

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.1 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: One ml contains 0.1 mg dexmedetomidine hydrochloride equivalent to 0.08 mg dexmedetomidine.

Excipients: Methyl parahydroxybenzoate (E 218) 2.0 mg/ml
Propyl parahydroxybenzoate (E 216) 0.2 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.

Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.

Premedication in dogs and cats before induction and maintenance of general anaesthesia.

4.3 Contraindications

Do not use in animals with cardiovascular disorders.

Do not use in animals with severe systemic disease or in animals that are moribund.

Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The administration of dexmedetomidine to puppies younger than 16 weeks and kittens younger than 12 weeks has not been studied.

The safety of dexmedetomidine has not been established in males intended for breeding.

In cats, corneal opacities may occur during sedation. The eyes should be protected by a suitable eye lubricant.

4.5 Special precautions for use

Special precautions for use in animals

Treated animals should be kept warm and at a constant temperature, both during the procedure and recovery.

It is recommended that animals are fasted for 12 hours prior to Dexdomitor administration. Water may be given.

After treatment, the animal should not be given water or food before it is able to swallow.

The eyes should be protected by a suitable lubricant.

To be used with precaution in elderly animals.

Nervous, aggressive or excited animals should be given the possibility to calm down before initiation of treatment.

Frequent and regular monitoring of respiratory and cardiac function should be performed. Pulse oximetry may be useful but is not essential for adequate monitoring. Equipment for manual ventilation should be available in case of respiratory depression or apnoea when dexmedetomidine and ketamine are used sequentially to induce anaesthesia in cats. It is also advisable to have oxygen readily available, should hypoxaemia be detected or suspected.

Sick and debilitated dogs and cats should only be premedicated with dexmedetomidine before induction and maintenance of general anaesthesia based on a risk-benefit assessment.

Use of dexmedetomidine as a premedicant in dogs and cats significantly reduces the amount of induction drug required for induction of anaesthesia. Attention should be given during the administration of intravenous induction drugs to effect. Volatile anaesthetic requirements for maintenance anaesthesia are also reduced.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package leaflet or the label to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.

Avoid skin, eye or mucosal contact; the use of impermeable gloves is advisable. In case of skin or mucosal contact, wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes that are in direct contact with skin. In case of eye contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

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 physicians: Dexdomitor is an α_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. The specific α_2 -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize dexmedetomidine-induced effects.

People with known hypersensitivity to the active substance or any of the excipients should administer the veterinary medicinal product with caution.

4.6 Adverse reactions (frequency and seriousness)

By virtue of its α_2 -adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

In some dogs and cats, a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. Blood pressure will increase initially and then return to normal or below normal. Due to peripheral vasoconstriction and venous desaturation in the presence of normal arterial oxygenation, the mucous membranes may appear pale and/or with a blue tinge.

Vomiting may occur 5–10 minutes after injection. Some dogs and cats may also vomit at the time of recovery.

Muscle tremors may occur during sedation.

Corneal opacities may occur during sedation (see also section 4.5).

When dexmedetomidine and ketamine are used sequentially, with a 10 minute interval, cats may occasionally experience AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into dexmedetomidine-ketamine anaesthesia. Vomiting, hypothermia and nervousness have been reported after such use.

When dexmedetomidine and butorphanol are used concomitantly in dogs, bradypnoea, tachypnoea, an irregular respiratory pattern (20-30 sec apnoea followed by several rapid breaths), hypoxaemia, muscle twitch or tremor or paddling, excitation, hypersalivation, retching, vomiting, urination, skin erythema, a sudden arousal, or prolonged sedation may occur. Brady- and tachyarrhythmias have been reported. These may include profound sinus bradycardia, 1st and 2nd degree AV block, sinus arrest or pause, as well as atrial, supraventricular and ventricular premature complexes.

When dexmedetomidine is used as a premedicant in dogs, bradypnoea, tachypnoea and vomiting may occur. Brady- and tachyarrhythmias have been reported and include profound sinus bradycardia, 1st and 2nd degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3rd degree AV block may be observed in rare cases.

When dexmedetomidine is used as a premedicant in cats, vomiting, retching, pale mucous membranes, and low body temperature may occur. Intramuscular dosing at 40 micrograms/kg (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1st degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2nd degree atrioventricular block, or escape beats/rhythms.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of dexmedetomidine has not been established during pregnancy and lactation in the target species. Therefore the use of the product during pregnancy and lactation is not recommended.

4.8 Interaction with other medicinal products and other forms of interaction

The use of other central nervous system depressants is expected to potentiate the effects of dexmedetomidine and therefore an appropriate dose adjustment should be made. Anticholinergics should be used with caution with dexmedetomidine.

Administration of atipamezole after dexmedetomidine rapidly reverses the effects and thus shortens the recovery period. Within 15 minutes dogs and cats are normally awake and standing.

Cats: After administration of 40 micrograms dexmedetomidine/kg bw intramuscularly concurrently with 5 mg ketamine/kg bw to cats, the maximum concentration of dexmedetomidine increased twofold but there was no effect on T_{max} . The mean half-life of elimination of dexmedetomidine increased to 1.6 h and the total exposure (AUC) increased by 50%.

A dose of 10 mg ketamine/ kg used concurrently with 40 micrograms dexmedetomidine/ kg may cause tachycardia.

For information on adverse reactions, see section 4.6. Adverse reactions.

For information on target animal safety in cases of overdosing, see section 4.10. Overdose.

4.9 Amounts to be administered and administration route

The product is intended for:

- Dogs: intravenous or intramuscular use
- Cats: intramuscular use

The product is not intended for repeat injections.

Dexdomitor, butorphanol and/or ketamine can be mixed in the same syringe as they have been shown to be pharmaceutically compatible.

Dosage: the following doses are recommended:

DOGS:

Dexmedetomidine doses are based on body surface area:

Intravenously: up to 375 micrograms/square metre body surface area

Intramuscularly: up to 500 micrograms/square metre body surface area

When administering in conjunction with butorphanol (0.1 mg/kg) for deep sedation and analgesia, the intramuscular dose of dexmedetomidine is 300 micrograms/square metre body surface area. The premedication dose of dexmedetomidine is 125–375 micrograms/square metre body surface area, administered 20 minutes prior to induction for procedures requiring anaesthesia. The dose should be adjusted to the type of surgery, length of procedure and patient temperament.

Concomitant use of dexmedetomidine and butorphanol produces sedative and analgesic effects beginning no later than 15 minutes after administration. The peak sedative and analgesic effects are reached within 30 minutes after administration. Sedation lasts for at least 120 minutes post administration and analgesia lasts for at least 90 minutes. Spontaneous recovery occurs within 3 hours.

Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol and thiopental was reduced by 30% and 60% respectively. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect. In a clinical study, dexmedetomidine contributed to postoperative analgesia for 0.5–4 hours. However this duration is dependent on a number of variables and further analgesia should be administered in accordance with clinical judgement.

The corresponding doses based on body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

Dog weight (kg)	Dexmedetomidine 125 micrograms/m ²		Dexmedetomidine 375 micrograms/m ²		Dexmedetomidine 500 micrograms/m ²	
	(mcg/kg)	(ml)	(mcg/kg)	(ml)	(mcg/kg)	(ml)
2-3	9.4	0.2	28.1	0.6	40	0.75
3.1-4	8.3	0.25	25	0.85	35	1
4.1-5	7.7	0.35	23	1	30	1.5
5.1-10	6.5	0.5	19.6	1.45	25	2
10.1-13	5.6	0.65	16.8	1.9		
13.1-15	5.2	0.75				
15.1-20	4.9	0.85				

For deep sedation and analgesia with butorphanol		
Dog weight (kg)	Dexmedetomidine 300 micrograms/m ² intramuscularly	
	(mcg/kg)	(ml)
2-3	24	0.6
3.1-4	23	0.8
4.1-5	22.2	1
5.1-10	16.7	1.25
10.1-13	13	1.5
13.1-15	12.5	1.75

For higher weight ranges, use DEXDOMITOR 0.5 mg/ml and its dosing tables.

CATS:

The dosage for cats is 40 micrograms dexmedetomidine hydrochloride/kg bw equal to a dose volume 0.4 ml Dexdomitor/kg bw when used for non-invasive, mildly to moderately painful procedures requiring restraint, sedation and analgesia.

When dexmedetomidine is used for premedication in cats, the same dose is used. Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol was reduced by 50%. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect.

Anaesthesia can be induced 10 minutes after premedication by intramuscular administration of a target dose of 5 mg ketamine/ kg bw or by intravenous administration of propofol to effect. Dosing for cats is presented in the following table.

Cat weight (kg)	Dexmedetomidine 40 micrograms/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.5
2.1-3	40	1

For higher weight ranges, use DEXDOMITOR 0.5 mg/ml and its dosing table.

The expected sedative and analgesic effects are reached within 15 minutes after administration and are maintained up to 60 minutes after administration. Sedation may be reversed with atipamezole. Atipamezole should not be administered prior to 30 minutes following ketamine administration.

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

Dogs: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate dose of atipamezole is 10 times the initial dose of dexmedetomidine (micrograms/ kg bw or micrograms/ square meter body surface area). The dose volume of atipamezole at the concentration of 5 mg/ml is one fifth (1/5) of the dose volume of Dexdomitor 0.1 mg/ml that was given to the dog, regardless of route of administration of Dexdomitor.

Cats: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate antagonist is atipamezole, administered by intramuscular injection, at the following dose: 5 times the initial dose dexmedetomidine in micrograms/kg bw.

After concurrent exposure to a triple (3X) overdose of dexmedetomidine and 15 mg ketamine/ kg, atipamezole can be administered at the recommended dose level for reversal of effects induced by dexmedetomidine. At high serum concentrations of dexmedetomidine sedation is not increased although the level of analgesia does increase with further dose increases. The dose volume of atipamezole at the concentration of 5 mg/ml equals one tenth (1/10) the volume of Dexdomitor 0.1 mg/ml that was given to the cat.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: other hypnotics and sedatives, ATCvet code: QN05CM18.

5.1 Pharmacodynamic properties

Dexdomitor contains dexmedetomidine as the active substance, which produces sedation and analgesia in dogs and cats. The duration and depth of the sedation and analgesia are dose-dependent. At maximal effect, the animal is relaxed, recumbent and does not respond to external stimulus.

Dexmedetomidine is a potent and selective α_2 -adrenoceptor agonist that inhibits the release of noradrenaline from noradrenergic neurons. Sympathetic neurotransmission is prevented and the level of consciousness decreases. Reduced heart rate and temporary AV-block can be seen after administration of dexmedetomidine. Blood pressure decreases to normal or below normal levels after an initial increase. Respiration rate can occasionally decrease. Dexmedetomidine also induces a number of other α_2 -adrenoceptor mediated effects, which include piloerection, depression of motor and secretory functions of the gastrointestinal tract, diuresis and hyperglycaemia.

A slight decrease in temperature may be observed.

5.2 Pharmacokinetic particulars

As a lipophilic compound, dexmedetomidine is well absorbed after intramuscular administration. Dexmedetomidine is also rapidly distributed in the body and penetrates the blood-brain barrier readily. According to studies in rats, the maximum concentration in the central nervous system is several times that of the corresponding concentration in plasma. In the circulation, dexmedetomidine is largely bound to plasma proteins (>90%).

Dogs: After an intramuscular dose of 50 micrograms/kg a maximum concentration in plasma of about 12 nanograms/ml is reached after 0.6 hours. The bioavailability of dexmedetomidine is 60% and the apparent volume of distribution (Vd) is 0.9 l/kg. The elimination half-life ($t_{1/2}$) is 40-50 minutes.

Major biotransformations in the dog include hydroxylation, glucuronic acid conjugation and N-methylation in the liver. All known metabolites lack pharmacological activity. Metabolites are excreted mainly in the urine and to a lesser extent in the faeces. Dexmedetomidine has a high clearance and its elimination depends on the hepatic blood flow. A prolonged elimination half-life is therefore expected with overdoses or when dexmedetomidine is coadministered with other substances, which affect hepatic circulation.

Cats: The maximum plasma concentration is reached about 0.24 h after intramuscular administration. After a 40 micrograms/kg bw intramuscular dose the C_{max} is 17 nanograms/ml. The apparent volume of distribution (Vd) is 2.2 l/kg and the elimination half-life ($t_{1/2}$) is one hour.

Biotransformations in the cat occur by hydroxylation in the liver. Metabolites are excreted mainly in the urine (51% of the dose), and to a lesser extent in the faeces. As in dogs dexmedetomidine has a high clearance in cats and its elimination depends on the hepatic blood flow. A prolonged elimination half-life is therefore expected with overdoses or when dexmedetomidine is coadministered with other substances, which affect hepatic circulation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate (E 216)

6.2 Major incompatibilities

None known.

Dexdomitor is compatible with butorphanol and ketamine in the same syringe at least for two hours.

