LAB0221 Prepared: 26/07/2011

LEAFLET

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

RLP Approved

TROCOXIL™
Chewable Tablets for Dogs

Description
Tablets containing 6, 20, 30, 75 or 95 mg of mavacoxib per tablet. Mavacoxib is a COX-2 non-steroidal anti-inflammatory (NSAID) which possesses analgesic and anti-inflammatory properties.

Indications
Dogs: For the treatment of pain and inflammation associated with degenerative joint disease in dogs.

Pharmacology
Pharmacokinetics
Mavacoxib is well absorbed after administration; bioavailability was 87% in fed dogs 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 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 patient studies with a predominantly older population (mean 9 years of age) showed the mean elimination half-life was 39 days with a small sub-population (<5%) having an elimination half-life of more than 80 days. Steady state pharmacokinetics was attained by the fifth to seventh dose in most patients. No association was demonstrated between plasma concentration and the incidence of adverse events.

Pharmacodynamics
Mavacoxib is a non-steroidal anti-inflammatory drug (NSAID) of the coxib class. Mavacoxib is a 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 synthesising 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 third and fifth doses. Therefore, clinical doses are predicted to produce low level inhibition of COX-1 and high level inhibition of COX-2.

DIRECTIONS FOR USE:
THIS IS NOT A DAILY TREATMENT
Restraint
NOT TO BE USED in food producing species of animals.

Contraindications:
Contraindicated for use in animals suffering from gastro-intestinal ulceration or bleeding, or where there is evidence of a haemorrhagic disorder.
Contraindicated for use in pregnant, breeding or lactating animals, in cases of impaired liver or kidney function, heart insufficiency, or if there is known hypersensitivity to sulphonamides. Contraindicated for use in dehydrated dogs.

The safety of mavacoxib in dogs younger than 12 months or less than 5kg, or in pregnant, breeding or lactating dogs has not been established, therefore TROCOXIL is not recommended for use in these classes of dog.

Precautions:
Mavacoxib exhibits an extended plasma half-life (up to >80 days, see pharmacokinetics section) due to its low rate of elimination and bio-accumulative effects. 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.

Trocoxil was found to have a narrow (2.5x) safety margin in a number of dogs included in the studies, with mongrel dogs having more frequent and severe adverse effects than beagles. The clinician should also take into account that the study used younger dogs, and therefore it is important that a higher level of monitoring is a feature of treatment of older dogs.

Other NSAIDs or glucocorticoids should not be used concurrently or within at least 1 month of the last administration of Trocoxil. 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 medicinal products should be avoided.

Animals should be carefully monitored if mavacoxib is administered simultaneously with an anticoagulant. Trocoxil is highly protein bound. The potential for increased free drug and therefore potentially increased risk of adverse events should be considered when treating dogs with hypoproteinaemia, reduced plasma protein binding ability (such as in aged dogs) or dogs receiving concurrent medications which may compete for protein binding.

Avoid use in dehydrated, hypovolaemic or hypotensive animals, as there is a potential risk of increased renal toxicity. Ensure appropriate hydration and haemodynamic status when animals receiving mavacoxib undergo anaesthesia and/or surgical procedures or develop conditions which may result in dehydration or compromised haemodynamic status. Patients with underlying renal disease may experience exacerbation or decompensation of their renal disease while on NSAID therapy.

Caution should be exercised in patients that have previously shown adverse reactions to drugs of the non-steroidal anti-inflammatory class.

Side Effects:
Typical adverse drug reactions of NSAIDs such as loss of appetite, diarrhoea, vomiting, apathy and a change in kidney biochemistry parameters and impaired kidney function have occasionally been reported. Adverse reactions of the digestive tract such as vomiting, diarrhoea were commonly reported, loss of appetite, haemorrhagic diarrhoea and malaena 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. Note that TROCOXIL™ has an extended duration of effect (up to 2 months after administration of the second dose and following doses). Adverse reactions could occur at any timepoint during this period.

