ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sileo 0.1 mg/ml oromucosal gel for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the oromucosal gel contains:

Active substance:
Dexmedetomidine hydrochloride 0.1 mg
(equivalent to 0.09 mg dexmedetomidine).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oromucosal gel.
Translucent, green gel.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Alleviation of acute anxiety and fear associated with noise in dogs.

4.3 Contraindications

Do not use in dogs with severe cardiovascular disorders.
Do not use in dogs with severe systemic disease (graded as ASA III-IV) e.g. end stage renal or liver failure.
Do not use in known cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs obviously sedated from previous dosing.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

If the oromucosal gel is swallowed it will become ineffective. Therefore feeding the dog or giving it treats within 15 minutes after administration of the gel should be avoided. In case the gel is swallowed the dog can be given another dose if necessary 2 hours after the previous dose.

In extremely nervous, excited or agitated animals, the levels of endogenous catecholamines are often high. The pharmacological response elicited by alpha-2 agonists (e.g. dexmedetomidine) in such animals may be reduced.

The safety of administering dexmedetomidine to puppies younger than 16 weeks and dogs over 17 years of age has not been studied.

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

In case of accidental ingestion or prolonged mucosal contact, seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive as sedation and changes in blood pressure may occur.

Avoid skin, eye or mucosal contact. Wear impermeable disposable gloves when handling the veterinary medicinal product.

In case of skin contact wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes. In case of eye or oromucosal contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

People with known hypersensitivity to dexmedetomidine or any of the excipients should avoid contact with the veterinary medicinal product.

Pregnant women should avoid contact with the product. Uterine contractions and decreased foetal blood pressure may occur after systemic exposure to dexmedetomidine.

Advice to the physician:
Dexmedetomidine, the active ingredient of Sileo is an alpha-2 adrenoceptor 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. Since effects are dose dependent they are more pronounced in small children than adults. Respiratory and haemodynamic symptoms should be treated symptomatically. The specific alpha-2 adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans but only experimentally to antagonize dexmedetomidine-induced effects.

4.6 Adverse reactions (frequency and seriousness)

Due to peripheral vasoconstriction, transient paleness of mucous membranes at the application site was commonly observed. Sedation, emesis and urinary incontinence were commonly observed in clinical trials.

Anxiety, periorbital oedema, drowsiness and signs of gastroenteritis were uncommonly observed in clinical trials.
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 this veterinary medicinal product has not been established during pregnancy and lactation in the target species.

Pregnancy and lactation
The use is not recommended during pregnancy and lactation.

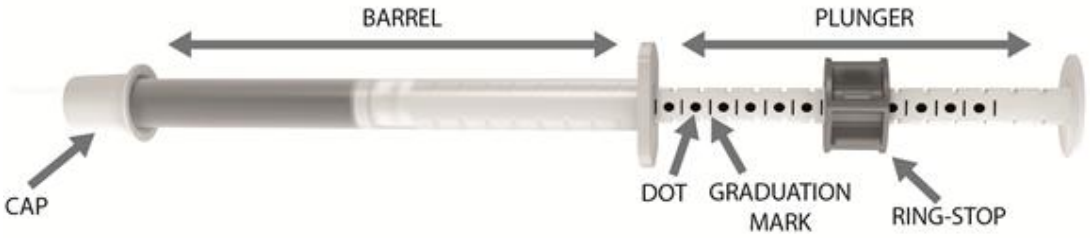
4.8 Interaction with other medicinal products and other forms of interaction

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.

4.9 Amounts to be administered and administration route

Oromucosal use.

The product should be administered onto the oral mucosa between dog's cheek and gum at a dose of 125 micrograms/m^2. The Sileo oral syringe is capable of delivering the product in 0.25 ml increments. Each increment is shown as one dot on the plunger. The dosing table provides the number of dots to be administered corresponding to the dog's bodyweight.



The following dosing table provides the dose volume (in dots) to be administered for the corresponding bodyweight. If the dose for the dog is more than 6 dots (1.5 ml), half of the dose should be administered to the oral mucosa on one side of the dog's mouth and the other half of the dose onto the other side. Do not exceed the recommended dose.