6.3 Shelf life

3 years

After withdrawal of the first dose, the product may be stored for 3 months at 25°C.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and composition of immediate packaging

Cardboard box with 1 glass (Type I) vial of 20 ml (with filling volume of 15 ml) with a bromobutyl rubber stopper and aluminium cap.

Package size: 15 ml and 10 x 15 ml
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/02/033/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30/08/2002
Date of last renewal: 02/08/2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: One ml contains 0.5 mg dexmedetomidine hydrochloride equivalent to 0.42 mg dexmedetomidine.

Excipients: Methyl parahydroxybenzoate (E 218) 1.6 mg/ml
Propyl parahydroxybenzoate (E 216) 0.2 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.

Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.

Premedication in dogs and cats before induction and maintenance of general anaesthesia.

4.3 Contraindications

Do not use in animals with cardiovascular disorders.

Do not use in animals with severe systemic disease or in animals that are moribund.

Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The administration of dexmedetomidine to puppies younger than 16 weeks and kittens younger than 12 weeks has not been studied.

The safety of dexmedetomidine has not been established in males intended for breeding.

In cats, corneal opacities may occur during sedation. The eyes should be protected by a suitable eye lubricant.

4.5 Special precautions for use

Special precautions for use in animals

Treated animals should be kept warm and at a constant temperature, both during the procedure and recovery.

It is recommended that animals are fasted for 12 hours prior to Dexdomitor administration. Water may be given.

After treatment, the animal should not be given water or food before it is able to swallow.

The eyes should be protected by a suitable lubricant.

To be used with precaution in elderly animals.

Nervous, aggressive or excited animals should be given the possibility to calm down before initiation of treatment.

Frequent and regular monitoring of respiratory and cardiac function should be performed. Pulse oximetry may be useful but is not essential for adequate monitoring. Equipment for manual ventilation should be available in case of respiratory depression or apnoea when dexmedetomidine and ketamine are used sequentially to induce anaesthesia in cats. It is also advisable to have oxygen readily available, should hypoxaemia be detected or suspected.

Sick and debilitated dogs and cats should only be premedicated with dexmedetomidine before induction and maintenance of general anaesthesia based on a risk-benefit assessment.

Use of dexmedetomidine as a premedicant in dogs and cats significantly reduces the amount of induction drug required for induction of anaesthesia. Attention should be given during the administration of intravenous induction drugs to effect. Volatile anaesthetic requirements for maintenance anaesthesia are also reduced.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package leaflet or the label to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.

Avoid skin, eye or mucosal contact; the use of impermeable gloves is advisable. In case of skin or mucosal contact, wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes that are in direct contact with skin. In case of eye contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

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 physicians: Dexdomitor is an α_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. The specific α_2 -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize dexmedetomidine-induced effects.

People with known hypersensitivity to the active substance or any of the excipients should administer the veterinary medicinal product with caution.

4.6 Adverse reactions (frequency and seriousness)

By virtue of its α_2 -adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

In some dogs and cats, a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. Blood pressure will increase initially and then return to normal or below normal. Due to peripheral vasoconstriction and venous desaturation in the presence of normal arterial oxygenation, the mucous membranes may appear pale and/or with a blue tinge.

Vomiting may occur 5–10 minutes after injection. Some dogs and cats may also vomit at the time of recovery.

Muscle tremors may occur during sedation.

Corneal opacities may occur during sedation (see also section 4.5).

When dexmedetomidine and ketamine are used sequentially, with a 10 minute interval, cats may occasionally experience AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into dexmedetomidine-ketamine anaesthesia. Vomiting, hypothermia and nervousness have been reported after such use.

When dexmedetomidine and butorphanol are used concomitantly in dogs, bradypnoea, tachypnoea, an irregular respiratory pattern (20-30 sec apnoea followed by several rapid breaths), hypoxaemia, muscle twitch or tremor or paddling, excitation, hypersalivation, retching, vomiting, urination, skin erythema, a sudden arousal, or prolonged sedation may occur. Brady- and tachyarrhythmias have been reported. These may include profound sinus bradycardia, 1st and 2nd degree AV block, sinus arrest or pause, as well as atrial, supraventricular and ventricular premature complexes.

When dexmedetomidine is used as a premedicant in dogs, bradypnoea, tachypnoea and vomiting may occur. Brady- and tachyarrhythmias have been reported and include profound sinus bradycardia, 1st and 2nd degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3rd degree AV block may be observed in rare cases.

When dexmedetomidine is used as a premedicant in cats, vomiting, retching, pale mucous membranes, and low body temperature may occur. Intramuscular dosing at 40 mcg/kg (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1st degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2nd degree atrioventricular block, or escape beats/rhythms.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of dexmedetomidine has not been established during pregnancy and lactation in the target species. Therefore the use of the product during pregnancy and lactation is not recommended.

4.8 Interaction with other medicinal products and other forms of interaction

The use of other central nervous system depressants is expected to potentiate the effects of dexmedetomidine and therefore an appropriate dose adjustment should be made. Anticholinergics should be used with caution with dexmedetomidine.

Administration of atipamezole after dexmedetomidine rapidly reverses the effects and thus shortens the recovery period. Within 15 minutes dogs and cats are normally awake and standing.

Cats: After administration of 40 micrograms dexmedetomidine/kg bw intramuscularly concurrently with 5 mg ketamine/kg bw to cats, the maximum concentration of dexmedetomidine increased twofold but there was no effect on T_{max} . The mean half-life of elimination of dexmedetomidine increased to 1.6 h and the total exposure (AUC) increased by 50%.

A dose of 10 mg ketamine/ kg used concurrently with 40 micrograms dexmedetomidine/ kg may cause tachycardia.

For information on adverse reactions, see section 4.6. Adverse reactions.

For information on target animal safety in cases of overdosing, see section 4.10. Overdose.

4.9 Amounts to be administered and administration route

The product is intended for:

- Dogs: intravenous or intramuscular use
- Cats: intramuscular use

The product is not intended for repeat injections.

Dexdomitor, butorphanol and/or ketamine can be mixed in the same syringe as they have been shown to be pharmaceutically compatible.

Dosage: the following doses are recommended:

DOGS:

Dexmedetomidine doses are based on body surface area:

Intravenously: up to 375 micrograms/square metre body surface area

Intramuscularly: up to 500 micrograms/square metre body surface area

When administering in conjunction with butorphanol (0.1 mg/kg) for deep sedation and analgesia, the intramuscular dose of dexmedetomidine is 300 micrograms/square metre body surface area. The premedication dose of dexmedetomidine is 125–375 micrograms/square metre body surface area, administered 20 minutes prior to induction for procedures requiring anaesthesia. The dose should be adjusted to the type of surgery, length of procedure and patient temperament.