This product may exacerbate pre-existing renal, hepatic and gastrointestinal lesions.

If an adverse reaction to the administration of mavacoxib occurs, no further tablets should be administered and general supportive therapy, as applied to clinical overdosage 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 may continue once the supportive therapy is discontinued.

Dosage and Administration:

THIS IS NOT A DAILY TREATMENT.
The oral dose of TROCOXIL™ Chewable Tablets is 2 mg / kg bodyweight.
The initial dose should be repeated 14 days later, thereafter the dosing interval is **one month**. A treatment cycle with TROCOXIL™ should not exceed 7 consecutive doses (6.5 months).

As the bioavailability of mavacoxib when given with food is nearly twice that in fasted dogs, treatment should be given immediately before or during the animal's main meal. Care should be taken to ensure that the tablet is ingested.

Use the number of tablets given in the table below at each dose

Body weight (kg)	Number of tablets				
	6 mg	20 mg	30 mg	75 mg	95 mg
5 – 6 *	2				
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	

* Correct dose for dogs less than 5kg cannot be achieved with TROCOXIL Tablets

Do not exceed the stated dose as indicated on the dosing table.

SAFETY DIRECTIONS: Harmful if swallowed. May irritate the eyes. Do not swallow. Avoid contact with eyes. Wash hands after use.

WARNING/SAFETY PRECAUTION – Ingestion of Mavacoxib can be harmful to children, and prolonged gastrointestinal and pharmacological effects may be observed upon accidental ingestion. To avoid accidental ingestion administer the tablet to the dog immediately after removal from the blister package.

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. *Phone Australia 131126;New Zealand 0800 764 766.*

Additional information is in the Material Safety Data Sheet

Storage
Store below 30°C (Room Temperature).

Presentation
TROCOXIL™ Chewable Tablets are triangular with a mottled brown appearance. There is a dose descriptor on the obverse and the Pfizer script on the reverse. Blister packs contain two tablets of the same strength per pack, each tablet containing 6 mg. 20 mg, 30 mg, 75 mg or 95 mg of mavacoxib.

Disposal
Dispose of empty container by wrapping with paper and putting in garbage.

WARRANTY
The manufacturer of this animal remedy extends/grants to the purchaser a warranty that this animal remedy is reasonably fit for the purposes for which its use is recommended, provided that the purchaser uses the remedy only for the purposes for which it is recommended and strictly in accordance with the directions on this container.

APVMA Approval Nos. 64462/48415, 64463/48416, 64464/48417, 64465/48418, 64466/48419

Pfizer Animal Health
A division of Pfizer Australia Pty Ltd
38-42 Wharf Road
West Ryde NSW 2114

Technical Information
Australia - 1800 814 883 TOLL FREE from anywhere in Australia

Pfizer [logo]

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CARTON
MAIN PANEL

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

TROCOXIL™
20 mg
Chewable Tablets for Dogs

20 mg/tablet MAVACOXIB

For the treatment of pain and inflammation associated with degenerative joint disease in dogs.

2 tablets

Pfizer[logo]

SIDE PANEL 1

TROCOXIL™ 20 mg **ChewableTablets for Dogs**

SIDE PANEL 2

EAN Barcode

END FLAP

Store below 30°C (Room Temperature).
batch
Expiry:

LAB0221 Prepared: 26/07/2011

CARTON
BACK PANEL

READ THE ENCLOSED LEAFLET BEFORE USING THIS PRODUCT

DIRECTIONS FOR USE
Restraint
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THIS IS NOT A DAILY TREATMENT
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APVMA Approval No. 64465/48418

Made in Italy
Pfizer Animal Health
A division of Pfizer Australia Pty Ltd
38-42 Wharf Rd
West Ryde NSW 2114.

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BLISTER FOIL
MAIN PANEL

To use UK/IE blister foil.