Bodyweight of dog (kg)	Number of dots
2.0–5.5	1 ●
5.6–12	2 ●●
12.1–20	3 ●●●
20.1–29	4 ●●●●
29.1–39	5 ●●●●●
39.1–50	6 ●●●●●●
50.1–62.5	7 ●●●●●●●
62.6–75.5	8 ●●●●●●●●
75.6–89	9 ●●●●●●●●●
89.1–100	10 ●●●●●●●●●●

The first dose should be given as soon as the dog shows the first signs of anxiety, or when the owner detects a typical stimulus (e.g. sound of fireworks or thunder) for eliciting anxiety or fear in the respective dog. Typical signs of anxiety and fear are panting, trembling, pacing (frequent change of place, running around, restlessness), seeking people (clinging, hiding behind, pawing, following), hiding (under furniture, in dark rooms), trying to escape, freezing (absence of movements), refusing to eat food or treats, inappropriate urination, inappropriate defecation, salivation, etc.

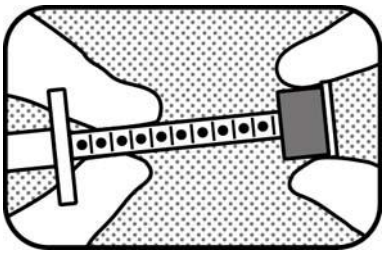
If the fear eliciting event continues and the dog shows signs of anxiety and fear again, re-dosing can be done when 2 hours have passed from the previous dose. The product can be dosed up to 5 times during each event.

<u>Instructions for dosing the gel:</u>

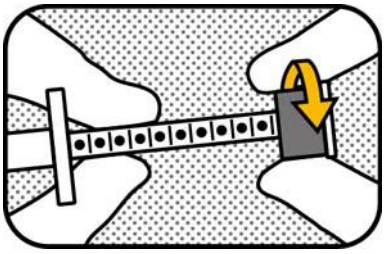
Dosing should be performed by an adult.

New oral syringe set up before first dosing:

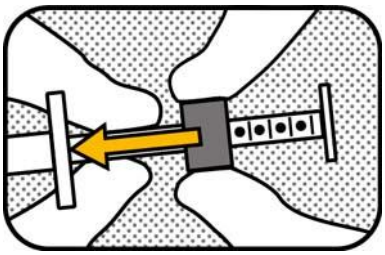
1. WEAR GLOVES
Wear impermeable disposable gloves when handling the veterinary medicinal product and handling the oral syringe.



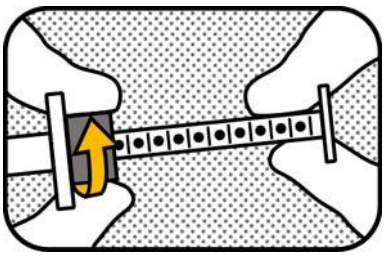
2. HOLD PLUNGER
Hold the oral syringe so that you can see the dot markings on the oral syringe plunger. Hold the plunger with your left hand.



3. UNLOCK
Hold the plunger with your left hand and unlock the green ring-stop by turning it towards you until it is able to slide freely.

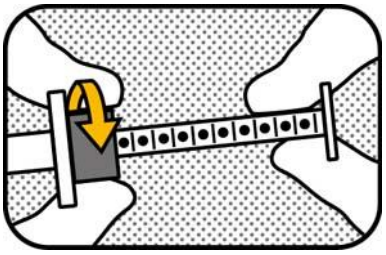


4. MOVE RING
Move the ring-stop to the opposite end of the plunger.

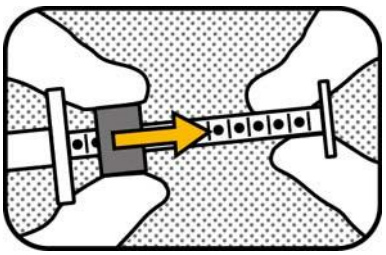


5. LOCK
Hold the plunger with your right hand and lock the ring-stop by turning it away from you.

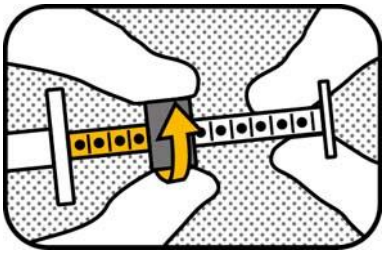
Dose selection and dosing:



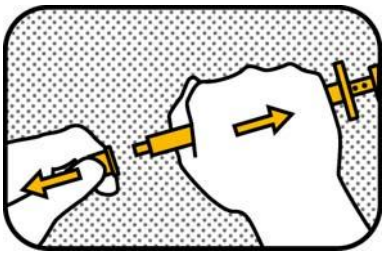
6. UNLOCK
Hold the plunger with your right hand and unlock the ring-stop by turning it towards you. **Do not pull the plunger!**



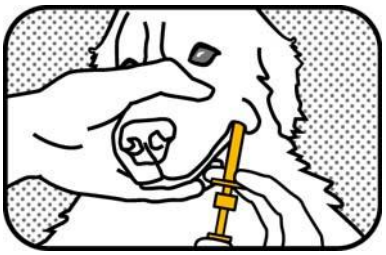
7. MOVE RING
Move the ring-stop towards the other end of the plunger for choosing the correct dose based on your veterinarian's prescription.