Concomitant use of dexmedetomidine and butorphanol produces sedative and analgesic effects beginning no later than 15 minutes. The peak sedative and analgesic effects are reached within 30 minutes after administration. Sedation lasts for at least 120 minutes post administration and analgesia lasts for at least 90 minutes. Spontaneous recovery occurs within 3 hours.

Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol and thiopental was reduced by 30% and 60% respectively. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect. In a clinical study, dexmedetomidine contributed to postoperative analgesia for 0.5–4 hours. However this duration is dependent on a number of variables and further analgesia should be administered in accordance with clinical judgement.

The corresponding doses based on body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

Dog weight (kg)	Dexmedetomidine 125 mcg/m ²		Dexmedetomidine 375 mcg/m ²		Dexmedetomidine 500 mcg/m ²	
	(mcg/kg)	(ml)	(mcg/kg)	(ml)	(mcg/kg)	(ml)
2-3	9.4	0.04	28.1	0.12	40	0.15
3-4	8.3	0.05	25	0.17	35	0.2
4-5	7.7	0.07	23	0.2	30	0.3
5-10	6.5	0.1	19.6	0.29	25	0.4
10-13	5.6	0.13	16.8	0.38	23	0.5
13-15	5.2	0.15	15.7	0.44	21	0.6
15-20	4.9	0.17	14.6	0.51	20	0.7
20-25	4.5	0.2	13.4	0.6	18	0.8
25-30	4.2	0.23	12.6	0.69	17	0.9
30-33	4	0.25	12	0.75	16	1.0
33-37	3.9	0.27	11.6	0.81	15	1.1
37-45	3.7	0.3	11	0.9	14.5	1.2
45-50	3.5	0.33	10.5	0.99	14	1.3
50-55	3.4	0.35	10.1	1.06	13.5	1.4
55-60	3.3	0.38	9.8	1.13	13	1.5
60-65	3.2	0.4	9.5	1.19	12.8	1.6
65-70	3.1	0.42	9.3	1.26	12.5	1.7
70-80	3	0.45	9	1.35	12.3	1.8
>80	2.9	0.47	8.7	1.42	12	1.9

For deep sedation and analgesia with butorphanol		
Dog weight (kg)	Dexmedetomidine 300 mcg/m ² intramuscularly	
	(mcg/kg)	(ml)
2-3	24	0.12
3-4	23	0.16
4-5	22.2	0.2
5-10	16.7	0.25
10-13	13	0.3
13-15	12.5	0.35
15-20	11.4	0.4
20-25	11.1	0.5
25-30	10	0.55
30-33	9.5	0.6
33-37	9.3	0.65
37-45	8.5	0.7
45-50	8.4	0.8
50-55	8.1	0.85

55-60	7.8	0.9
60-65	7.6	0.95
65-70	7.4	1
70-80	7.3	1.1
>80	7	1.2

CATS:

The dosage for cats is 40 micrograms dexmedetomidine hydrochloride/kg bw equal to a dose volume 0.08 ml Dexdomitor/kg bw when used for non-invasive, mildly to moderately painful procedures requiring restraint, sedation and analgesia.

When dexmedetomidine is used for premedication in cats, the same dose is used. Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol was reduced by 50%. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect.

Anaesthesia can be induced 10 minutes after premedication by intramuscular administration of a target dose of 5 mg ketamine/ kg bw or by intravenous administration of propofol to effect. Dosing for cats is presented in the following table.

Cat weight (kg)	Dexmedetomidine 40 mcg/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.1
2-3	40	0.2
3-4	40	0.3
4-6	40	0.4
6-7	40	0.5
7-8	40	0.6
8-10	40	0.7

The expected sedative and analgesic effects are reached within 15 minutes after administration and are maintained up to 60 minutes after administration. Sedation may be reversed with atipamezole. Atipamezole should not be administered prior to 30 minutes following ketamine administration.

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

Dogs: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate dose of atipamezole is 10 times the initial dose of dexmedetomidine (micrograms/ kg bw or micrograms/ square meter body surface area). The dose volume of atipamezole at the concentration of 5 mg/ml equals the dose volume of Dexdomitor that was given to the dog, regardless of route of administration of Dexdomitor.

Cats: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate antagonist is atipamezole, administered by intramuscular injection, at the following dose: 5 times the initial dose dexmedetomidine in micrograms/kg bw.

After concurrent exposure to a triple (3X) overdose of dexmedetomidine and 15 mg ketamine/ kg, atipamezole can be administered at the recommended dose level for reversal of effects induced by dexmedetomidine. At high serum concentrations of dexmedetomidine sedation is not increased although the level of analgesia does increase with further dose increases. The dose volume of atipamezole at the concentration of 5 mg/ml equals one-half the volume of Dexdomitor that was given to the cat.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: other hypnotics and sedatives, ATCvet code: QN05CM18.

5.1 Pharmacodynamic properties

Dexdomitor contains dexmedetomidine as the active substance, which produces sedation and analgesia in dogs and cats. The duration and depth of the sedation and analgesia are dose-dependent. At maximal effect, the animal is relaxed, recumbent and does not respond to external stimulus.

Dexmedetomidine is a potent and selective α_2 -adrenoceptor agonist that inhibits the release of noradrenaline from noradrenergic neurons. Sympathetic neurotransmission is prevented and the level of consciousness decreases. Reduced heart rate and temporary AV-block can be seen after administration of dexmedetomidine. Blood pressure decreases to normal or below normal levels after an initial increase. Respiration rate can occasionally decrease. Dexmedetomidine also induces a number of other α_2 -adrenoceptor mediated effects, which include piloerection, depression of motor and secretory functions of the gastrointestinal tract, diuresis and hyperglycaemia.

A slight decrease in temperature may be observed.

5.2 Pharmacokinetic particulars

As a lipophilic compound, dexmedetomidine is well absorbed after intramuscular administration. Dexmedetomidine is also rapidly distributed in the body and penetrates the blood-brain barrier readily. According to studies in rats, the maximum concentration in the central nervous system is several times that of the corresponding concentration in plasma. In the circulation, dexmedetomidine is largely bound to plasma proteins (>90%).

Dogs: After an intramuscular dose of 50 micrograms/kg a maximum concentration in plasma of about 12 ng/ml is reached after 0.6 hours. The bioavailability of dexmedetomidine is 60% and the apparent volume of distribution (Vd) is 0.9 l/kg. The elimination half-life ($t_{1/2}$) is 40-50 minutes.

