receiving Domitor. Allowing animals to rest quietly for 10 to 15 minutes after injection may improve the response to Domitor.

4.5 Special precautions for use

i. Special precautions for use in animals

A clinical examination should be carried out in all animals before the use of drugs for sedation and/or general anaesthesia.

Care should be taken when using Domitor in animals with cardiovascular disease.

Care should be taken when combining medetomidine with other anaesthetics or sedatives. Before using any combinations consult the contraindications and warnings that appear on the concomitant product's data sheet.

Medetomidine has marked anaesthetic-sparing effects. The dose of the anaesthetic should be reduced accordingly (see section 4.9).

Special care is recommended when treating very young animals and older animals.

Domitor, ketamine and propofol are metabolised in the liver and excreted primarily via the kidneys. Pre-existing liver or kidney pathology should be carefully evaluated to confirm adequate function prior to using these products.

Fasting is recommended before Domitor administration. After treatment, the animal should not be given water or food before it is able to swallow properly.

Treated animals should be kept in a warm and even temperature during the procedure and for 12 hours after sedation.

During prolonged procedures an ophthalmic preparation should be administered at regular intervals to lubricate the cornea especially in cats and sometimes also in dogs if their eyes remain open.

In cats, when Domitor is used in combination with ketamine, laryngeal and pharyngeal reflexes are retained during anaesthesia.

ii. 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 alpha-2 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)

Blood pressure will increase initially and then return to normal or slightly below normal. Bradycardia with occasional atrioventricular block may occur. Cyanosis has been reported.

Some dogs and most cats vomit 5 to 15 minutes after injection. Some cats may also vomit upon recovery.

Body temperature is slightly or moderately decreased and prolonged recovery may lead to hypothermia.

An increase in blood glucose concentration is seen due to alpha-2 adrenoreceptor-mediated inhibition of insulin secretion.

Urination typically occurs during recovery at about 90 to 120 minutes post-treatment.

Some animals experience muscle tremors and may be sensitive to loud sounds.

Incidents of prolonged sedation and recurrence of sedation after initial recovery have been reported.

Isolated cases of hypersensitivity, paradoxical response (excitation) and lack of efficacy have been reported.

Death from circulatory failure with severe congestion of the lungs, liver, or kidney has been reported. Decreased respiratory rates with or without transient apnoea may occur. If the animal has a pre-existing subclinical respiratory disease, administration of Domitor can cause some significant respiratory depression which could predispose the animal to cardiac arrest. Pulmonary oedema has been reported.

The combination of Domitor and ketamine is reported to elicit a pain response in some cats when administered intramuscularly. Heart rates will generally decrease to approximately 50% of pre-anaesthetic levels and in some cats very slow respiratory rates are observed (4-6 breaths per minute).

In dogs, when Domitor is used in combination with propofol, movement of the forelegs may occur during induction of anaesthesia. In some cases at higher dosages, a decline in arterial oxygen tension may occur.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy or lactation.

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 must not be mixed with other products, with the exception of Vetalar and Ketaset Injection and Torbugesic injection.

Medetomidine has marked anaesthetic-sparing effects. The dose of compounds such as propofol and volatile anaesthetics should be reduced accordingly, by up to 50-90%, depending on the individual animal.

Although bradycardia may be partially prevented by prior administration (at least 5 minutes before Domitor) of an anticholinergic agent, the administration of anticholinergic agents to treat bradycardia either simultaneously with medetomidine or following sedation with medetomidine could lead to adverse cardiovascular effects.

4.9 Amounts to be administered and administration route

An appropriately graduated syringe must be used to allow accurate administration of the required dose volume. This is particularly important when injecting small volumes. Administration by intramuscular (IM), intravenous (IV) and subcutaneous (SC) routes are possible. The effect is most rapid after IV administration and slowest after SC administration. The dosage is dependent on the degree of sedation and analgesia required.

Domitor	Dose mcg/kg
Dogs	10-80
Cats	50-150

For sedation, small dogs require more Domitor per kg of body weight than large dogs, thus the dosage per square meter of body surface could be more accurate. If this approach is used, the dosage is 750 to 1000 mcg/square meter.

The following table gives the dosage for dogs on the basis of body weight.

