1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Clevor 30 mg/ml eye drops, solution in single-dose container for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains:

Active substance:
Ropinirole (ropinirol) 30 mg
(equivalent to 34.2 mg ropinirole hydrochloride)

Excipients:

Qualitative composition of excipients and other constituents
Citric acid monohydrate
Sodium citrate
Sodium chloride
Sodium hydroxide (to adjust pH)
Hydrochloric acid (to adjust pH)
Water for injections

Very slightly yellow to yellow clear solution.

3. CLINICAL INFORMATION

3.1 Target species

Dogs

3.2 Indications for use for each target species

Induction of vomiting in dogs.

3.3 Contraindications

Do not use in dogs with depression of the central nervous system, seizures or other marked neurologic impairments that could lead to aspiration pneumonia.

Do not use in dogs which are hypoxic, dyspnoeic or lacking pharyngeal reflexes.

Do not use in cases of the ingestion of sharp foreign objects, corrosive agents (acids or alkalis), volatile substances or organic solvents.

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

3.4 Special warnings

The efficacy of the veterinary medicinal product has not been established in dogs weighing less than 1.8 kg, or in dogs under 4.5 months of age or in elderly dogs. Use only according to the benefit-risk assessment by the responsible veterinarian.

Based on the clinical trial results, most dogs are expected to respond to a single dose of the veterinary medicinal product; however, a small proportion of dogs will require a second dose to induce vomiting. A very small proportion of dogs may fail to respond to the treatment despite administration of a

second dose. It is not recommended to administer further doses to these dogs. Please refer to sections 3.9 and 4.2 for further information.

3.5 Special precautions for use

Special precautions for safe use in the target species:

This veterinary medicinal product may cause a transient increase in heart rate up to 2 hours after administration. The safety of the veterinary medicinal product has not been studied in dogs with diagnosed cardiac disease/dysfunction. Use only according to the benefit-risk assessment by the responsible veterinarian.

The safety of this veterinary medicinal product in dogs with clinical signs due to the ingestion of foreign materials has not been investigated.

Ropinirole is metabolised by the liver. The safety of the veterinary medicinal product has not been studied in dogs with hepatic impairment. Use only according to the benefit-risk assessment by the responsible veterinarian.

The safety and efficacy of the veterinary medicinal product have not been studied in dogs with ocular disease or injury. In case of a pre-existing ocular condition with clinical signs, use the veterinary medicinal product only according to the benefit-risk assessment by the responsible veterinarian.

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

People with known hypersensitivity to ropinirole should avoid contact with the veterinary medicinal product. Administer the veterinary medicinal product with caution.

The veterinary medicinal product should not be administered by pregnant or breast-feeding women. Ropinirole might reduce the level of prolactin due to its inhibitory effect on prolactin secretion as a dopamine agonist.

This veterinary medicinal product can cause eye irritation. Administer the veterinary medicinal product with caution. In case of accidental eye or skin contact, rinse immediately the affected area with plenty of fresh water. If symptoms occur, seek medical advice and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Very common (> 1 animal / 10 animals treated):	Increased heart rate[1] Eye redness[2], Ocular discharge[2], Third eyelid protrusion[2], Blepharospasm[2] Lethargy[1]
Common (1 to 10 animals / 100 animals treated):	Vomiting[3], Diarrhoea[1] Conjunctival oedema[1], Eye itching[1]

	Ataxia[1], Incoordination[1], Tremor[1] Tachypnoea[1]
Uncommon (1 to 10 animals / 1 000 animals treated):	Corneal ulcer

[1]Transient mild
[2]Transient mild or moderate
[3]Extended vomiting (for more than 60 minutes) should be evaluated by the responsible veterinarian as it might need appropriate treatment.

In dogs with extended vomiting and other clinical signs related to the pharmacological action of the active substance (e.g. eye redness, increased heart rate or tremor), dopamine antagonists such as metoclopramide or domperidone may be used to manage these clinical signs.

Maropitant does not reverse the clinical signs related to the pharmacological action of ropinirole.