Major biotransformations in the dog include hydroxylation, glucuronic acid conjugation and N-methylation in the liver. All known metabolites lack pharmacological activity. Metabolites are excreted mainly in the urine and to a lesser extent in the faeces. Dexmedetomidine has a high clearance and its elimination depends on the hepatic blood flow. A prolonged elimination half-life is therefore expected with overdoses or when dexmedetomidine is coadministered with other substances, which affect hepatic circulation.

Cats: The maximum plasma concentration is reached about 0.24 h after intramuscular administration. After a 40 micrograms/kg bw intramuscular dose the C_{max} is 17 ng/ml. The apparent volume of distribution (Vd) is 2.2 l/kg and the elimination half-life ($t_{1/2}$) is one hour.

Biotransformations in the cat occur by hydroxylation in the liver. Metabolites are excreted mainly in the urine (51% of the dose), and to a lesser extent in the faeces. As in dogs dexmedetomidine has a high clearance in cats and its elimination depends on the hepatic blood flow. A prolonged elimination half-life is therefore expected with overdoses or when dexmedetomidine is coadministered with other substances, which affect hepatic circulation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E 218)

Propyl parahydroxybenzoate (E 216)

6.2 Major incompatibilities

None known.

Dexdomitor is compatible with butorphanol and ketamine in the same syringe at least for two hours.

6.3 Shelf life

3 years

After withdrawal of the first dose, the product may be stored for 3 months at 25°C.

6.4. Special precautions for storage

Do not freeze.

6.5 Nature and composition of immediate packaging

Cardboard box with 1 glass (Type I) vial of 10 ml with a chlorobutyl or bromobutyl rubber stopper and aluminium cap.

Package size: 10 ml and 10 x 10 ml

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation

Orionintie 1

FI-02200 Espoo

Finland

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/02/033/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30/08/2002

Date of last renewal: 02/08/2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. STATEMENT OF THE MRLs**
- D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Orion Corporation Orion Pharma
Orionintie 1
FI-02200 Espoo
Finland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The Marketing Authorisation Holder must ensure that the system of pharmacovigilance, as described in Part 1 of the marketing authorisation application, is in place and functioning before and whilst the veterinary medicinal product is on the market.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.1 mg/ml solution for injection
dexmedetomidine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains:
0.1 mg dexmedetomidine hydrochloride equivalent to 0.08 mg dexmedetomidine.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

15 ml

5. TARGET SPECIES

Dogs and cats.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Dogs: intravenous or intramuscular use
Cats: intramuscular use
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP:

Shelf life after first opening: 3 months at 25°C.

11. SPECIAL STORAGE CONDITIONS

Do not freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/02/033/003

17. MANUFACTURER'S BATCH NUMBER

Batch:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS/
MULTI PACKAGE**

VIAL/MULTI PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.1 mg/ml solution for injection
dexmedetomidine hydrochloride

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

0.1 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

15 ml
10 x 15 ml

4. ROUTE(S) OF ADMINISTRATION

Dogs: IM, IV
Cats: IM

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Batch:

7. EXPIRY DATE

EXP:

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.5 mg/ml solution for injection
dexmedetomidine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains:
0.5 mg dexmedetomidine hydrochloride equivalent to 0.42 mg dexmedetomidine.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

10 ml

5. TARGET SPECIES

Dogs and cats

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Dogs: intravenous or intramuscular use
Cats: intramuscular use
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP:

Shelf life after first opening: 3 months at 25°C.

11. SPECIAL STORAGE CONDITIONS

Do not freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/02/033/001

17. MANUFACTURER'S BATCH NUMBER

Batch:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS/
MULTI PACKAGE**

VIAL/MULTI PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.5 mg/ml solution for injection
dexmedetomidine hydrochloride

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

0.5 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

10 ml
10 x 10 ml

4. ROUTE(S) OF ADMINISTRATION

Dogs: IV, IM
Cats: IM

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Batch:

7. EXPIRY DATE

EXP:

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET
DEXDOMITOR 0.1 mg/ml solution for injection

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Orion Corporation Orion Pharma
Orionintie 1
FI-02200 Espoo
Finland

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.1 mg/ml solution for injection
dexmedetomidine hydrochloride

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Active substance: One ml contains 0.1 mg dexmedetomidine hydrochloride equivalent to 0.08 mg dexmedetomidine.

List of excipients: Methyl parahydroxybenzoate (E 218) 2.0 mg/ml
Propyl parahydroxybenzoate (E 216) 0.2 mg/ml

4. INDICATION(S)

Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.

Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.

Premedication in dogs and cats before induction and maintenance of general anaesthesia.

5. CONTRAINDICATIONS

Do not use in animals with cardiovascular disorders.

Do not use in animals with severe systemic disease or in animals that are moribund.

Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

By virtue of its α_2 -adrenergic activity, dexmedetomidine causes decreases in heart rate and body temperature.

In some dogs and cats a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. Blood pressure will increase initially and then return to normal or below normal.

Due to peripheral vasoconstriction and venous desaturation in the presence of normal arterial oxygenation, the mucous membranes may appear pale and/or with a blue tinge.

Vomiting may occur 5–10 minutes after injection.
Some dogs and cats may also vomit at the time of recovery.
Muscle tremors may occur during sedation.

When dexmedetomidine and ketamine are used sequentially, with a 10 minute interval, cats may occasionally experience AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into dexmedetomidine-ketamine anaesthesia. Vomiting, hypothermia and nervousness have been reported after such use.

When dexmedetomidine and butorphanol are used concomitantly in dogs, bradypnoea, tachypnoea, an irregular respiratory pattern (20-30 sec apnoea followed by several rapid breaths), hypoxaemia, muscle twitch or tremor or paddling, excitation, hypersalivation, retching, vomiting, urination, skin erythema, a sudden arousal, or prolonged sedation may occur. Brady- and tachyarrhythmias have been reported. These may include profound sinus bradycardia, 1st and 2nd degree AV block, sinus arrest or pause, as well as atrial, supraventricular and ventricular premature complexes.

When dexmedetomidine is used as a premedicant in dogs, bradypnoea, tachypnoea and vomiting may occur. Brady- and tachyarrhythmias have been reported and include profound sinus bradycardia, 1st and 2nd degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3rd degree AV block may be observed in rare cases.

When dexmedetomidine is used as a premedicant in cats, vomiting, retching, pale mucous membranes, and low body temperature may occur. Intramuscular dosing at 40 micrograms/kg (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1st degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2nd degree atrioventricular block, or escape beats/rhythms.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs and cats

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

The product is intended for:

- Dogs: intravenous or intramuscular use
- Cats: intramuscular use

The product is not intended for repeat injections.