Body weight (kg) IV administration	Injection volume (ml)	Body weight (kg) IM/SC administration
1.5-2.2	0.1	
2.3-3.5	0.15	1.8-2.3
3.6-5.1	0.2	2.4-3.3
5.2-6.9	0.25	3.4-4.5
7.0-9.9	0.3	4.6-6.4
10.0-14.4	0.4	6.5-9.4
14.5-19.5	0.5	9.5-12.7
19.6-25.1	0.6	12.8-16.3
25.2-31.1	0.7	16.4-20.2
31.2-37.6	0.8	20.3-24.4
37.7-44.4	0.9	24.5-28.9
44.5-55.3	1.0	29.0-36.1
55.4-71.1	1.2	36.2-46.3
71.2-88.2	1.4	46.4-57.3
88.3 +	1.6	57.4-75.8
	2.0	75.9 +

Anaesthesia:

Domitor is suitable for use as an anaesthetic premedication prior to general 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

Combinant	Dosage (Dogs)		Dosage (Cats)	
	Domitor (mcg/kg)	Combinant (mg/kg)	Domitor (mcg/kg)	Combinant (mg/kg)
Propofol	10-40	1-4	N/A	N/A
Ketamine	N/A	N/A	80	2.5-7.5

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Overdose is mainly manifested by delayed recovery after sedation or anaesthesia. In a few individuals, circulatory and respiratory depression may occur.

The effects of Domitor can be eliminated using the specific alpha-2 adrenergic antagonist atipamezole (Antisedan). In the dog, the Antisedan dosage expressed in mcg is 5 times that of Domitor. In the cat, the Antisedan dosage expressed in mcg is 2.5 times that of Domitor.

4.11 Withdrawal period

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: sedative and analgesic.

ATC vet Code: QN05CM91.

5.1 Pharmacodynamic properties

The active ingredient of Domitor is medetomidine. Its chemical structure is 4 [1 (2,3 dimethylphenyl)ethyl] 1H imidazole hydrochloride. Medetomidine is an alpha-2 adrenergic agonist with central and peripheral effects inhibiting the transmission of noradrenaline-mediated nerve impulses by activating pre- and post-synaptic alpha-2 adrenoceptors. In the animal, the level of consciousness is lowered and the pain threshold is raised. The action of medetomidine is dose-dependent: small doses cause mild sedation and analgesia, while larger doses produce high levels of sedation and analgesia.

Medetomidine lowers the heart rate and initially elevates the blood pressure; blood pressure returns to baseline or slightly below baseline over fifteen minutes. The cardiovascular changes observed are either centrally mediated (bradycardia, hypotension) or due to direct effects on alpha-2 receptors (vasoconstriction, increased systemic vascular resistance).

The vasoconstriction may turn the mucous membranes pale or slightly bluish. Dogs may develop benign conductivity disturbances (first or second degree AV block). The respiratory rate is lowered. Local muscular twitching may occur in a few individuals. Blood glucose levels are elevated in both animal species. Body temperature decreases.

5.2 Pharmacokinetic particulars

Medetomidine is rapidly absorbed after intramuscular injection; the t_{max} varies from 15 to 30 min. Medetomidine is also rapidly distributed in the organism. The V_d varies between 2.8 and 3.6 L/kg. Protein binding is 85 to 90%. Medetomidine is oxidised in the liver and a small proportion is methylated in the kidneys. Most metabolites are excreted in the urine. The $t_{1/2}$ is 1-2 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

Sodium chloride

Water for injections

6.2 Incompatibilities

Medetomidine must not be mixed with other products with the exception of Ketaset injection.

6.3 Shelf-life

Do not use the veterinary medicinal product after the expiry date (exp. Date) mentioned on the package. The expiry date refers to the last day of that month.

Shelf-life after first opening the immediate packaging: 28 days. Discard unused material.

6.4 Special precautions for storage

Do not store above 25°C. Protect from freezing.

This medicine and any other medicine must be kept in a safe place out of the reach of children and/or infants to avoid poisoning.

6.5 Nature and composition of immediate packaging

Sterile aqueous solution and presented in clear, Type I glass vials of 10 ml capacity. Vials are fitted with a chlorobutyl rubber bung and sealed with an aluminium seal.

7. MARKETING AUTHORISATION HOLDER

Zoetis Israel Holding B.V.

5 Atir Yeda Street, Kfar Saba, Israel

8. MARKETING AUTHORISATION NUMBER

082 58 92306 00

9. MANUFACTURER

Orion Corporation Orion Pharma, Finland

Orionintie 1, 02200 Espoo, Finland

10. VETERINARY USE

The veterinary medicine is dispensed with a veterinarian's prescription only

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