1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Trocoxil 20 mg Chewable Tablets Veterinary
Trocoxil 30 mg Chewable Tablets Veterinary
Trocoxil 75 mg Chewable Tablets Veterinary
Trocoxil 95 mg Chewable Tablets Veterinary

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

Active substance:

Mavacoxib	20 mg
Mavacoxib	30 mg
Mavacoxib	75 mg
Mavacoxib	95 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablets

Triangular tablet with mottled brown appearance embossed with the tablet strength on one side.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs aged 12 months or more.

4.2 Indications for use, specifying the target species

For the treatment of pain and inflammation associated with degenerative joint disease in dogs in cases where continuous treatment exceeding one month is indicated.

4.3 Contraindications

Do not use in dogs less than 12 months of age and/or less than 7 kg body weight
Do not use in dogs suffering from gastro-intestinal disorders including ulceration and bleeding.
Do not use where there is evidence of a haemorrhagic disorder.
Do not use in cases of impaired renal or hepatic function
Do not use in cases of cardiac insufficiency
Do not use in pregnant, breeding or lactating dogs.
Do not use in case of hypersensitivity to the active substance or to any of the excipients
Do not use in cases of known hypersensitivity to sulphonamides.
Do not use concomitantly with glucocorticoids or other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), see section 4.8.
Avoid use in any dehydrated, hypovolaemic or hypotensive animal, as there is a potential risk of increased renal toxicity.

4.4 Special warnings for each target species

Do not administer other NSAIDs or glucocorticoids concurrently or within 1 month of the last administration of Trocoxil.

4.5 Special precautions for use

Special precautions for use in animals

Mavacoxib exhibits an extended plasma half life (up to > 80 days, see section 5.2) due to its low rate of elimination. This corresponds to a duration of effect of 1-2 months after administration of the second dose (and following doses). Care should be taken to avoid treatment of animals that might not tolerate prolonged NSAID exposure. A maximum treatment administration of 6.5 months continuous therapy is recommended so as to manage plasma levels of mavacoxib in animals which exhibit reduced elimination

Animals should undergo a thorough clinical examination before commencing treatment with Trocoxil and appropriate laboratory tests to monitor haematology and clinical chemistry are recommended. Animals with evidence of impaired renal or hepatic function, or with evidence of a protein or blood losing enteropathy are not suitable for treatment with Trocoxil. It is recommended to repeat the clinical examination one month after commencing treatment with Trocoxil and prior to administration of the third dose with additional monitoring of clinical pathology as appropriate during treatment.

Mavacoxib is excreted via bile and in dogs with hepatic disorders reduced elimination and thus excessive accumulation could occur. For this reason dogs with hepatic disorders should not be treated.

Avoid use in any dehydrated, hypovolaemic or hypotensive animal, as there is a potential risk of increased renal toxicity. Concurrent administration of potentially nephrotoxic medicinal products should be avoided.

Ensure appropriate hydration and haemodynamic status when animals receiving Trocoxil undergo anaesthesia and/or surgical procedures or develop conditions which may result in dehydration or compromised haemodynamic status. The key aim of intervention is to maintain renal perfusion. Patients with underlying renal disease may experience exacerbation or decompensation of their renal disease while on NSAID therapy. (See also section 4.6).

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

In case of accidental self-ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Ingestion of Trocoxil may be harmful for children, and prolonged pharmacological effects leading to e.g. gastrointestinal disorders may be observed. To avoid accidental ingestion administer the tablet to the dog immediately after removal from the blister packaging.
People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product.
Do not eat, drink, or smoke when handling the product. Wash hands after handling the product.

4.6 Adverse reactions (frequency and seriousness)

Adverse reactions of the digestive tract such as vomiting and diarrhoea were commonly reported, loss of appetite, haemorrhagic diarrhoea and melaena have been reported in uncommon cases. Gastrointestinal ulceration was reported in rare cases. Apathy, degradation of renal biochemistry parameters and impaired renal function have been reported in uncommon cases. In rare cases these adverse reactions may be fatal.

