1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Milbactor 12.5 mg/125 mg tablets for dogs weighing at least 5 kg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances		
Milbemycin Oxime	12.5	mg
Praziquantel	125.0	mg
Excipients		

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Yellowish-white with brown spots, round, slightly biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Target Species

Dogs (weighing at least 5 kg).

4.2 Indications for use, specifying the target species

In dogs: treatment of mixed infections by adult cestodes and nematodes of the following species:

- Cestodes:
Dipylidium caninum
Taenia spp.
Echinococcus spp.
Mesocestoides spp.

- Nematodes:
Ancylostoma caninum
Toxocara canis
Toxascaris leonina
Trichuris vulpis
Crenosoma vulpis (Reduction of the level of infection)
Angiostrongylus vasorum (Reduction of the level of infection by immature adult (L5) and adult parasite stages; see specific treatment and disease prevention schedules under section 4.9 ''Amounts to be administered and administration route'')

Thelazia callipaeda (see specific treatment schedule under section 4.9 ''Amounts to be administered and administration route'')

The product can also be used in the prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

4.3 Contraindications

Do not use in dogs weighing less than 5 kg.
Do not use in case of hypersensitivity to the active substances or to any of the excipients.
See also point Special precautions for use.

4.4 Special warnings for each target species

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class.

4.5 Special precautions for use

Special precautions for use in animals

Studies with milbemycin oxime indicate that the margin of safety in certain dogs of Collie or related breeds is less than in other breeds. In these dogs, the recommended dose should be strictly observed.
The tolerance of the product in young puppies from these breeds has not been investigated.
Clinical signs in Collies are similar to those seen in the general dog population when overdosed (see in point 4.10).

Treatment of dogs with a high number of circulating microfilariae can sometimes lead to the appearance of hypersensitivity reactions, such as pale mucous membranes, vomiting, trembling, laboured breathing or excessive salivation. These reactions are associated with the release of proteins from dead or dying microfilariae and are not a direct toxic effect of the product. The use in dogs suffering from microfilaremia is thus not recommended.

In heartworm risk-areas, or in the case it is known that a dog has been travelling to and from heartworm risk regions, before using the product, a veterinary consultation is advised to exclude the presence of any concurrent infestation of *Dirofilaria immitis*. In the case of a positive diagnosis, adulticidal therapy is indicated before administering the product.

Echinococcosis represents a hazard for humans. In case of Echinococcosis, specific guidelines on the treatment and follow up and on the safeguard of persons have to be followed. Experts or institutes of parasitology should be consulted.

No studies have been performed with severely debilitated dogs or individuals with seriously compromised kidney or liver function. The product is not recommended for such animals or only according to a benefit/risk assessment by the responsible veterinarian.

In dogs less than 4 weeks old, tape worm infection is unusual. Treatment of animals less than 4 weeks old with a combination product may therefore not be necessary.

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

Wash hands after use.
In the event of accidental ingestion of the tablets, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the doctor.

4.6 Adverse reactions (frequency and seriousness)

On very rare occasions, systemic signs (such as lethargy), neurological signs (such as muscle tremors and ataxia) and/or gastrointestinal signs (such as emesis, diarrhoea, anorexia and drooling) have been observed in dogs after administration of the combination of milbemycin oxime and praziquantel.

4.7 Use during pregnancy, lactation or lay

The product may be used in breeding dogs including pregnant and lactating bitches.

4.8 Interaction with other medicinal products and other forms of interaction

No interactions were observed when the recommended dose of the macrocyclic lactone selamectin was administered during treatment with the combination of milbemycin oxime and praziquantel at the recommended dose. In the absence of further studies, caution should be taken in the case of concurrent use of the product and other macrocyclic lactones. Also, no such studies have been performed with reproducing animals.

4.9 Amounts to be administered and administration route

Oral use.
Dogs should be weighed to ensure accurate dosing
Minimum recommended dose rate: 0.5 mg of milbemycin oxime and 5 mg of praziquantel per kg are given once orally.
The product should be administered with or after some food.