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 in the target species. Ropinirole inhibits prolactin secretion by activation of dopamine D_2 receptors located in the striatum and on lactotroph cells of pituitary gland. Therefore, use of this veterinary medicinal product is not recommended during pregnancy or lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Dopamine antagonists (such as metoclopramide), neuroleptics (e.g., chlorpromazine, acepromazine) and other medicinal products with antiemetic properties (e.g., maropitant or antihistamines) may reduce the effectiveness of this veterinary medicinal product.

3.9 Administration routes and dosage

Ocular use.

The veterinary medicinal product is to be administered into the eye, at a dose of 1–8 eye drops. The volume of one drop is approximately 27 µl. Each eye drop contains 810 mcg of ropinirole. The dose is equivalent to 2–15 µl/kg bodyweight (bw) in dogs. The number of eye drops in each body weight group corresponds to the target dose of 3.75 mg/m^2 body surface area (dose range 2.7–5.4 mg/m^2). These doses have been tested in dogs weighing between 1.8 kg and 100 kg (0.15–2.21 m^2 body surface area).

When a quantity of 2 to 4 drops is to be administered, the dose should be divided between both eyes. For example, for the administration of 3 drops: administer 2 drops into the right eye and 1 drop into the left eye.

When a quantity of 6 or 8 drops is to be administered, the dose should be divided into 2 alternate administrations given 1–2 minutes apart. For example, for the administration of 6 drops: administer 2 drops into the right eye and 2 drops into the left eye, then after 1–2 minutes pause, administer a further 1 drop into each eye.

If the dog does not vomit within 15 minutes after administration of the initial dose a second dose may be given 15 to 20 minutes after administration of the initial dose. The second dose should be the same number of drops as the initial dose. It is recommended to record the time of first administration.

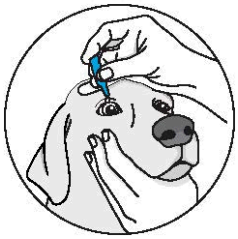
Be careful not to touch the dropper tip after opening the container in case a second dose is necessary.

The following dosing table provides the dose in drops to be administered corresponding to the dog's bodyweight.

Body weight (kg)	**Body surface area (m^2)**	**Number of eye drops**	**Ropinirole (mcg)**	**Ropinirole (mg/m^2 body surface area)**	**Ropinirole (mcg/kg)**
1.8–5	0.15–0.30	**1**	810	5.4–2.7	450–162
5.1–10	0.30–0.47	**2**	1620	5.4–3.4	318–162
10.1–20	0.48–0.75	**3**	2430	5.1–3.2	240–121
20.1–35	0.75–1.09	**4**	3240	4.3–3.0	161–93
35.1–60	1.10–1.57	**6**	4860	4.4–3.1	138–81
60.1–100	1.57–2.21	**8**	6480	4.1–2.9	108–64.5

Instructions for use

OPENING THE CONTAINER:
Open the container by twisting off the tail.
Be careful not to touch the dropper tip after opening the container.



ADMINISTRATION:
Keep the dog's head steady in a slightly upright position. Hold the container in an upright position without touching the eye. Rest your little finger on the forehead of the dog to maintain the distance between the container and the eye. Squeeze the prescribed number of drops into the eye(s).

STORING THE OPENED CONTAINER:
After opening place the container back into the pouch in case a second dose is necessary.

REPEATED DOSE:
In case the dog does not vomit within 15 minutes after the initial administration, a second dose can be given 15 to 20 minutes after administration of the initial dose. The additional dose should be the same as the initial dose.

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

The tolerance of this veterinary medicinal product was investigated in a target animal safety study at all dose levels up to 5 times the clinical dose (that is, up to 124.6 µl/kg) when given on two occasions, 15–20 minutes apart, every day for 3 days. The clinical signs (lethargy, tachycardia, tremor, ataxia, incoordination, hyperaemia of the eye, ocular discharge, protrusion of the 3rd eyelid and blepharospasm) were comparable in frequency and severity between the different dose groups. Increased mean heart rate was observed one hour after treatment with all three doses (1X, 3X, 5X) and went back to normal levels after 6 hours.

