SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Frontline Combo 134.00 mg / 120.60 mg spot-on solution for dog M

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pipette of 1.34 ml contains:

Active substances:

Fipronil .....134.00 mg
(S)-methoprene.....120.60 mg

Excipients:

Butylhydroxyanisole (E320) .....0.27 mg
Butylhydroxytoluene (E321).....0.13 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear amber spot-on solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs (weighing 10 to 20 kg bw).

4.2 Indications for use, specifying the target species

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 of 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 veterinary medicinal product has a persistent acaricidal efficacy for up to 4 weeks against ticks.

- Treatment of infestations with biting lice (*Trichodectes canis*).

The veterinary medicinal product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

4.3 Contraindications

In the absence of available data, the veterinary medicinal product should not be used on puppies less than 8 weeks old.
Do not use in rabbits, as adverse reactions with even mortality could occur. In absence of studies, the use of the veterinary medicinal product is not recommended in non-target species.
Do not use on sick (e.g. systemic diseases, fever) or convalescent animals.
This veterinary medicinal product is specifically developed for dogs. Do not use in cats and ferrets, as this could lead to overdosing.
Do not use in cases of hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings for each target species

Unnecessary use of antiparasitics or use deviating from the instructions given in the SPC may increase the resistance selection pressure and lead to reduced efficacy.
The decision to use the product should be based on confirmation of the parasitic species and burden, or of the risk of based on its epidemiological features, for each individual animal.
Bathing/immersion in water within 2 days after application of the veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal product. Weekly bathing with a 2% chlorhexidine medicated shampoo did not affect efficacy against fleas during a 6 week long study.
There may be an attachment of a few ticks. For this reason a transmission of infectious diseases cannot be completely excluded if conditions are unfavourable.
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.
Other animals living in the same household should also be treated with a suitable product.

4.5 Special precautions for use

<u>Special precautions for use in animals</u>

Avoid contact with the animal's eyes.
It is important to make sure that the veterinary medicinal 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.

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

This veterinary medicinal product can cause mucous membrane, skin and eye irritation. Therefore, contact of the veterinary medicinal product with mouth, skin and eyes should be avoided.
People with a known hypersensitivity to fipronil or (S)-methoprene, or alcohol 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 with pure water.

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.

Special precautions for the protection of the environment

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

Other precautions
Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Dogs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Application site reactions (skin discoloration[1], hair loss[1], itching[1], reddening[1]). Generalised itching or hair loss. Hypersalivation[2], vomiting, respiratory signs. Increased sensitivity to stimulation[3], depression[3], other nervous signs[3].

[1] Transient.
[2] If licking occurs, a brief period of hypersalivation may be observed due mainly to the nature of the carrier.
[3] Reversible.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details..

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 Amount(s) to be administered and administration route

Spot-on use.

The minimum dose is 6.7 mg/kg bw of fipronil and 6 mg/kg bw of (S)-methoprene, corresponding to one pipette of 1.34 ml (M) per dog (weighing over 10 and up to 20 kg). To ensure a correct dosage, body weight should be determined as accurately as possible. Underdosing could result in ineffective use and may favour resistance development.

For infestations with fleas and/or ticks, the need for and frequency of re-treatment(s)should be based on professional advice and should take into account the local epidemiological situation and the animal's lifestyle.
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

Do not overdose.
No adverse events 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 events (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 QP53

ATCvet code: QP53AX65

The veterinary medicinal product is an insecticidal and acaricidal solution for topical use, containing an association of an adulticidal active ingredient, fipronil, in combination with an ovicidal and larvicidal active ingredient, (S)-methoprene.

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 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 hair coat 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
Polysorbate 80 (E433)
Polyvidone
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: 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

Nature of primary packaging

A green pipette composed of a heat-formed shell (polyacrylonitrile-methyl acrylate copolymer / polypropylene) and a film (polyacrylonitrile-methyl acrylate copolymer / aluminium / polyethylene terephthalate).
Or
A green pipette composed of a heat-formed shell (polyethylene / ethylene vinyl alcohol / polyethylene / polypropylene / cyclic-olefin-copolymer / polypropylene) and a film (polyethylene / ethylene vinyl alcohol / polyethylene / aluminium / polyethylene terephthalate).

Sales presentation(s) and administrative number(s) of identification

Blister card of 1 x 1.34 ml pipette with a scored tip
Box of 1 blister card of 3 x 1.34 ml pipettes with a scored tip
Box of 1 blister card of 4 x 1.34 ml pipettes with a scored tip
Box of 2 blister cards of 3 x 1.34 ml pipettes with a scored tip

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

Medicines should not be disposed of via wastewater.
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
The veterinary medicinal product should not enter water courses as fipronil and (S)-methoprene may be dangerous for fish and other aquatic organisms. Do not contaminate ponds, waterways or ditches with the veterinary medicinal product or empty containers.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Animal Health UK Limited
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vm 08327/5014

9. DATE OF FIRST AUTHORISATION

29 January 2004

10. DATE OF REVISION OF THE TEXT

October 2024

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Find more product information by searching for the ‘Product Information Database’ or ‘PID’ on www.gov.uk.

Approved 15 October 2024

Gavin Hall