Depending on the bodyweight of the dog, the practical dosing is as follows:

Body weight	**Tablets**
5 – 25 kg	1 tablet
>25 – 50 kg	2 tablets
>50 – 75 kg	3 tablets

In cases when heartworm disease prevention is used and at the same time treatment against tapeworm is required, the product can replace the monovalent product for the prevention of heartworm disease.

For treatment of *Angiostrongylus vasorum* infections, milbemycin oxime should be given four times at weekly intervals. It is recommended, where concomitant treatment against cestodes is indicated, to treat once with the product and continue with the monovalent product containing milbemycin oxime alone, for the remaining three weekly treatments.

In endemic areas administration of the product every four weeks will prevent angiostrongylosis by reducing immature adult (L5) and adult parasite burden, where concomitant treatment against cestodes is indicated.

For the treatment of *Thelazia callipaeda*, milbemycin oxime should be given in 2 treatments, seven days apart. Where concomitant treatment against cestodes is indicated, the product can replace the monovalent product containing milbemycin oxime alone.

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

No data available.

4.11 Withdrawal period(s)

Not applicable.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endectocides, Macrocyclic lactones
ATCvet code: QP54AB51

5.1 Pharmacodynamic properties

Milbemycin oxime belongs to the group of macrocyclic lactones, isolated from the fermentation of *Streptomyces hygroscopicus* var. *aureolacrimosus*. It is active against mites, against larval and adult stages of nematodes as well as against larvae of *Dirofilaria immitis*.
The activity of milbemycin is related to its action on invertebrate neurotransmission: Milbemycin oxime, like avermectins and other milbemycins, increases nematode and insect membrane permeability to chloride ions via glutamate-gated chloride ion channels (related to vertebrate $GABA_A$ and glycine receptors). This leads to hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the parasite.
Praziquantel is an acylated pyrazino-isoquinoline derivative. Praziquantel is active against cestodes and trematodes. It modifies the permeability for calcium (influx of Ca^{2+}) in the membranes of the parasite inducing an imbalance in the membrane structures, leading to membrane depolarisation and almost instantaneous contraction of the musculature (tetany), rapid vacuolization of the syncytial tegument and subsequent tegumental disintegration (blebbing), resulting in easier expulsion from the gastrointestinal tract or death of the parasite.

5.2 Pharmacokinetic properties

After oral administration of praziquantel in the dog, after a small amount of food, peak serum levels of parent are rapidly attained (T_{max} approximately 0.25-2.5 hours) and decline quickly ($t_{1/2}$ approximately 1 hour); there is a substantial hepatic first-pass effect, with very rapid and almost complete hepatic biotransformation, principally to monohydroxylated (also some di- and tri-hydroxylated) derivatives, which are mostly glucuronide and/or sulfate conjugated before excretion. Plasma binding is about 80%. Excretion is fast and complete (about 90% in 2 days); the principal route of elimination is renal.
After oral administration of milbemycin oxime in dogs, after a small amount of food, peak plasma levels occur at about 0.75-3.5 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 1-4 days. Bioavailability is about 80%.
In the rat, metabolism appears to be complete although slow, since unchanged milbemycin oxime has not been found in urine or faeces. Main metabolites in the rat are monohydroxylated derivatives, attributable to hepatic biotransformation. In addition to relatively high liver concentrations, there is some concentration in fat, reflecting its lipophilicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Lactose monohydrate
Povidone
Croscarmellose sodium
Silica, colloidal anhydrous
Meat Flavour
Yeast powder
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. This veterinary medicinal product does not require any special temperature storage conditions.

6.5 Nature and composition of immediate packaging

Blister packs consisting of cold formed OPA/Al/PVC foil and aluminium foil.
Box with 1 blister of 4 tablets.
Box with 12 blisters, each blister contains 4 tablets.
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 derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
The product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

7 MARKETING AUTHORISATION HOLDER

Krka, d.d., Novo mesto
Šmarješka cesta 6,
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

VPA10774/030/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th January 2015

10 DATE OF REVISION OF THE TEXT

October 2017