SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

AMFLEE combo 50 mg/60 mg spot-on solution for cats and ferrets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 ml pipette contains:

Active substances:

Fipronil	50 mg
S-Methoprene	60 mg

Excipients:

Butylhydroxyanisole (E320)	0.1 mg
Butylhydroxytoluene (E321)	0.05 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

Cats and ferrets.

4.2 Indications for use, specifying the target species

In cats:
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 4 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity), larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for six weeks after application.
- Treatment of tick infestations (*Ixodes ricinus, Dermacentor variabilis, Rhipicephalus sanguineus*). The product has a persistent acaricidal efficacy for up to 2 weeks against ticks.
- Treatment of infestations with biting lice (*Felicola subrostratus*).

In ferrets:
To be used against infestations with fleas, alone or in association with ticks:

- Treatment of flea infestations (*Ctenocephalides* spp.). Insecticidal efficacy against new infestations with adult fleas persists for 4 weeks. Prevention of the

multiplication of fleas by inhibiting the development of eggs (ovicidal activity), larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas.
- Treatment of tick infestations (*Ixodes ricinus*). The product has a persistent acaricidal efficacy for 4 weeks against ticks.

4.3 Contraindications

In the absence of available data, the product should not be used on kittens less than 8 weeks old and/or weighing less than 1 kg. The product should not be used on ferrets less than 6 months old.
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.
Do not use in case of hypersensitivity (allergy) to Fipronil or (S)-methoprene or to any other ingredients. In the absence of studies, the use of the product is not recommended in non-target species.

4.4 Special warnings for each target species

All stages of fleas can infest the cat's basket, bedding, and regular resting areas such as carpets and soft furnishings. In cases of massive flea infestation and at the beginning of the control measures these areas should be treated with a suitable environmental insecticide product and vacuumed regularly. When treating infestations of parasites, all in-contact animals should be treated with an appropriate product at the same time.

No data on the effect of bathing/shampooing on the efficacy of the product in cats and ferrets are available. However, based on information available for dogs shampooed as from 2 days after application of the product, it is not recommended to bath animals within 2 days after application of the product.

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. For use during pregnancy or lay see section 4.7.

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 (allergy) to fipronil, (s)-methoprene, polysorbates, alcohol, or additives E320 or E321, 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 eye contact, rinse carefully in clean water.
Wash hands after use.
If the product is accidentally swallowed, 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.

Other precautions

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 (scaling, 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) or vomiting 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

In cats
Laboratory studies in cats have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
The product can be used during pregnancy
The potential toxicity of the product for kittens of less than 8 weeks of age in contact with a treated queen is not documented. Special care should be taken in this case.

In ferrets
The safety of the veterinary medicinal product has not been established in ferrets during pregnancy and lactation. Use only according to the risk-benefit assessment by the responsible veterinarian.

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.

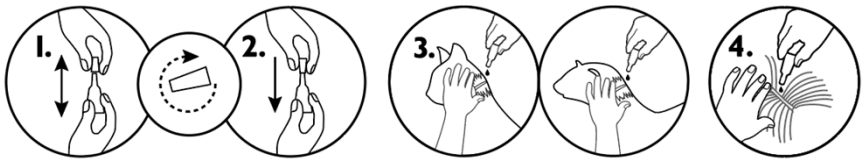
4.9 Amounts to be administered and administration route

For external use only, topical spot-on application to the skin.

One pipette of 0.5 ml per cat, corresponding to a minimum recommended dose of 5 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.

One pipette of 0.5 mL per ferret corresponding to a dose of 50 mg for fipronil and 60 mg for (S)-methoprene per ferret, by topical application to the skin.
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.



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

The risk of experiencing adverse effects may increase with overdosing (see section 4.6).

In cats
No undesirable effects were observed in target animal safety studies in cats and kittens aged 8 weeks and older and weighing about 1 kg treated once a month at five times the recommended dose for six consecutive months.
Itching may occur following treatment.
Overdose application of the product will cause a sticky appearance of hairs at the treatment spot. However, should this occur, it will disappear within 24 hours post application.

In ferrets
In ferrets aged 6 months and older and treated once every 2 weeks for four treatments, at five times the recommended dose, body weight loss was observed in some animals.

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, ticks (*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 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 cats in comparison to intravenous dosing of fipronil or (S)-methoprene alone. This established absorption and other pharmacokinetic parameters under conditions mimicking clinical practice. The topical application, with additional potential oral exposure from licking, resulted in overall systemic absorption of fipronil (18%) with a mean maximum concentration (C_{max}) of approximately 100 ng/ml fipronil and 13 ng/ml of fipronil sulfone in plasma.
Peak fipronil plasma concentrations are rapidly attained (mean t_{max} approximately 6 h) and decline with a mean terminal half-life of approximately 25 h.

Fipronil is slightly metabolised to fipronil sulfone in cats.

Plasma concentrations of (S)-methoprene were generally below the limit of quantitation (20 ng/ml) in cats after topical application.

Both (S)-methoprene and fipronil, together with its major metabolite, are well-distributed in the haircoat of cats 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 59 days after dosing. Parasites are killed through contact rather than by systemic exposure.
No pharmacological interaction between fipronil and (S)-methoprene was noted.

The pharmacokinetic profile of the product has not been investigated in ferrets.

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 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 products 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

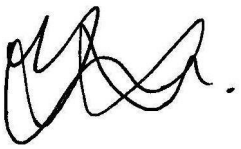
Vm 01656/5039

9. DATE OF FIRST AUTHORISATION

13 July 2016

10. DATE OF REVISION OF THE TEXT

September 2022



Approved: 30 September 2022