Dexdomitor, butorphanol and/or ketamine can be mixed in the same syringe as they have been shown to be pharmacologically compatible.

The following doses are recommended:

DOGS:

Dexdomitor doses are based on body surface area:

Intravenously: up to 375 micrograms/square metre body surface area

Intramuscularly: up to 500 micrograms/square metre body surface area

When administering in conjunction with butorphanol (0.1 mg/kg) for deep sedation and analgesia, the intramuscular dose of dexmedetomidine is 300 micrograms/square metre body surface area. The premedication dose of dexmedetomidine is 125–375 micrograms/square metre body surface area, administered 20 minutes prior to induction for procedures requiring anaesthesia. The dose should be adjusted to the type of surgery, length of procedure and patient temperament.

Concomitant use of dexmedetomidine and butorphanol produces sedative and analgesic effects beginning no later than 15 minutes after administration. The peak sedative and analgesic effects are reached within 30 minutes after administration. Sedation lasts for at least 120 minutes post administration and analgesia lasts for at least 90 minutes. Spontaneous recovery occurs within 3 hours.

Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol and thiopental was reduced by 30% and 60% respectively. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect. In a clinical study, dexmedetomidine contributed to postoperative analgesia for 0.5–4 hours. However this duration is dependent on a number of variables and further analgesia should be administered in accordance with clinical judgement.

The corresponding doses based on body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

Dog weight (kg)	Dexmedetomidine 125 micrograms/m ²		Dexmedetomidine 375 micrograms/m ²		Dexmedetomidine 500 micrograms/m ²	
	(mcg/kg)	(ml)	(mcg/kg)	(ml)	(mcg/kg)	(ml)
2-3	9.4	0.2	28.1	0.6	40	0.75
3.1-4	8.3	0.25	25	0.85	35	1
4.1-5	7.7	0.35	23	1	30	1.5
5.1-10	6.5	0.5	19.6	1.45	25	2
10.1-13	5.6	0.65	16.8	1.9		
13.1-15	5.2	0.75				
15.1-20	4.9	0.85				

For deep sedation and analgesia with butorphanol		
Dog weight (kg)	Dexmedetomidine 300 micrograms/m ² intramuscularly	
	(mcg/kg)	(ml)
2-3	24	0.6
3.1-4	23	0.8
4.1-5	22.2	1
5.1-10	16.7	1.25
10.1-13	13	1.5
13.1-15	12.5	1.75

For higher weight ranges, use DEXDOMITOR 0.5 mg/ml and its dosing tables.

CATS:

The dosage for cats is 40 micrograms dexmedetomidine hydrochloride/ kg bw equal to a dose volume 0.4 ml Dexdomitor/ kg bw when used for non-invasive, mildly to moderately painful procedures requiring restraint, sedation and analgesia.

When dexmedetomidine is used for premedication in cats, the same dose is used. Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol was reduced by 50%. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect.

Anaesthesia can be induced 10 minutes after premedication by intramuscular administration of a target dose of 5 mg ketamine/kg bw or by intravenous administration of propofol to effect. Dosing for cats is presented in the following table.

Cat weight (kg)	Dexmedetomidine 40 micrograms/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.5
2.1-3	40	1

For higher weight ranges, use DEXDOMITOR 0.5 mg/ml and its dosing table.

The expected sedative and analgesic effects are reached within 15 minutes after administration and are maintained up to 60 minutes after administration. Sedation may be reversed with atipamezole. Atipamezole should not be administered prior to 30 minutes following ketamine administration.

9. ADVICE ON CORRECT ADMINISTRATION

It is recommended that animals are fasted for 12 hours prior to administration. Water may be given.

After treatment, the animal should not be given water or food before it is able to swallow.

10. WITHDRAWAL PERIOD(S)

Not applicable

11. SPECIAL STORAGE PRECAUTIONS

Do not freeze. After withdrawal of the first dose, the product may be stored for 3 months at 25°C. Keep out of the sight and reach of children. Do not use this medicinal product after the expiry date which is stated on the label and carton after EXP.

12. SPECIAL WARNINGS(S)

Treated animals should be kept warm and at a constant temperature, both during the procedure and recovery.

Nervous, aggressive or excited animals should be given the possibility to calm down before initiation of treatment.

The safety of dexmedetomidine has not been established during pregnancy and lactation in the target species. Therefore the use of the product during pregnancy and lactation is not recommended.

The safety of dexmedetomidine has not been established in males intended for breeding. To be used with precaution in elderly animals.

The administration of dexmedetomidine to puppies younger than 16 weeks and kittens younger than 12 weeks has not been studied.

In cats, corneal opacities may occur during sedation. The eyes should be protected by a suitable eye lubricant.

The use of other central nervous system depressants is expected to potentiate the effects of dexmedetomidine and therefore an appropriate dose adjustment should be made. Use of dexmedetomidine as a premedicant in dogs significantly reduces the amount of induction drug required for induction of anaesthesia. Attention should be given during the administration of intravenous induction drugs to effect. Volatile anaesthetic requirements for maintenance anaesthesia are also reduced.

Anticholinergics should be used with caution with dexmedetomidine.

Cats: After administration of 40 micrograms dexmedetomidine/ kg bw intramuscularly concurrently with 5 mg ketamine /kg bw to cats, the maximum concentration of dexmedetomidine increased twofold but there was no effect on T_{max} . The mean half-life of elimination of dexmedetomidine increased to 1.6 h and the total exposure (AUC) increased by 50%.

A dose of 10 mg ketamine/kg used concurrently with 40 micrograms dexmedetomidine/ kg may cause tachycardia.

Administration of atipamezole after dexmedetomidine rapidly reverses the effects and thus shortens the recovery period. Within 15 minutes dogs and cats are normally awake and standing

For information on adverse reactions, see section: Adverse reactions.

Frequent and regular monitoring of respiratory and cardiac function should be performed. Pulse oximetry may be useful but is not essential for adequate monitoring. Equipment for manual ventilation should be available in case of respiratory depression or apnoea when dexmedetomidine and ketamine are used sequentially to induce anaesthesia in cats. It is also advisable to have oxygen readily available, should hypoxaemia be detected or suspected.

Sick and debilitated dogs and cats should only be premedicated with dexmedetomidine before induction and maintenance of general anaesthesia based on a risk-benefit assessment.

In cases of overdosing the following recommendations should be followed:

DOGS: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate dose of atipamezole is 10 times the initial dose of dexmedetomidine (micrograms/ kg bw or micrograms/ square meter body surface area). The dose volume of atipamezole at the concentration of 5 mg/ml is one fifth (1/5) of the dose volume of Dexdomitor 0.1 mg/ml that was given to the dog, regardless of route of administration of Dexdomitor.