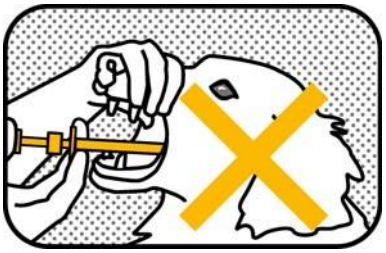
8. SET DOSE AND LOCK
Position the ring-stop so that the side nearest the barrel is in line with the graduation mark (black line), and the required number of dots shows between the ring-stop and the barrel. Lock the ring-stop by turning it away from you. **Before dosing make sure that the ring-stop is locked.**



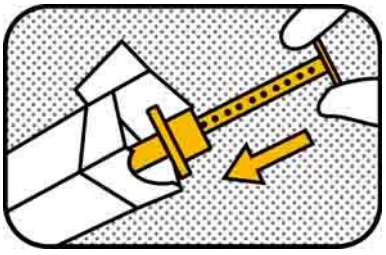
9. PULL CAP (TIGHT)
Pull the cap strongly while holding the barrel. **Note** the cap is very tight (pull, do not twist). Save the cap for replacement.



10. DOSE INTO CHEEK
Place the oral syringe tip between the dog's cheek and gum and press the plunger until the ring-stop causes the plunger to stop.
IMPORTANT: The gel should not be swallowed. If the gel is swallowed, it may not be effective.



NOT SWALLOWED



11. BACK TO PACKAGE
Recap the oral syringe and return it to the outer package as the product is sensitive to light. Make sure that the carton is closed properly. Keep the package out of sight and reach of children at all times. Remove and discard gloves.

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

Signs of sedation may occur when the dose is exceeded. The level and duration of sedation is dose dependent. If sedation occurs, the dog should be kept warm.

Reduced heart rate may be seen after administration of higher than recommended doses of Sileo gel. Blood pressure decreases slightly below normal levels. Respiration rate can occasionally decrease.

Higher than recommended doses of Sileo gel may also induce a number of other alpha-2 adrenoceptor mediated effects, which include mydriasis, depression of motor and secretory functions of the gastrointestinal tract, temporary AV-blocks, diuresis and hyperglycaemia. A slight decrease in body temperature may be observed.

The effects of dexmedetomidine can be eliminated using a specific antidote, atipamezole (alpha-2 adrenoceptor antagonist). In case of overdose, the appropriate dose of atipamezole calculated in micrograms is 3 times (3X) the dose of administered dexmedetomidine hydrochloride in Sileo gel. Atipamezole (at the concentration of 5 mg/ml) dose in millilitres is one sixteenth ($1/16^{th}$) of the dose volume of Sileo gel.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: psycholeptics, hypnotics and sedatives.
ATCvet code**:** QN05CM18.

5.1 Pharmacodynamic properties

Sileo contains dexmedetomidine (as the hydrochloride salt) as the active substance. Dexmedetomidine is a potent and selective alpha-2 adrenoceptor agonist that inhibits the release of noradrenaline (NA) from noradrenergic neurons, blocks the startle reflex and thus counteracts arousal.

Dexmedetomidine as an alpha-2 adrenoceptor agonist alters the levels of NA, serotonin (5-HT) and dopamine (DA) in the hippocampus and frontal cortex, indicating that such compounds affect also the regions of the brain involved in creating and maintaining complex anxieties. In rodents alpha-2 adrenoceptor agonists reduce synthesis of NA, DA, 5-HT and the 5-HT precursor, 5-HTP (5-hydroxytryptophan), in the frontal cortex, hippocampus, striatum and hypothalamus and as a result decreases motor behaviour and signalling associated with distress.

In summary, dexmedetomidine, by decreasing central noradrenergic and serotonergic neurotransmission, is effective in alleviating canine acute anxiety and fear associated with noise. In addition to anxiolytic effect, dexmedetomidine has other well-known dose dependent pharmacological effects such as lowering of heart rate and rectal temperature, and peripheral vasoconstriction. These and other effects are described in more detail in section 4.10 on overdose.