If an adverse reaction following the administration of Trocoxil occurs, no further tablets should be administered and general supportive therapy, as applied to clinical overdose with NSAIDs, should be applied. Particular attention should be paid to maintaining haemodynamic status.

Gastrointestinal protectants and parenteral fluids, as appropriate, may be required for animals that experienced gastrointestinal or renal adverse reactions. Veterinarians should be aware that clinical signs of adverse reactions may continue when supportive therapy (such as gastro protectants) is discontinued.

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).

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
https://sideeffects.health.gov.il/.

4.7 Use during pregnancy, lactation or lay

Do not use in pregnant, breeding, or lactating animals. The safety of Trocoxil has not been established during pregnancy and lactation. However, studies in laboratory animals administered other NSAIDs have shown increased pre- and post-implantation loss, embryo-foetal lethality, and malformations.

4.8 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed. In common with other NSAIDs, Trocoxil should not be administered simultaneously with other NSAIDs or glucocorticosteroids. Risks for interactions have to be accounted for throughout the effect period i.e. 1-2 months after administration of Trocoxil. Dogs should be carefully monitored if Trocoxil is administered simultaneously with an anticoagulant.

NSAIDs are highly bound to plasma proteins and may compete with other highly bound substances, such that concomitant administration may result in toxic effects.

Pre-treatment with other anti-inflammatory substances may result in additional or increased adverse effects. To avoid such effects when Trocoxil is to be administered in replacement of another NSAID, ensure an appropriate treatment-free period of at least 24 hours before administering the first dose of Trocoxil. The treatment-free period should however, take into account the pharmacology of the medicinal products used previously. Should another NSAID be administered after Trocoxil treatment, a treatment-free period of at least ONE MONTH should be ensured to avoid adverse effects.

Concurrent administration of potentially nephrotoxic veterinary medicinal products should be avoided.

4.9 Amounts to be administered and administration route

Oral use.

THIS IS NOT A DAILY NSAID. The dose is 2 mg mavacoxib per kg body weight given immediately before or with the dog's main meal. Care should be taken to ensure that the tablet is ingested. The treatment should be repeated 14 days later, thereafter the dosing interval is ONE MONTH. A treatment cycle should not exceed 7 consecutive doses (6.5 months).

Bodyweight (kg)	Number and Strength of Tablets to be Administered			
	20 mg	30 mg	75 mg	95 mg
7-10	1			
11-15		1		
16-20	2			
21-23	1	1		
24-30		2		
31-37			1	
38-47				1
48-52		1	1	
53-62		1		1
63-75			2	

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

In the overdose studies, in common with other NSAIDs, adverse pharmacodynamic events occur affecting the gastrointestinal system. Similarly adverse reactions occurring at the use dose in the animal population principally involved the gastrointestinal system.

In overdose safety studies, repeated doses of 5 mg/kg and 10 mg/kg were not associated with adverse clinical events, abnormal clinical chemistry or significant histological abnormalities. At 15 mg/kg there was evidence of vomiting, and softened/mucoid faeces and an increase in clinical chemistry parameters reflecting renal function. At 25 mg/kg there was evidence of gastrointestinal ulceration.

There is no specific antidote for mavacoxib overdose, but general supportive therapy, as applied to clinical overdose with NSAIDs, should be given.

4.11 Withdrawal period

Not applicable

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, Coxibs.
ATCvet code: QM01AH92.

5.1 Pharmacodynamic properties

Mavacoxib is a non-steroidal anti-inflammatory drug (NSAID) of the coxib class. Mavacoxib is 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide. It is a diarylsubstituted pyrazole. The principal mode of action is inhibition of cyclooxygenase (COX).

