SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

AMFLEE combo 402 mg/ 361.8 mg spot-on solution for extra large dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4.02 ml pipette contains:

Active substance:

Fipronil	402 mg
S-Methoprene	361.8 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 yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs over 40 kg

4.2 Indications for use, specifying the target species

For the treatment of dogs, dosage defined by bodyweight grouping (refer to section 4.9):

- 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 persistent acaricidal efficacy for up to 4 weeks against ticks.
- Treatment of infestations with biting lice (*Trichodectes canis*).

The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD), where this has been previously diagnosed by a veterinary surgeon.

4.3 Contraindications

In the absence of available data, the product should not be used 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 due to a risk of adverse reactions or even death.
This product is specifically developed for dogs. Do not use in cats and ferrets, as this could lead to overdosing.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

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 week long study.
For the treatment and control of flea allergy dermatitis it is recommended that allergic patients and all other animals in the household should be treated on a regular basis.
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.

4.5 Special precautions for use

i) Special precautions for use in animals

The attachment of single ticks after treatment cannot be ruled out. Therefore the transmission of infectious disease cannot be completely excluded if conditions are unfavourable.
For external use only. Do not administer orally.
Avoid contact with the eyes of the animal. If the product is in contact with eyes, rinse immediately with plenty of water.
Do not apply the product on wounds or skin lesions.
It is important to make sure that the veterinary medicinal product is applied directly onto an area of dry skin where the animal cannot lick it off and to make sure that animals do not lick each other following treatment.
Wait for the application site to dry before allowing the treated dog to come into contact with valuable fabrics or furnishings.

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

This product can cause mucous membrane, skin and eye irritation. Therefore, contact of the product with mouth, skin and eyes should be avoided.

People with known hypersensitivity to fipronil or s-methoprene and/or any of the ingredients should avoid contact with the veterinary medicinal product.
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 in clean water.
Wash hands after use.
In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician.
Do not smoke, drink or eat during application.
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.
Keep pipettes in the original packaging until ready to use, and dispose of used pipettes immediately.

iii) Other precautions

Dogs should not be allowed to swim in watercourses for 2 days after application (see section 6.6).

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.

In the case of licking the administration site, 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, lactation or lay

Can be used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

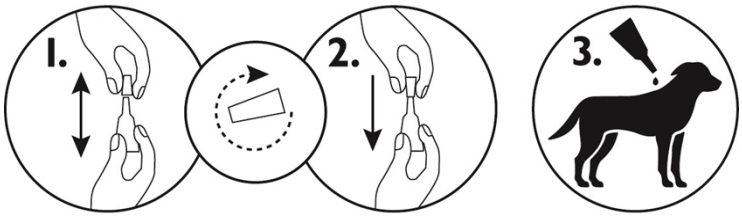
External use only, spot-on use.

Administer by topical application to the skin; one pipette of 4.02 ml (402 mg fipronil + 361.8 mg (S)-methoprene) per dog weighing over 40 kg. This corresponds to a minimum recommended dose of 6.7 mg/kg for fipronil and 6 mg/kg for (S)-methoprene, by topical application to the skin.

In the absence of safety studies the minimum treatment interval is 4 weeks.

Method of administration:

1. Remove the pipette from its packaging. Hold the pipette in an upright position, twist and pull the cap off.
2. Turn the cap around and place the other end of the cap back on the pipette. Push and twist the cap to break the seal, then remove the cap from the pipette.
3. 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 onto 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, incl. Insecticides, fipronil combinations.
ATCvet 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 scapularis, Ixodes ricinus, Haemaphysalis longicornis, Haemaphysalis flava, Haemaphysalis campanulata*) 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 the treated animals with the immature stages of fleas.

5.2 Pharmacokinetic particulars

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)
Povidone (K25)
Polysorbate 80
Ethanol 96 per cent
Diethylene glycol monoethyl ether

6.2 Major incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years

6.4 Special precautions for storage

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

6.5 Nature and composition of immediate packaging

White polypropylene unit-dose pipette with polyethylene or polyoxymethylene closure with spike packaged into laminated triplex bag composed of polyester, aluminium and polyethylene.
Cardboard box containing 1, 3, 6, 10, 30 pipettes.
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

Vm 01656/4112

9. DATE OF FIRST AUTHORISATION

13 July 2016

10. DATE OF REVISION OF THE TEXT

April 2021

Approved 22 April 2021