## 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:**
0.1 mg dexmedetomidine hydrochloride equivalent to 0.09 mg dexmedetomidine.

**Excipients:**

| **Qualitative composition of excipients and other constituents** |
|---|
| Water, purified |
| Propylene glycol |
| Hydroxypropylcellulose |
| Sodium lauryl sulfate |
| Brilliant blue (E133) |
| Tartrazine (E102) |
| Sodium hydroxide (for pH adjustment) |
| Hydrochloric acid (for pH adjustment) |

Translucent, green gel.

## 3. CLINICAL INFORMATION

### 3.1 Target species

Dogs.

### 3.2 Indications for use for each target species

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

### 3.3 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 cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs obviously sedated from previous dosing.

### 3.4 Special warnings

None.

## 3.5 Special precautions for use

Special precautions for safe use in the target species:
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 accidental spillage onto skin, 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 veterinary medicinal product. Uterine contractions and decreased foetal blood pressure may occur after systemic exposure to dexmedetomidine.

Advice to the physician:
Dexmedetomidine, the active substance 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.

Special precautions for the protection of the environment:
Not applicable.

## 3.6 Adverse events

Dogs:

| | |
|---|---|
| Common<br>(1 to 10 animals / 100 animals treated): | Emesis<br>Sedation<br>Urinary incontinence<br>Pale mucous membrane[1] |
| Uncommon<br>(1 to 10 animals / 1 000 animals treated): | Anxiety<br>Gastroenteritis<br>Periorbital oedema<br>Drowsiness |

[1]Transient, observed at the application site due to peripheral vasoconstriction.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

### 3.7 Use during pregnancy, lactation or lay

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

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

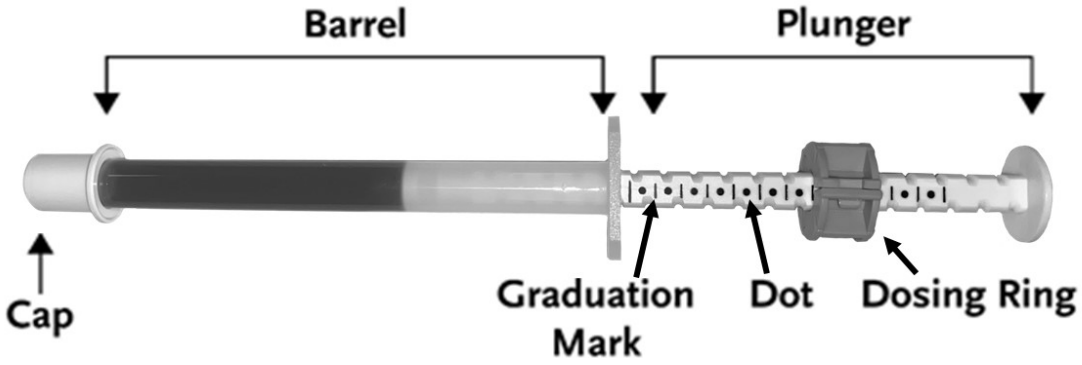
### 3.8 Interaction with other medicinal products and other forms of interaction

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.

### 3.9 Administration routes and dosage

Oromucosal use.

The veterinary medicinal 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 veterinary medicinal 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 ● |

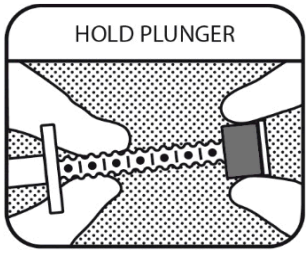
| | |
|---|---|
| 5.6–12 | 2 ●● |
| 12.1–20 | 3 ●●● |
| 20.1–29 | 4 ●●●● |
| 29.1–39 | 5 ●●●●● |
| 39.1–50 | 6 ●●●●●● |
| 50.1–62.5 | 7 ●●●●●●● |
| 62.6–75.5 | 8 ●●●●●●●● |
| 75.6–89 | 9 ●●●●●●●●● |
| 89.1–100 | 10 ●●●●●●●●●● |

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 veterinary medicinal product can be dosed up to 5 times during each event.

Instructions for dosing the gel:
Dosing should be performed by an adult.