CATS: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate antagonist is atipamezole, administered by intramuscular injection, at the following dose: 5 times the initial dose dexmedetomidine in micrograms/kg bw. After concurrent exposure to a triple (3X) overdose of dexmedetomidine and 15 mg ketamine/ kg, atipamezole can be administered at the recommended dose level for reversal of effects induced by dexmedetomidine.

At high serum concentration of dexmedetomidine sedation is not increased although the level of analgesia does increase with further dose increases.

The dose volume of atipamezole at the concentration of 5 mg/ml equals one-tenth (1/10) the volume of Dexdomitor 0.1 mg/ml that was given to the cat.

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.

Avoid skin, eye or mucosal contact; the use of impermeable gloves is advisable. In case of skin or mucosal contact, wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes that are in direct contact with skin. In case of eye contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

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 physicians: Dexdomitor is an α_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. The specific α_2 -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize dexmedetomidine-induced effects.

Persons with known hypersensitivity to the active substance or any of the excipients should administer the product with caution.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

15. OTHER INFORMATION

Package size: 15 ml, 10 x 15 ml.
Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

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PACKAGE LEAFLET
DEXDOMITOR 0.5 mg/ml solution for injection

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Orion Corporation Orion Pharma
Orionintie 1
FI-02200 Espoo
Finland

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

DEXDOMITOR 0.5 mg/ml solution for injection
dexmedetomidine hydrochloride

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Active substance: One ml contains 0.5 mg dexmedetomidine hydrochloride equivalent to 0.42 mg dexmedetomidine.

List of excipients: Methyl parahydroxybenzoate (E 218) 1.6 mg/ml
Propyl parahydroxybenzoate (E 216) 0.2 mg/ml

4. INDICATION(S)

Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.

Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.

Premedication in dogs and cats before induction and maintenance of general anaesthesia.

5. CONTRAINDICATIONS

Do not use in animals with cardiovascular disorders.

Do not use in animals with severe systemic disease or in animals that are moribund.

Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

By virtue of its α_2 -adrenergic activity, dexmedetomidine causes decreases in heart rate and body temperature.

In some dogs and cats a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. Blood pressure will increase initially and then return to normal or below normal.

Due to peripheral vasoconstriction and venous desaturation in the presence of normal arterial oxygenation, the mucous membranes may appear pale and/or with a blue tinge.

Vomiting may occur 5–10 minutes after injection.
Some dogs and cats may also vomit at the time of recovery.
Muscle tremors may occur during sedation.

When dexmedetomidine and ketamine are used sequentially, with a 10 minute interval, cats may occasionally experience AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into dexmedetomidine-ketamine anaesthesia. Vomiting, hypothermia and nervousness have been reported after such use.

When dexmedetomidine and butorphanol are used concomitantly in dogs, bradypnoea, tachypnoea, an irregular respiratory pattern (20-30 sec apnoea followed by several rapid breaths), hypoxaemia, muscle twitch or tremor or paddling, excitation, hypersalivation, retching, vomiting, urination, skin erythema, a sudden arousal, or prolonged sedation may occur. Brady- and tachyarrhythmias have been reported. These may include profound sinus bradycardia, 1st and 2nd degree AV block, sinus arrest or pause, as well as atrial, supraventricular and ventricular premature complexes.

When dexmedetomidine is used as a premedicant in dogs, bradypnoea, tachypnoea and vomiting may occur. Brady- and tachyarrhythmias have been reported and include profound sinus bradycardia, 1st and 2nd degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3rd degree AV block may be observed in rare cases.

When dexmedetomidine is used as a premedicant in cats, vomiting, retching, pale mucous membranes, and low body temperature may occur. Intramuscular dosing at 40 mcg/kg (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1st degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2nd degree atrioventricular block, or escape beats/rhythms.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs and cats

8. DOSAGE FOR EACH SPECIES, ROUTES AND METHOD OF ADMINISTRATION

The product is intended for:

- Dogs: intravenous or intramuscular use
- Cats: intramuscular use

The product is not intended for repeat injections.

Dexdomitor, butorphanol and/or ketamine can be mixed in the same syringe as they have been shown to be pharmacologically compatible.

The following doses are recommended:

DOGS:

Dexdomitor doses are based on body surface area:

Intravenously: up to 375 micrograms/square metre body surface area

Intramuscularly: up to 500 micrograms/square metre body surface area

When administering in conjunction with butorphanol (0.1 mg/kg) for deep sedation and analgesia, the intramuscular dose of dexmedetomidine is 300 micrograms/square metre body surface area. The premedication dose of dexmedetomidine is 125–375 micrograms/square metre body surface area, administered 20 minutes prior to induction for procedures requiring anaesthesia. The dose should be adjusted to the type of surgery, length of procedure and patient temperament.

Concomitant use of dexmedetomidine and butorphanol produces sedative and analgesic effects beginning no later than 15 minutes after administration. The peak sedative and analgesic effects are reached within 30 minutes after administration. Sedation lasts for at least 120 minutes post administration and analgesia lasts for at least 90 minutes. Spontaneous recovery occurs within 3 hours.

Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol and thiopental was reduced by 30% and 60% respectively. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect. In a clinical study, dexmedetomidine contributed to postoperative analgesia for 0.5–4 hours. However this duration is dependent on a number of variables and further analgesia should be administered in accordance with clinical judgement.

The corresponding doses based on body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

Dog weight (kg)	Dexmedetomidine 125 mcg/m ²		Dexmedetomidine 375 mcg/m ²		Dexmedetomidine 500 mcg/m ²	
	(mcg/kg)	(ml)	(mcg/kg)	(ml)	(mcg/kg)	(ml)
2-3	9.4	0.04	28.1	0.12	40	0.15
3-4	8.3	0.05	25	0.17	35	0.2
4-5	7.7	0.07	23	0.2	30	0.3
5-10	6.5	0.1	19.6	0.29	25	0.4
10-13	5.6	0.13	16.8	0.38	23	0.5
13-15	5.2	0.15	15.7	0.44	21	0.6
15-20	4.9	0.17	14.6	0.51	20	0.7
20-25	4.5	0.2	13.4	0.6	18	0.8
25-30	4.2	0.23	12.6	0.69	17	0.9
30-33	4	0.25	12	0.75	16	1.0
33-37	3.9	0.27	11.6	0.81	15	1.1
37-45	3.7	0.3	11	0.9	14.5	1.2
45-50	3.5	0.33	10.5	0.99	14	1.3
50-55	3.4	0.35	10.1	1.06	13.5	1.4
55-60	3.3	0.38	9.8	1.13	13	1.5
60-65	3.2	0.4	9.5	1.19	12.8	1.6
65-70	3.1	0.42	9.3	1.26	12.5	1.7
70-80	3	0.45	9	1.35	12.3	1.8
>80	2.9	0.47	8.7	1.42	12	1.9