5.2 Pharmacokinetic particulars

Oral bioavailability of dexmedetomidine is poor due to extensive first-pass metabolism. No measurable concentrations were found after gastro-intestinal gavage of dexmedetomidine to dogs. When administered via the oral mucosa, enhanced bioavailability is observed as a result of absorption in the oral cavity and the avoidance of first-pass metabolism in the liver.

The maximum concentration of dexmedetomidine occurs at about 0.6 hours after intramuscular or oromucosal administration. In a pharmacokinetic study in dogs the oromucosal mean bioavailability of dexmedetomidine was 28%. The apparent volume of distribution of dexmedetomidine in dogs is 0.9 l/kg. In the circulation, dexmedetomidine is largely bound to plasma proteins (93%). When studied in rats, the distribution of dexmedetomidine into rat tissues was rapid and wide with concentrations higher than in plasma for many tissues. Its levels in the brain were from 3-fold to 6-fold higher than the levels in plasma.

Dexmedetomidine is eliminated by biotransformation mainly in the liver, with a half-life in dogs ranging from 0.5 to 3 hours after oromucosal administration. Metabolism accounts for more than 98% of the elimination. Known metabolites show no or negligible activity. The major metabolic routes in dogs are hydroxylation of a methyl substituent and further oxidation to a carboxylic acid or O-glucuronidation of the hydroxylated product. N-methylation, N-glucuronidation and oxidation in the imidazole ring have also been observed. Metabolites are excreted mainly in the urine with a minor fraction found in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water, purified
Propylene glycol
Hydroxypropylcellulose
Sodium lauryl sulfate
Brilliant blue (E133)
Tartrazine (E102)
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging (removal of the cap): 4 weeks.

6.4. Special precautions for storage

Store the oral syringe in the carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Pre-filled 3 ml HDPE oral syringes with graduations from 0.25 ml (1 dot) to 3 ml (12 dots). The oral syringe is fitted with a plunger, dosing ring and end cap (for sealing it).

Each oral syringe is packed in an individual child-resistant carton.
Pack sizes: single pack of 1 oral syringe and multipacks of 3 (3 packs of one), 5 (5 packs of one), 10 (10 packs of one) and 20 (20 packs of one).
Multipacks of 5, 10 and 20 oral syringes are intended to be supplied only to veterinarians.

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
Tel.: +358 10 4261

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/181/001–005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/06/2015
Date of last renewal: 24/04/2020

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Orion Corporation
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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON (1 pre-filled syringe)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sileo 0.1 mg/ml oromucosal gel for dogs
dexmedetomidine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml: Dexmedetomidine hydrochloride 0.1 mg

3. PHARMACEUTICAL FORM

Oromucosal gel

4. PACKAGE SIZE

1 x 3 ml oral syringe

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For oromucosal use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {month/year}
Once opened use within 4 weeks.
Once opened use by...

11. SPECIAL STORAGE CONDITIONS

Replace cap after use.
Return the oral syringe to the outer carton immediately after each use.

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

Disposal: read package leaflet.

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/2/15/181/001 (1 x 3 ml oral syringe)

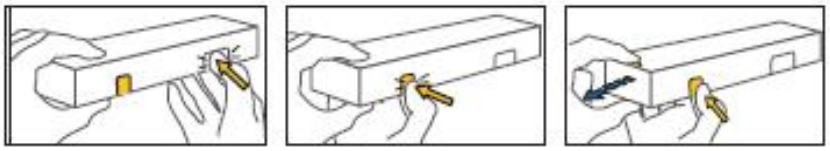
17. MANUFACTURER'S BATCH NUMBER

Lot

QR code to be included + www.sileodog.com

Instructions for opening the package:

1. 2. 3.



1. Push to break white seal.
2. Push to break yellow seal.
3. Push yellow seal and pull open

Text on the seals:
Push
Pull

On the inner part of the carton:
When closing, make sure that the pictures of the dogs are aligned and that the carton is closed properly.

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON (3 x 1, 5 x 1, 10 x 1 and 20 x 1 pre-filled syringes)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sileo 0.1 mg/ml oromucosal gel for dogs
dexmedetomidine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml: Dexmedetomidine hydrochloride 0.1 mg

3. PHARMACEUTICAL FORM

Oromucosal gel

4. PACKAGE SIZE

3 packs of (3 ml) oral syringes
5 packs of (3 ml) oral syringes
10 packs of (3 ml) oral syringes
20 packs of (3 ml) oral syringes

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For oromucosal use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {month/year}

11. SPECIAL STORAGE CONDITIONS

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

Disposal: read package leaflet.