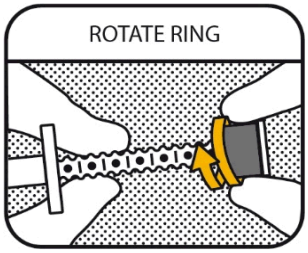
**PREPARATIONS FOR DOSING:**


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

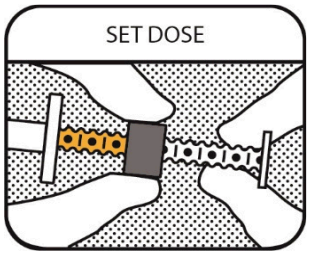



**2. HOLD PLUNGER**
Hold the oral syringe plunger so that you can see the dot markings.

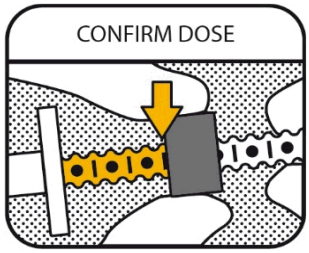
**DOSE SELECTION AND DOSING:**



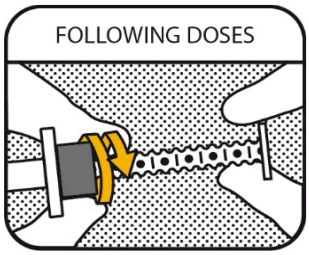

**3. ROTATE RING**
Hold the plunger and rotate the ring towards the barrel to select the dose your veterinarian has prescribed to your dog. **Do not pull the plunger!**



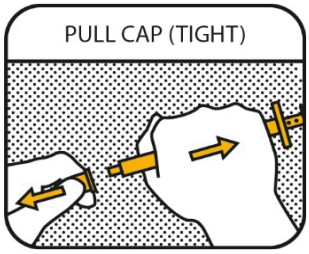

**4. SET THE DOSE**
Position the dosing ring so that the side nearest the barrel is in line with the graduation mark (black line), and the required number of dots shows between the dosing ring and the barrel.




**5. CONFIRM THE DOSE**
Make sure that you count the dots from the correct part of the plunger (shown in yellow) and that the ring is in line with the graduation mark (shown with the yellow arrow).

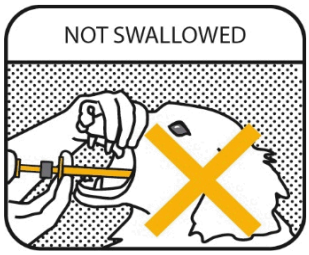



**6. FOLLOWING DOSES**
To administer following doses from the same syringe: Repeat the previous "4. Set the dose" and "5. Confirm the dose" parts of the instructions.

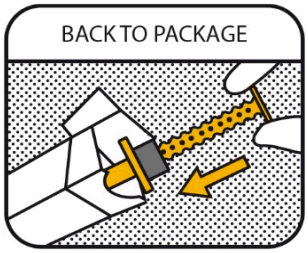



**7. PULL CAP (TIGHT)**
Pull the cap strongly while holding the barrel. **Note** the cap is very tight (pull, do not twist). Save the cap for replacement.


**8. DOSE INTO CHEEK**
Place the oral syringe tip between the dog's cheek and gum and press the plunger until the dosing ring causes the plunger to stop.




**9. NOT SWALLOWED**
**IMPORTANT: The gel should not be swallowed. If the gel is swallowed, it may not be effective.**




**10. BACK TO PACKAGE**
Recap the oral syringe and return it to the outer package as the veterinary medicinal 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.

### 3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

### 3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

### 3.12 Withdrawal periods

Not applicable.

## 4. PHARMACOLOGICAL INFORMATION

### 4.1 ATCvet code: QN05CM18

### 4.2 Pharmacodynamics

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 3.10 on overdose.

### 4.3 Pharmacokinetics

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.

## 5. PHARMACEUTICAL PARTICULARS

### 5.1 Major incompatibilities

Not applicable.

### 5.2 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.

### 5.3 Special precautions for storage

Keep the oral syringe in the outer carton in order to protect from light.

### 5.4 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.
- Multipacks of 3 (3 packs of one), 5 (5 packs of one), 10 (10 packs of one) and 20 (20 packs of one) oral syringes.

Multipacks of 5, 10 and 20 oral syringes are intended to be supplied only to veterinarians.

Not all pack sizes may be marketed.

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

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

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

## 6. NAME OF THE MARKETING AUTHORISATION HOLDER

Orion Corporation

## 7. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/181/001–005

## 8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 10/06/2015

## 9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD/MM/YYYY}

## 10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).