SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TermaFlea Combo 402 mg/361.80 mg Spot-on Solution for Extra Large Dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pipette of 4.02 ml contains:

Active substances:

Fipronil	402.00 mg
(S)-methoprene	361.80 mg

Excipients:

Butylhydroxyanisole (E320)	0.80 mg
Butylhydroxytoluene (E321)	0.40 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Spot-on solution.
Clear amber solution.

4. CLINICAL PARTICULARS

4.1 Target Species

Dogs (40-60 kg).

4.2 Indications for use, specifying the target species

For the treatment of dogs weighing over 40 kg bodyweight:
- To be used against infestations with fleas, alone or in association with ticks and/or biting lice.
- Treatment of flea infestations (*Ctenocephalides* spp.). Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity) and larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for eight weeks after application.

- Treatment of tick infestations (*Ixodes ricinus*, *Dermacentor variabilis*, *Dermacentor reticulatus*, *Rhipicephalus sanguineus*). The product has a persistent acaricidal efficacy for up to 4 weeks against ticks.
- Treatment of infestations with biting lice (*Trichodectes canis*).

4.3 Contraindications

In the absence of available data, do not use the product on puppies less than 8 weeks old and/or weighing less than 2 kg.
Do not use on sick (e.g. systemic diseases, fever) or convalescent animals.
Do not use in rabbits, as adverse reactions, including death, could occur.
In the absence of studies, the use of the product is not recommended in non-target species.
This product is specifically developed for dogs. Do not use in cats and ferrets, as this could lead to overdosing.
Do not use in known cases of hypersensitivity (allergy) to the active substances (Fipronil or (S)-methoprene) or to any other excipients (ingredients).

4.4 Special warnings for each target species

Bathing/immersion in water within 2 days after application of the product and more frequent bathing than once a week should be avoided, as no study has been performed to investigate how this affects the efficacy of the product. Emollient shampoos can be used prior to treatment but reduce the duration of protection against fleas to approximately 5 weeks when used weekly after application of the product. Weekly bathing with a 2% chlorhexidine medicated shampoo did not affect efficacy against fleas during a 6 weeklong study.

Fleas from pets often infest the animal's basket, bedding and regular resting areas such as carpets and soft furnishings which should be treated, in case of massive infestation and at the beginning of the control measures, with a suitable insecticide and vacuumed regularly. When treating infestations of parasites, all in-contact animals should be treated with an appropriate product at the same time.

4.5 Special precautions for use

Special precautions for use in animals

For external use only. Do not administer orally.
Avoid contact with the animal's eyes. If the product is in contact with eyes, rinse immediately with plenty of water.
It is important to make sure that the product is applied to an area where the animal cannot lick it off and to make sure that animals do not lick each other following treatment. Do not apply the product on wounds or skin lesions.

The attachment of single ticks after treatment cannot be ruled out . Therefore, the transmission of infectious diseases cannot be completely excluded if conditions are unfavourable.

For use during pregnancy, lactation or lay see section 4.7.

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

Keep the pipettes in the original packaging until ready to use and dispose of used pipettes immediately.

People with a known hypersensitivity (allergy) to insecticides or alcohol should avoid contact with the product.
This product can cause mucous membrane, skin and eye irritation. Therefore, contact of the product with mouth, skin and eyes should be avoided.
Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water.
After accidental ocular exposure the eye should be rinsed carefully with clean water. If eye irritation persists, seek medical advice immediately and show the package leaflet or label to the physician.
Wash hands after use.
Treated animals should not be handled until the application site is dry, and children should not be allowed to play with treated animals until the application site is dry. It is therefore recommended that animals are not treated during the day, but should be treated during the early evening, and that recently treated animals are not allowed to sleep with owners, especially children.
Do not smoke, drink or eat during application.

Other precautions
Fipronil and (S)-methoprene may adversely affect aquatic organisms. Dogs should not be allowed to swim in watercourses for 2 days after application.

The alcohol carrier may have adverse effects on painted, varnished or other household surfaces or furnishings.

4.6 Adverse reactions (frequency and seriousness)

Among the very rare suspected adverse reactions, transient skin reactions on the application site (skin discoloration, local hair loss, itching, redness) and general itching or hair loss have been reported after use. Excessive salivation, reversible nervous signs (increased sensitivity to stimulation, depression, other nervous signs), vomiting or respiratory symptoms have also been observed after use.
If licking occurs, a brief period of excessive salivation may be observed due mainly to the nature of the carrier. 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).

4.7 Use during pregnancy and lactation

The product can be used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use simultaneously with other flea products which are applied directly on to the animal.

