

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cerenia Injection Veterinary

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Maropitant (as maropitant citrate monohydrate) 10 mg/ml

Excipients:

Metacresol (as preservative) 3.3 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

In dogs above age 8 weeks and cats above age 16 weeks: for the prevention of vomiting except that induced by motion sickness. For the treatment of vomiting, in combination with other supportive measures.

Dogs age 8 - 10 weeks must be under close medical supervision or hospitalized.

4.3 Contraindications

None.

4.4 Special warnings for each target species

Vomiting can be associated with serious, severely debilitating conditions including gastrointestinal obstructions; therefore, appropriate diagnostic evaluations should be employed.

Good veterinary practice indicates that antiemetics should be used in conjunction with other veterinary and supportive measures such as dietary control and fluid replacement therapy while addressing the underlying causes of the vomiting.

The use of Cerenia Injection Veterinary against vomiting due to motion sickness is not recommended.

Dogs:

Although Cerenia Injection Veterinary has been demonstrated to be effective in both the treatment and prevention of emesis induced by chemotherapy, it was found more efficacious if used preventively. Therefore, it is recommended to administer the antiemetic prior to administration of the chemotherapeutic agent.

Cats:

The efficacy of Cerenia Injection Veterinary in reduction of nausea was demonstrated in studies using a model (xylazine-induced nausea).

4.5 Special precautions for use

Special precautions for use in animals:

The safety of the veterinary medicinal product has not been established in dogs less than 8 weeks of age, or in cats less than 16 weeks of age, and in pregnant or lactating dogs and cats.

Maropitant is metabolised in the liver and therefore should be used with caution in patients with hepatic disease. As maropitant is accumulated in the body during a 14-day treatment period due to metabolic saturation, careful monitoring of liver function and any adverse events should be implemented during long-term treatment.

Cerenia Injection Veterinary should be used with caution in animals suffering from or with predisposition for cardiac diseases as maropitant has affinity to Ca- and K-ion channels. Increases of approximately 10% in the QT interval of the ECG were observed in a study on healthy beagle dogs administered 8 mg/kg orally; however, such an increase is unlikely to be of clinical significance.

Due to the frequent occurrence of transient pain during subcutaneous injection, appropriate animal restraining measures may have to be applied. Injecting the product at refrigerated temperature may reduce pain at injection.

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

Wash hands after use. In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician. In laboratory studies, maropitant has been shown to be a potential eye irritant. In the case of accidental eye exposure, flush the eyes with plenty of water and seek medical attention.

4.6 Adverse reactions (frequency and seriousness)

Pain at injection site may occur when injected subcutaneously. In cats, moderate to severe response to injection is very commonly observed (in approximately one third of cats).

In very rare cases, anaphylactic-type reactions (allergic oedema, urticaria, erythema, collapse, dyspnoea, pale mucous membranes) may occur.

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

- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

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

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

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

4.7 Use during pregnancy, lactation or lay

Use only according to the benefit-risk assessment by the responsible veterinarian, because conclusive reproductive toxicity studies have not been conducted in any animal species.

4.8 Interaction with other medicinal products and other forms of interaction

Cerenia Injection Veterinary should not be used concomitantly with Ca-channel antagonists as maropitant has affinity to Ca-channels.

Maropitant is highly bound to plasma proteins and may compete with other highly bound medicines.

4.9 Amounts to be administered and administration route

For subcutaneous use in dogs and cats.

Cerenia Injection Veterinary should be injected subcutaneously, once daily, at a dose of 1 mg/kg bodyweight (1 ml/10 kg bodyweight) for up to 5 consecutive days.

In dogs, Cerenia Injection Veterinary can be used to treat or prevent vomiting when administered once daily. Cerenia Injection Veterinary may be administered for up to five days.

To prevent vomiting, Cerenia Injection Veterinary solution for injection should be administered more than 1 hour in advance. The effect duration is approximately 24 h and therefore treatment can be given the night before administration of an agent that may cause emesis, e.g. chemotherapy.

As the pharmacokinetic variation is large and maropitant accumulates in the body after once-daily repeated administration, lower doses than recommended might be sufficient in some individuals and when repeating the dose.

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

Apart from transient reactions at the injection site following subcutaneous administration, Cerenia Injection Veterinary was well tolerated in dogs and young cats injected daily with up to 5 mg/kg (5 times the recommended dose) for 15 consecutive days (3 times the recommended duration of administration). No data have been presented on overdoses in adult cats.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiemetics. ATCvet code: QA04AD90.