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.
This multipack is not intended to be supplied directly to the animal owner.
(for 5 x 1, 10 x 1 and 20 x 1 multipacks only)

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/2/15/181/002 (3 (1 x 3 ml) oral syringes)
EU/2/15/181/003 (5 (1 x 3 ml) oral syringes)
EU/2/15/181/004 (10 (1 x 3 ml) oral syringes)
EU/2/15/181/005 (20 (1 x 3 ml) oral syringes)

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ORAL SYRINGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sileo 0.1 mg/ml oromucosal gels

dexmedetomidine HCl

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Dexmedetomidine hydrochloride 0.1 mg/ml

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

3 ml

4. ROUTE(S) OF ADMINISTRATION

Oromucosal use.

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot

7. EXPIRY DATE

EXP: {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Sileo 0.1 mg/ml oromucosal gel for dogs

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

Orion Corporation
Orionintie 1
FI-02200 Espoo
FINLAND

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sileo 0.1 mg/ml oromucosal gel for dogs
dexmedetomidine hydrochloride

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

Active substance:
Dexmedetomidine hydrochloride 0.1 mg/ml
(equivalent to 0.09 mg/ml dexmedetomidine).

Other ingredients: Brilliant blue (E133) and tartrazine (E102).

Sileo is a translucent, green oromucosal gel.

4. INDICATION(S)

For the alleviation of acute anxiety and fear associated with noise in dogs.

5. CONTRAINDICATIONS

Your dog should not be given Sileo if it:
- has severe liver, kidney or heart disease.
- is hypersensitive to the active substance or to any of the excipients.
- is drowsy due to previous medication.

6. ADVERSE REACTIONS

Sileo may cause the following adverse reactions.

Common reactions:
- paleness of the mucous membranes at the application site
- tiredness (sedation)
- vomiting
- uncontrolled urination.

Uncommon reactions:
- distress

- swelling around the eyes
- drowsiness
- loose stools.

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

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

Oromucosal gel.

Sileo is administered onto the oral mucosa between the dog's cheek and gum.
The Sileo oral syringe delivers the product in small increments (0.25 ml). Each increment is shown as one dot on the plunger. The dosing table provides the number of dots to be administered corresponding to the dog's bodyweight.

The following dosing table provides the dose volume (in dots) to be administered for the corresponding bodyweight. If the dose for the dog is more than 6 dots, half of the dose should be administered to the oral mucosa on one side of the dog's mouth and the other half of the dose onto the other side. Do not exceed the recommended dose.

Bodyweight of dog (kg)	Number of dots
2.0–5.5	1 ●
5.6–12	2 ●●
12.1–20	3 ●●●
20.1–29	4 ●●●●
29.1–39	5 ●●●●●
39.1–50	6 ●●●●●●
50.1–62.5	7 ●●●●●●●
62.6–75.5	8 ●●●●●●●●
75.6–89	9 ●●●●●●●●●
89.1–100	10 ●●●●●●●●●●

9. ADVICE ON CORRECT ADMINISTRATION

Dosing should be performed by an adult. Wear impermeable disposable gloves when handling the veterinary medicinal product.

The first dose should be given as soon as the dog shows the first signs of anxiety, or when the owner detects a typical stimulus (e.g. sound of fireworks or thunder) for eliciting anxiety or fear in the

respective dog. Typical signs of anxiety and fear are panting, trembling, pacing (frequent change of place, running around, restlessness), seeking people (clinging, hiding behind, pawing, following), hiding (under furniture, in dark rooms), trying to escape, freezing (absence of movements), refusing to eat food or treats, inappropriate urination, inappropriate defecation, salivation, etc.

If the fear eliciting event continues and the dog shows signs of anxiety and fear again, re-dosing can be done when 2 hours have passed from the previous dose. The product can be dosed up to 5 times during each event.

See the detailed instructions and pictures in the end of this leaflet.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Return the oral syringe to the outer carton immediately after each use for child safety and also in order to protect from light.
Replace cap after use.
Do not use this veterinary medicinal product after the expiry date which is stated on the oral syringe label and outer carton after "EXP". The expiry date refers to the last day of that month.
Shelf life after first opening the oral syringe: 4 weeks. Add a note on the carton after "Once opened use by..." to remind you when the 4 weeks have passed.