For deep sedation and analgesia with butorphanol		
Dog weight (kg)	Dexmedetomidine 300 mcg/m² intramuscularly	
	(mcg/kg)	(ml)
2-3	24	0.12
3-4	23	0.16
4-5	22.2	0.2
5-10	16.7	0.25
10-13	13	0.3
13-15	12.5	0.35
15-20	11.4	0.4
20-25	11.1	0.5
25-30	10	0.55
30-33	9.5	0.6
33-37	9.3	0.65
37-45	8.5	0.7
45-50	8.4	0.8
50-55	8.1	0.85
55-60	7.8	0.9
60-65	7.6	0.95
65-70	7.4	1
70-80	7.3	1.1
>80	7	1.2

CATS:

The dosage for cats is 40 micrograms dexmedetomidine hydrochloride/ kg bw equal to a dose volume 0.08 ml Dexdomitor/ kg bw when used for non-invasive, mildly to moderately painful procedures requiring restraint, sedation and analgesia.

When dexmedetomidine is used for premedication in cats, the same dose is used. Premedication with dexmedetomidine will significantly reduce the dosage of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol was reduced by 50%. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect.

Anaesthesia can be induced 10 minutes after premedication by intramuscular administration of a target dose of 5 mg ketamine/kg bw or by intravenous administration of propofol to effect. Dosing for cats is presented in the following table.

Cat weight (kg)	Dexmedetomidine 40 mcg/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.1
2-3	40	0.2
3-4	40	0.3
4-6	40	0.4
6-7	40	0.5
7-8	40	0.6
8-10	40	0.7

The expected sedative and analgesic effects are reached within 15 minutes after administration and are maintained up to 60 minutes after administration. Sedation may be reversed with atipamezole. Atipamezole should not be administered prior to 30 minutes following ketamine administration.

9. ADVICE ON CORRECT ADMINISTRATION

It is recommended that animals are fasted for 12 hours prior to administration. Water may be given.

After treatment, the animal should not be given water or food before it is able to swallow.

10. WITHDRAWAL PERIOD(S)

Not applicable

11. SPECIAL STORAGE PRECAUTIONS

Do not freeze. After withdrawal of the first dose, the product may be stored for 3 months at 25°C. Keep out of the sight and reach of children. Do not use this medicinal product after the expiry date which is stated on the label and carton after EXP.

12. SPECIAL WARNING(S)

Treated animals should be kept warm and at a constant temperature, both during the procedure and recovery.

Nervous, aggressive or excited animals should be given the possibility to calm down before initiation of treatment.

The safety of dexmedetomidine has not been established during pregnancy and lactation in the target species. Therefore the use of the product during pregnancy and lactation is not recommended.

The safety of dexmedetomidine has not been established in males intended for breeding.
To be used with precaution in elderly animals.

The administration of dexmedetomidine to puppies younger than 16 weeks and kittens younger than 12 weeks has not been studied.

In cats, corneal opacities may occur during sedation. The eyes should be protected by a suitable eye lubricant.

The use of other central nervous system depressants is expected to potentiate the effects of dexmedetomidine and therefore an appropriate dose adjustment should be made. Use of dexmedetomidine as a premedicant in dogs significantly reduces the amount of induction drug required for induction of anaesthesia. Attention should be given during the administration of intravenous induction drugs to effect. Volatile anaesthetic requirements for maintenance anaesthesia are also reduced.

Anticholinergics should be used with caution with dexmedetomidine.

Cats: After administration of 40 micrograms dexmedetomidine/ kg bw intramuscularly concurrently with 5 mg ketamine /kg bw to cats, the maximum concentration of dexmedetomidine increased twofold but there was no effect on T_{max} . The mean half-life of elimination of dexmedetomidine increased to 1.6 h and the total exposure (AUC) increased by 50%.

A dose of 10 mg ketamine/kg used concurrently with 40 micrograms dexmedetomidine/ kg may cause tachycardia.

Administration of atipamezole after dexmedetomidine rapidly reverses the effects and thus shortens the recovery period. Within 15 minutes dogs and cats are normally awake and standing.

For information on adverse reactions, see section: Adverse reactions.

Frequent and regular monitoring of respiratory and cardiac function should be performed. Pulse oximetry may be useful but is not essential for adequate monitoring.

Equipment for manual ventilation should be available in case of respiratory depression or apnoea when dexmedetomidine and ketamine are used sequentially to induce anaesthesia in cats. It is also advisable to have oxygen readily available, should hypoxaemia be detected or suspected.

Sick and debilitated dogs and cats should only be premedicated with dexmedetomidine before induction and maintenance of general anaesthesia based on a risk-benefit assessment.

In cases of overdosing the following recommendations should be followed:

DOGS: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate dose of atipamezole is 10 times the initial dose of dexmedetomidine (micrograms/ kg bw or micrograms/ square meter body surface area). The dose volume of atipamezole at the concentration of 5 mg/ml equals the dose volume of Dexdomitor that was given to the dog, regardless of route of administration of Dexdomitor.

CATS: In cases of overdosage, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate antagonist is atipamezole, administered by intramuscular injection, at the following dose: 5 times the initial dose dexmedetomidine in micrograms/kg bw. After concurrent exposure to a triple (3X) overdose of dexmedetomidine and 15 mg ketamine/ kg, atipamezole can be administered at the recommended dose level for reversal of effects induced by dexmedetomidine.

At high serum concentration of dexmedetomidine sedation is not increased although the level of analgesia does increase with further dose increases.

The dose volume of atipamezole at the concentration of 5mg/ml equals one-half the volume of Dexdomitor that was given to the cat.

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician but **DO NOT DRIVE** as sedation and changes in blood pressure may occur.

Avoid skin, eye or mucosal contact; the use of impermeable gloves is advisable. In case of skin or mucosal contact, wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes that are in direct contact with skin. In case of eye contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

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 physicians: Dexdomitor is an α_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. The specific α_2 -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize dexmedetomidine-induced effects.

Persons with known hypersensitivity to the active substance or any of the excipients should administer the product with caution.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

15. OTHER INFORMATION

Package size: 10 ml, 10 x 10 ml.
Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

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