COX is a key enzyme in pathways of arachidonic acid metabolism. Its activity culminates in the synthesis of local hormones and inflammatory mediators, termed eicosanoids, which include several prostaglandins. There are two isoforms of COX, COX-1, and COX-2. COX-1 is a widely distributed constitutive enzyme, primarily involved in maintaining organ and tissue function, whilst COX-2 is

inducible at sites of tissue damage but in some organs it is also constitutive. COX-2 exerts the major role in synthesizing prostaglandins which have pivotal roles as mediators of pain, inflammation and fever. Mavacoxib acts by preferential inhibition of COX-2-mediated prostaglandin synthesis. It therefore possesses analgesic and anti-inflammatory properties. The products of COX-2 metabolism are also involved in ovulation, implantation and closure of the ductus arteriosus. Both COX-1 and COX-2 are present constitutively in the kidney and are assumed to possess protective roles in adverse physiological circumstances.

Based on the results of canine whole blood assays, plasma concentrations producing 20% COX-1 inhibition and 80% COX-2 inhibition were 2.46 µg/mL and 1.28 µg/mL, respectively, so that the IC_{20}COX-1:IC_{80}COX-2 potency ratio is approximately 2:1, whilst the IC_{80}COX-1:IC_{80}COX-2 potency ratio is approximately 40:1. These IC concentrations may be compared with mean trough concentrations of mavacoxib in plasma in clinical subjects of 0.52 and 1.11 µg/mL, respectively, after the first and fifth doses. Therefore, clinical doses are predicted to produce low level inhibition of COX-1 and high level inhibition of COX-2.

5.2 Pharmacokinetic particulars

Mavacoxib is well absorbed after oral administration; bioavailability was 87% in fed dogs and 46 % in fasted conditions and the recommended dose is based on administration with food. Therapeutic concentrations in fed dogs are reached rapidly and peak concentrations are obtained in less than 24 hours after administering a dose. Mavacoxib is approximately 98% bound to plasma proteins. It is extensively distributed throughout the body and almost all the mavacoxib-related residues in plasma comprise parent drug. The rate of body clearance of mavacoxib is slow and the major route of elimination is by biliary excretion of the parent drug.

Multiple-dose pharmacokinetic studies provided no evidence that mavacoxib produces autoinhibition or autoinductive changes in its clearance, and it exhibits linear pharmacokinetics with oral doses ranging from 2 to 50 mg/kg. In laboratory studies with young adult dogs, mean elimination half-life values ranged from 13.8 to 19.3 days. Mavacoxib possessed a longer elimination half-life in client-owned animals. Population pharmacokinetic data derived from studies in dogs with a predominantly older population with heavier dogs as compared to the experimental studies (mean 9 years of age) showed that the mean elimination half-life was 39 days with a small sub-population (<5%) having an elimination half-life of more than 80 days and correspondingly an increased exposure was recorded in these individuals. The reason for this longer half-life is unknown. Steady state pharmacokinetics was attained by the fourth treatment in most animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Compressible sugar
Silicified cellulose microcrystalline
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate
Artificial powdered beef flavor

6.2 Major incompatibilities

Not applicable.

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.

6.4 Special precautions for storage

Store below 30℃

6.5 Nature and composition of immediate packaging

Carton boxes containing one blister. Each blister contains two tablets of 20 mg, 30 mg, 75 mg or 95 mg mavacoxib, respectively.
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 from such veterinary medicinal products should be disposed of as a toxic waste. Do not dispose of in the sewage system.

7. MARKETING AUTHORISATION HOLDER

Zoetis Israel Holding B.V.,
5 Atir Yeda Street, Kfar Saba, Israel

8. MARKETING AUTHORISATION NUMBER(S)

Trocoxil 20 mg Chewable Tablets Veterinary: 150-15-33567-00
Trocoxil 30 mg Chewable Tablets Veterinary: 150-14-33568-00
Trocoxil 75 mg Chewable Tablets Veterinary: 150-13-33569-00
Trocoxil 95 mg Chewable Tablets Veterinary: 150-12-33570-00

9. MANUFACTURER

Pfizer Italia S.R.L., Italy; 63046 Localita Morino Del Tronto, Ascoli piceno, Italy

10. DATE OF REVISION OF THE TEXT

Revised in October 2021 according to MOHs guidelines