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

The veterinary medicinal product should only be administered by a veterinarian or under their close supervision.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN04BC04

4.2 Pharmacodynamics

Ropinirole is a full dopamine agonist with high selectivity for the dopamine D_2-like receptor family (D_2, D_3 and D_4 receptors). It induces emesis by activating the D_2-like receptors in the chemoreceptor trigger zone, located in the area postrema, which transmits the information to the emesis centre to trigger vomiting. In a clinical field trial including 100 clinically healthy dogs treated with Clevor, the time from administration to first vomit was 3–37 minutes with a mean time of 12 minutes and median time of 10 minutes. The time between the first to the last vomit was 0–108 minutes (0 if the dog vomited only once) with a mean duration of 23 minutes and a median duration of 16 minutes. Within 30 minutes 95 % of the dogs vomited. An additional dose was administered after 20 minutes to 13 % of the dogs because of lack of efficacy. Three dogs (3 %) did not vomit at all despite an additional dose. 5 % of the dogs in the clinical study received anti-emetic treatment (metoclopramide) because their vomiting persisted for more than 60 minutes.

4.3 Pharmacokinetics

Absorption

Ropinirole is rapidly absorbed into the systemic circulation of dogs after administration as a solution on their eye surface. At the target dose of 3.75 mg/m² (equivalent to 2–15 µl/kg bw), a peak plasma concentration (C_{max}) of 26 ng/ml is reached 10 to 20 minutes (t_{max}) after administration. The systemic bioavailability of the veterinary medicinal product by this ocular route of administration is 23 %. Vomiting starts before the C_{max} in plasma is reached; at 4–6 minutes in a pharmacokinetic study in dogs. No direct correlation between ropinirole concentration in plasma and the duration of vomiting was observed after ocular administration. The time to last vomit ranged from 30 to 82 minutes following ocular administration in a pharmacokinetic study in dogs.

Distribution

Ropinirole is rapidly distributed and has a relatively high apparent volume of distribution. In dogs, the volume of distribution (V_z) is 5.6 l/kg after intravenous administration. The fraction bound to plasma proteins in dogs is low (37 %).

Elimination

Ropinirole is mainly eliminated by hepatic metabolism. The half-life of elimination ($t_{½}$) is 4 hours after intravenous administration to dogs. Biotransformation occurs by dealkylation, hydroxylation and subsequent conjugation with glucuronic acid or oxidation to carboxylic acid. About 40 % of radioactive ropinirole is excreted in the urine within 24 hours after intravenous administration to dogs. Excretion in the urine occurs mainly as metabolites. The portion recovered as unchanged ropinirole in the urine is below 3 % within the first 24 hours.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 30 months.
Shelf life after first opening the immediate packaging (pouch and container): 30 minutes.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Store the container in the pouch in order to protect from light.

After opening the pouch, the container should be kept in the pouch to protect from light.
Discard any opened individual pouch or container with any remaining liquid after 30 minutes.

5.4 Nature and composition of immediate packaging

Low density polyethylene plastic single-dose container containing 0.6 ml.

Each plastic container is packed in an individual aluminium foil laminate pouch. The pouch/pouches are then packed in a cardboard box together with the same number of package leaflets (intended for the animal owners) as the number of single-dose containers in the outer package.

Pack sizes: 1, 2, 3, 4, 5, 6, 8 and 10 single-dose containers.

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/2/17/222/001 – 1 single-dose container
EU/2/17/222/002 – 2 single-dose containers
EU/2/17/222/003 – 4 single-dose containers
EU/2/17/222/004 – 5 single-dose containers
EU/2/17/222/005 – 6 single-dose containers
EU/2/17/222/006 – 8 single-dose containers
EU/2/17/222/007 – 10 single-dose containers
EU/2/17/222/008 – 3 single-dose containers

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 13/04/2018

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

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*).