12. SPECIAL WARNING(S)

Special precautions for use in animals:
Unlike most other oral veterinary products, this product is not meant to be swallowed. Instead, it must be placed onto the mucosa between the dog's cheek and gum of the dog. Feeding and giving the dog treats within 15 minutes after administration of the gel should therefore be avoided. If the oromucosal gel is swallowed it will become less effective. In case the gel is swallowed the dog can be given another dose if necessary 2 hours after the previous dose.

In extremely nervous, excited or agitated animals the response to the medicine may be reduced.

The safety of administering Sileo to puppies younger than 16 weeks and dogs over 17 years of age has not been studied.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
In case of accidental ingestion or prolonged mucosal contact, seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive as sedation and changes in blood pressure may occur.

Avoid skin, eye or mucosal contact. Wear impermeable disposable gloves when handling the veterinary medicinal product.

In case of skin contact wash the skin immediately with large amounts of water and remove contaminated clothes. In case of eye or oromucosal contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

People with known hypersensitivity to dexmedetomidine or any of the excipients should avoid contact with the veterinary medicinal product.

Pregnant women should avoid contact with the product. Uterine contractions and decreased foetal blood pressure may occur after systemic exposure to dexmedetomidine.

Advice to physicians:
Dexmedetomidine, the active ingredient of Sileo, is an alpha-2 adrenoceptor 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. Since effects are dose dependent they are more pronounced in small children than adults. Respiratory and haemodynamic symptoms should be treated symptomatically. The specific alpha-2 adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans but only experimentally to antagonize dexmedetomidine-induced effects.

Pregnancy and lactation:
The safety of this veterinary medicinal product 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.

Interaction with other medicinal products and other forms of interaction:
Inform your veterinary surgeon if your dog is using other medicines.
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 by the veterinary surgeon.

Overdose (symptoms, emergency procedures, antidotes):
Overdose can cause excessive tiredness. If this occurs the animal should be kept warm.
If an overdose occurs, contact a veterinary surgeon as soon as possible.
The effects of dexmedetomidine can be eliminated using a specific antidote (reversal medicine).

Information for the veterinary surgeon:
Do not exceed the recommended dose. Signs of sedation may occur when the dose is exceeded. The level and duration of sedation is dose dependent. If sedation occurs, the dog should be kept warm.

Reduced heart rate may be seen after administration of higher than recommended doses of Sileo gel. Blood pressure decreases slightly below normal levels. Respiration rate can occasionally decrease. Higher than recommended doses of Sileo gel may also induce a number of other alpha-2 adrenoceptor mediated effects, which include mydriasis, depression of motor and secretory functions of the gastrointestinal tract, temporary AV-blocks, diuresis and hyperglycaemia. A slight decrease in body temperature may be observed.

The effects of dexmedetomidine can be eliminated using a specific antidote, atipamezole (alpha-2 adrenoceptor antagonist). In case of overdose, the appropriate dose of atipamezole calculated in micrograms is 3 times (3X) the dose of administered dexmedetomidine hydrochloride in Sileo gel. Atipamezole (at the concentration of 5 mg/ml) dose in millilitres is one sixteenth ($1/16^{th}$) of the dose volume of Sileo gel.

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

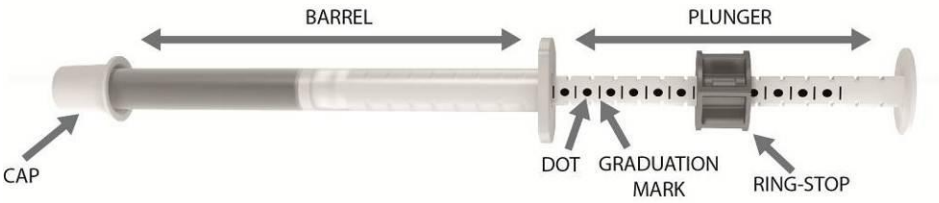
Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

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/).

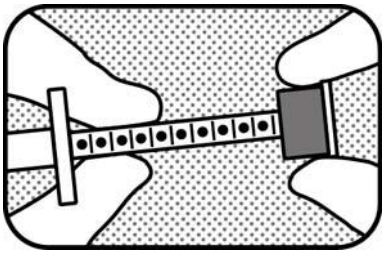
15. OTHER INFORMATION

INSTRUCTIONS FOR DOSING THE GEL:

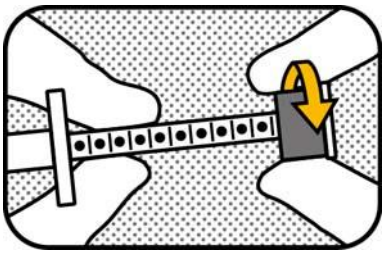


NEW ORAL SYRINGE SET UP BEFORE FIRST DOSING:

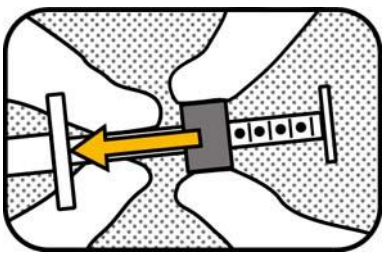
1. WEAR GLOVES
Wear impermeable disposable gloves when handling the veterinary medicinal product and handling the oral syringe.