Maropitant is a potent and selective neurokinin (NK₁) receptor antagonist, which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family, in the CNS.

5.1 Pharmacodynamic properties

Vomiting is a complex process coordinated centrally by the emetic centre. This centre consists of several brainstem nuclei (area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus) that receive and integrate sensory stimuli from central and peripheral sources and chemical stimuli from the circulation and the cerebro-spinal fluid.

Maropitant is a neurokinin 1 (NK₁) receptor antagonist, which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. Substance P is found in significant concentrations in the nuclei comprising the emetic centre and is considered the key neurotransmitter involved in vomiting. By inhibiting the binding of substance P within the emetic centre, maropitant is effective against neural and humoral (central and peripheral) causes of vomiting.

A variety of *in vitro* assays have demonstrated that maropitant binds selectively at the NK₁ receptor with dose-dependent functional antagonism of substance P activity.

Maropitant is effective against vomiting. The anti-emetic efficacy of maropitant against central and peripheral emetics was demonstrated in experimental studies including apomorphine, cisplatin and syrup of ipecac (dogs) and xylazine (cats).

Signs of nausea in dogs, including excessive salivation and lethargy, might remain after treatment.

5.2 Pharmacokinetic particulars

Dogs

The pharmacokinetic profile of maropitant when administered as a single subcutaneous dose of 1 mg/kg body weight to dogs was characterised by a maximum concentration (C_{max}) in plasma of approximately 92 ng/ml; this was achieved within 0.75 hours post-dosing (T_{max}). Peak concentrations were followed by a decline in systemic exposure with an apparent elimination half-life (t_{1/2}) of 8.84 hours.

During clinical studies maropitant plasma levels conferred efficacy from 1 hour after administration.

The bioavailability of maropitant after subcutaneous administration in dogs was 90.7%. Maropitant displays linear kinetics when administered subcutaneously within the 0.5–2 mg/kg dose range.

Following repeated subcutaneous administration of once-daily doses of 1 mg/kg bodyweight for five consecutive days, accumulation was 146%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP2D15 and CYP3A12 were identified as the canine isoforms involved in the hepatic biotransformation of maropitant.

Renal clearance is a minor route of elimination, with less than 1% of a 1 mg/kg subcutaneous dose appearing in the urine as either maropitant or its major metabolite. Plasma protein binding of maropitant in dogs is more than 99%.

Cats

The pharmacokinetic profile of maropitant when administered as a single subcutaneous dose of 1 mg/kg body weight to cats was characterised by a maximum concentration (C_{max}) in plasma of approximately 165 ng/ml; this was achieved on average 0.32 hours (19 min) post-dosing (T_{max}).

Peak concentrations were followed by a decline in systemic exposure with an apparent elimination half-life (t_{1/2}) of 16.8 hours. There appears to be an age-related effect on the pharmacokinetics of maropitant in cats, with kittens having higher clearance than adults.

During clinical studies maropitant plasma levels conferred efficacy from 1 hour after administration.

The bioavailability of maropitant after subcutaneous administration in cats was 91.3%. Maropitant displays linear kinetics when administered subcutaneously within the 0.25–3 mg/kg dose range.

Following repeated subcutaneous administration of once-daily doses of 1 mg/kg bodyweight for five consecutive days, accumulation was 250%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP1A- and CYP3A-related enzymes were identified as the feline isoforms involved in the hepatic biotransformation of maropitant.

Renal and faecal clearances are minor routes of elimination for maropitant, with less than 1% of a 1 mg/kg subcutaneous dose appearing in the urine or faeces as maropitant. For the major metabolite 10.4% of the maropitant dose was recovered in urine and 9.3% in faeces. Plasma protein binding of maropitant in cats was estimated to be 99.1%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphobutyl ether β-cyclodextrin Sodium (SBECD)

Metacresol

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products in the same syringe.

6.3 Shelf life

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

Shelf life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

Store at room temperature below 30°C

6.5 Nature and composition of immediate packaging

Amber molded glass type I vial, 20 ml, chlorobutyl rubber stopper and aluminium overseal with flip-off button.

Each cardboard box contains 1 vial.

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

Zoetis Israel Holding B.V.,

5 Atir Yeda Street, Kfar Saba, Israel

8. MARKETING AUTHORISATION NUMBER

143-27-92448-00

9. MANUFACTURER:

FAREVA AMBOISE, FRANCE

Zone Industrielle, 29 Route Des Industries,

37530 Poce-Sur-Cisse, France

10. VETERINARY USE

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

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