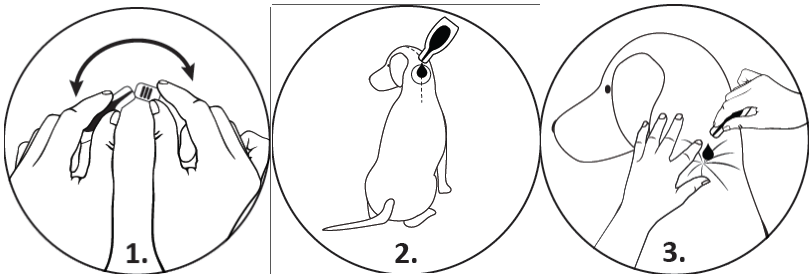
4.9 Amounts to be administered and administration route

For external use only, topical spot-on application to the skin. Animals should be weighed accurately prior to treatment.

One pipette of 4.02 ml (S) per dog weighing over 40 kg and up to 60 kg, corresponding to a minimum recommended dose of 6.7 mg/kg for fipronil and 6 mg/kg for (S)-methoprene.

Do not overdose.
In the absence of safety studies, the minimum treatment interval is 4 weeks.

Method of administration:
Hold the pipette upright. Tap the narrow part of the pipette to ensure the contents remain within the main body of the pipette. Snap back the tip. Part the coat on the back of the animal at the base of the neck in front of the shoulder blades until the skin is visible. Place the tip of the pipette on the skin and squeeze the pipette several times to empty its contents completely and directly onto the skin in one spot.



Temporary changes to the coat (clumped/greasy hair) may be noted at the application site.

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

No adverse effects were observed in target animal safety studies in 8 week-old puppies, growing dogs and dogs weighing about 2 kg treated once at five times the recommended dose. The risk of experiencing adverse effects (see section 4.6) may however increase when overdosing, so animals should always be treated with the correct pipette size according to bodyweight.

4.11 Withdrawal Period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Ectoparasiticides for topical use.
ATC vet code: QP53AX65

5.1 Pharmacodynamic properties

Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by interacting with ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarines. Fipronil kills fleas within 24 hours and ticks (*Dermacentor reticulatus, Dermacentor variabilis, Rhipicephalus sanguineus, Ixodes ricinus*), and lice within 48 hours post-exposure.

(S)-Methoprene is an insect growth regulator (IGR) of the class of compounds known as juvenile hormone analogues that inhibit the development of immature stages of insects. This compound mimics the action of juvenile hormone and causes impaired development and death of the developing stages of fleas. The on-animal ovicidal activity of (S)- methoprene results from either direct penetration of the eggshell of newly laid eggs or from absorption through the cuticle of the adult fleas. (S)-methoprene is also effective in preventing flea larvae and pupae from developing, which prevents contamination of the environment of treated animals with the immature stages of fleas.

5.2 Pharmacokinetic properties

Studies of metabolism of fipronil have demonstrated that the major metabolite is the sulfone derivative of fipronil. (S)-methoprene is extensively degraded into carbon dioxide and acetate that are subsequently incorporated into endogenous materials.

The pharmacokinetic profiles after topical application of fipronil and (S)-methoprene in combination were studied in dogs in comparison to intravenous dosing of fipronil or (S)-methoprene alone. This established absorption and other pharmacokinetic parameters. The topical application resulted in low systemic absorption of fipronil (11%) with a mean maximum concentration (C_{max}) of approximately 35 ng/ml fipronil and 55 ng/ml of fipronil sulfone in plasma.

Peak fipronil plasma concentrations are slowly attained (mean t_{max} approximately 101 h) and decline slowly (mean terminal half-life approximately 154 h, highest values are observed for males). Fipronil is extensively metabolised to fipronil sulfone after topical administration.
Plasma concentrations of (S)-methoprene were below the limit of quantitation (20 ng/ml) in dogs after topical application.

Both (S)-methoprene and fipronil, together with its major metabolite, are well-distributed in the haircoat of a dog within one day after application. The concentrations of fipronil, fipronil sulfone and (S)-methoprene in the hair coat decrease with time and are detectable for at least 60 days after dosing. Parasites are killed through contact rather than systemic exposure.

No pharmacological interaction between fipronil and (S)-methoprene was noted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxyanisole (E320)
Butylhydroxytoluene (E321)
Ethanol, anhydrous
Polysorbate 80 (E433)
Povidone
Diethylene glycol monoethyl ether

6.2 Major 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

Do not store above 30°C.
Store in the original package.

6.5 Nature and composition of immediate packaging

A white pipette composed of a heat-formed shell of composed of polypropylene/cyclic olefin copolymer/polypropylene layer and polyethylene/ethylene vinyl alcohol/polyethylene layer.

1, 2, 3, 4, 5 or 6 pipettes in individual foil sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
Fipronil and (S)-methoprene should not enter water courses as this may be dangerous for fish and other aquatic organisms.

7. MARKETING AUTHORISATION HOLDER

EU Pharmaceuticals Ltd
37 Geraldine Road
London
SW18 2NR

8. MARKETING AUTHORISATION NUMBER

Vm 39787/4133

9. DATE OF THE FIRST AUTHORISATION

05 November 2021

10. DATE OF REVISION OF THE TEXT

March 2023

Approved 03 March 2023