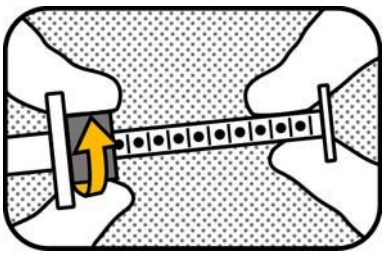
2. HOLD PLUNGER
Hold the oral syringe so that you can see the dot markings on the oral syringe plunger. Hold the plunger with your left hand.



3. UNLOCK
Hold the plunger with your left hand and unlock the green ring-stop by turning it towards you until it is able to slide freely.



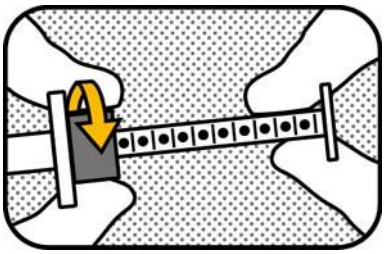
4. MOVE RING
Move the ring-stop to the opposite end of the plunger.



5. LOCK

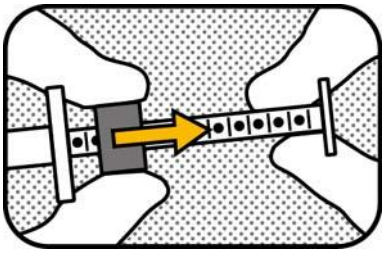
Hold the plunger with your right hand and lock the ring-stop by turning it away from you.

DOSE SELECTION AND DOSING:



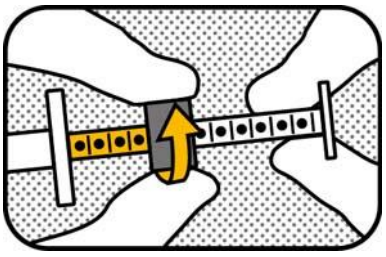
6. UNLOCK

Hold the plunger with your right hand and unlock the ring-stop by turning it towards you. **Do not pull the plunger!**



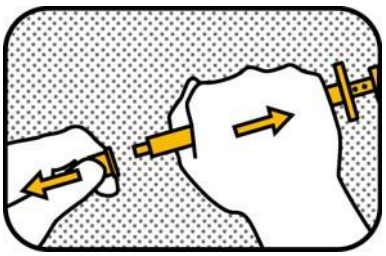
7. MOVE RING

Move the ring-stop towards the other end of the plunger for choosing the correct dose based on your veterinarian's prescription.



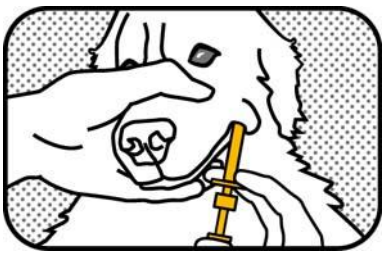
8. SET DOSE AND LOCK

Position the ring-stop so that the side nearest the barrel is in line with the graduation mark (black line), and the required number of dots shows between the ring-stop and the barrel. Lock the ring-stop by turning it away from you. **Before dosing make sure that the ring-stop is locked.**

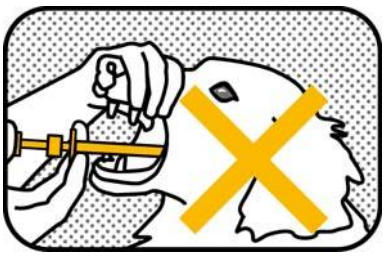


9. PULL CAP (TIGHT)

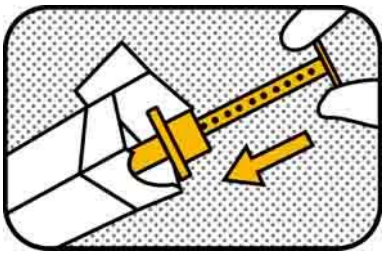
Pull the cap strongly while holding the barrel. **Note** the cap is very tight (pull, do not twist). Save the cap for replacement.



10. DOSE INTO CHEEK
Place the oral syringe tip between the dog's cheek and gum and press the plunger until the ring-stop causes the plunger to stop.
IMPORTANT: The gel should not be swallowed. If the gel is swallowed, it may not be effective.



NOT SWALLOWED



11. BACK TO PACKAGE
Recap the oral syringe and return it to the outer package as the product is sensitive to light. Make sure that the carton is closed properly. Keep the package out of sight and reach of children at all times. Remove and discard gloves.

Pack sizes: single pack of 1 oral syringe and multipacks of 3 (3 packs of one oral syringe). Multipacks of 5, 10 and 20 oral syringes are also available but are intended to be supplied only to veterinarians.

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.

Sverige
Orion Pharma AB, Animal Health
Golfvägen 2
Box 85
SE-182 11 Danderyd
Tel: +46 8 623 64 40

Norge
Orion Pharma AS Animal Health
P.O. Box 4366 Nydalen
N-0402 Oslo
Tlf: +47 40 00 41 90

Danmark
Orion Pharma Animal Health
Ørestads Boulevard 73
2300 København S
Tlf: +45 86 14 00 00

Suomi/Finland
ORION PHARMA Eläinlääkkeet
PL 425, 20101 Turku
Puh: +358 10 4261

Polska
Orion Pharma Poland Sp. z o.o.
ul. Fabryczna 5A
00-446 Warszawa
Tel: +48 22 8333177

Magyarország
Orion Pharma Kft.
1139 Budapest, Pap Károly u. 4-6
Tel: +36 1 886 3015

Česká republika
Orion Pharma s.r.o.
Zelený pruh 95/97
140 00, Praha, ČR
Tel: +420 227 027 263

Slovenská republika
Orion Pharma s.r.o.
Ružová dolina 6,
821 08 Bratislava, SR
Tel: +421 250 221 215

România
Orion Pharma Romania srl
B-dul Tudor Vladimirescu nr 22 , Green Gate Building
Floor 5, office 518, Bucuresti, 050883
Tel: +40 31 845 1646

Slovenija
IRIS d.o.o.
1000 Ljubljana
Cesta vGorice 8
Tel: +386 1 200 66 50

Eesti, Latvija, Lietuva
UAB Orion Pharma
Kubiliaus str.6
LT-08234 Vilnius
Tel: +370 5 276 9499

Ísland
Icepharma hf
Lynghálsi 13
1100 Reykjavík
Sîmi: 540 8080

Nederland
Ecuphar bv,
Verlengde Poolseweg 16,
4818 CL Breda
Tel: +31 (0)88 003 38 00
Email : info@ecuphar.nl

België/Belgique/Belgien
Ecuphar nv/sa,
Legeweg 157-i,
8020 Oostkamp
Tel: +32 (0)50 31 42 69
Email : animal.health@ecuphar.be

Luxembourg/Luxemburg
Ecuphar sa,
Legeweg 157-i,
8020 Oostkamp
Belgique

Deutschland
Ecuphar GmbH,
Brandteichstraße 20,
17489 Greifswald,
Deutschland

Tel: +32 (0)50 31 42 69
Email : animal.health@ecuphar.be

España
Ecuphar Veterinaria S.L.U.
Avenida Río de Janeiro, 60-66, planta 13
08016 Barcelona (España)
Tel: + 34 93 5955000

Portugal
Belphar LDA
Sintra Business Park, Nº7, Edifício 1 - Escritório 2K
Zona Industrial de Abrunheira
2710-089 Sintra
Tel: + 351 308808321

United Kingdom
Zoetis UK Limited
Tel: +44 (0) 845 300 8034

France
TVM France
57 rue des Bardines
63370 LEMPDES
France
Tel: +33 (0)4 73 61 75 76

Tel: +49 (0)3834 83 584 0
Email : info@ecuphar.de

Italia
Ecuphar Italia S.R.L.
Viale Francesco Restelli, 3/7
20124 Milano (Italia)
Tel: + 39 0282950604

Österreich
Richter Pharma AG
Feldgasse 19
A - 4600 Wels
Tel.: +43 7242 490 0

Република България, Ελλάδα, Hrvatska, Malta, Κύπρος
Orion Corporation
Orionintie 1
Espoo, FI-02200, Finland
Tel: + 358 10 4261

Ireland
Zoetis Belgium S.A.
Tel: +353 (0) 1 256 9800