SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Frontline Tri-Act spot-on solution for dogs 10-20 kg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml pipette contains:

Active substance(s)
Fipronil…….. 135.2 mg
Permethrin…… 1009.6 mg

Excipient(s)
N-methyl pyrrolidone…… 787.4 mg
Butylhydroxytoluene (E321)…….. 2.250 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Spot-on solution
Clear colourless to yellow-brown solution

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

In dogs:
For the treatment and prevention of flea (killing effect) and/or tick (killing and repellent effects) infestations where repellent activity is necessary against mosquitoes, sandflies and/or biting flies.

- Fleas

Treatment and prevention of *Ctenocephalides felis* flea infestations and prevention of *Ctenocephalides canis* flea infestations. One treatment prevents new flea infestations for 4 weeks.
The product can be used as part of a treatment strategy for flea allergy dermatitis where this has been previously diagnosed by a veterinarian.

- Ticks

Treatment and prevention of tick infestations (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus*). One treatment kills (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus*) and repels (*Ixodes ricinus, Rhipicephalus sanguineus)* ticks for 4 weeks after treatment, and repels *Dermacentor reticulatus* from 7 days up to 4 weeks after treatment.

- Mosquitoes and sandflies

Repels (anti-feeding activity) sandflies (*Phlebotomus perniciosus*) for 3 weeks and mosquitoes *(Culex pipiens, Aedes albopictus*) for 4 weeks.
Kills sandflies (*Phlebotomus perniciosus)* and mosquitoes *(Aedes albopictus)* for 3 weeks.

- Biting flies (Stable flies)

Repels (anti-feeding activity) and kills stable flies (*Stomoxys calcitrans*) for 5 weeks.

4.3 Contraindications

Do not use on sick or convalescent animals.
This product is for use on dogs only. Do not use in cats and rabbits, as adverse reactions and even death could occur (see also section 4.5).
Do not use in cases of hypersensitivity to the active substances or to any of the excipients. (see also section 4.5).

4.4 Special warnings for each target species

There may be an attachment of single ticks or bites by single mosquitoes or sandflies. For this reason, transmission of pathogens by these arthropods cannot be completely excluded if conditions are unfavorable. Single ticks may attach and detach within the first 24 hours after infestation and if ticks are present when the product is applied not all ticks may be killed within 48 hours after treatment.
The product remains effective against fleas when treated animals are immersed in water occasionally (*e.g.*, swimming, bathing). However, dogs should not be allowed to swim or be shampooed within 48 hours after treatment. Avoid frequent swimming or shampooing of treated dogs as this may adversely affect maintenance of product effectiveness.
To reduce re-infestation from emergence of new fleas, it is recommended that all dogs in a household be treated. Other animals living in the same household should also be treated with a suitable product. To aid further in reducing environmental challenge, the additional use of a suitable environmental treatment against adult fleas and their developmental stages could be recommended.

4.5 Special precautions for use

Special precautions for use in animals
In the absence of specific studies, the use of the product is not recommended in dogs younger than 8 weeks of age, or in dogs weighing less than 2 kg.

Care should be taken to avoid contact of the veterinary medicinal product with the dog's eyes.
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 other animals do not lick the treatment sites following application.
Animals should be weighed accurately prior to treatment.
Seek veterinary advice if the product is accidentally ingested or comes into contact with your dog's eyes.
Due to the unique physiology of cats which prevents them from metabolizing certain compounds, including permethrin, the product can induce potentially fatal convulsions in this species. In case of accidental dermal (skin) exposure, wash the cat with shampoo or soap, and seek veterinary advice rapidly. To prevent cats from being accidentally exposed to the product, keep treated dogs away from cats until the application site is dry. It is important to ensure that cats do not groom the site of application on a dog which has been treated with this product. In case of exposure of this type seek veterinary advice immediately.
Do not use in cats and rabbits.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This product can cause skin and eye irritation, therefore, avoid contact of the product with skin and eyes. Do not open the pipette near or towards the face. In case of ocular (eye) exposure or if eyes become irritated during administration, immediately flush the eyes with plenty of water. If ocular (eye) irritation persists, seek medical attention. In case of dermal (skin) exposure or if skin becomes irritated during administration, immediately wash the skin with plenty of soap and water. If skin irritation persists or recurs, seek medical attention.
People with known hypersensitivity to fipronil and/or permethrin should avoid contact with the product.
The product is harmful if swallowed. Avoid hand-to-mouth contact. Do not smoke, drink or eat during application. Wash hands after use. If swallowed rinse mouth and seek medical attention if you feel unwell.
Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. The veterinary medicinal product should not be administered by pregnant women and women suspected of being pregnant. Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product by women of childbearing age.
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 the stored pipettes in the original blister and once used, the empty pipette should immediately be disposed of appropriately, preventing further access.

Other precaution
The product may adversely affect aquatic organisms. Treated dogs should not be allowed to enter surface water for 2 days after treatment.

4.6 Adverse reactions (frequency and seriousness)

Transient skin reactions at the application site (skin discolouration, local hair loss, itching, redness) and general itching, hair loss and erythema (redness) have been reported very rarely after use. Reversible nervous signs (increased sensitivity to stimulation, hyperactivity, muscle tremor, lethargy, ataxia (loss of coordination), other nervous signs), vomiting, anorexia (not eating) and hypersalivation have also been reported very rarely after use.
If licking of the application site occurs, transient hypersalivation and emesis (vomiting) may be observed.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s)) during the course of one treatment)
- 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

Laboratory studies using fipronil or permethrin have not produced any evidence of teratogenic (capable of causing embryonic or foetal malformation) or embryotoxic (capable of causing toxicity to the embryo) effects. The safety of the veterinary medicinal product has not been established in dogs during pregnancy and lactation or in animals intended for breeding.
Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects.Use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use simultaneously with other products active against fleas, ticks or flies which are applied directly on to the animal.

4.9 Amounts to be administered and administration route

For external use.

The recommended minimum dose is 6.76 mg fipronil/kg bodyweight, and 50.48 mg/kg permethrin equivalent to 0.1 ml spot-on solution per kg bodyweight.

The use of the product should be based on a confirmed infestation or risk of infestation with fleas and/or ticks when repellent activity is also necessary against mosquitoes, sandflies and/or biting flies. Depending on the ectoparasite challenge repetition of the treatment might be indicated. In such instances, the interval between two treatments should be at least 4 weeks.

<u>Method of administration:</u>
Spot-on use.

Select the appropriate pipette size for the weight of the dog. For dogs over 60 kg, use the appropriate combination of two pipette sizes that most closely matches the bodyweight.
The product should be applied in two out-of-reach spots so that the dog cannot lick the application site. These sites are at the base of the neck in front of the shoulder blades and the middle of the neck between the base of the skull and the shoulder blades.
Remove the blister card from the package and separate one blister. Remove the pipette by cutting along the dotted line with a pair of scissors or tearing open after folding the marked corner. Holding the pipette upright away from face and body, cut the pipette tip with scissors to open. Part the coat on the back of the dog until the skin is visible. Place the tip of the pipette on the skin. Squeeze the pipette, applying about half of the contents half way down the neck between the base of the skull and the shoulder blades. Repeat the application at the base of the neck in front of the shoulder blades to empty the pipette. For best results, ensure that the product is applied directly to the skin rather than on the hair.

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

Safety has been assessed with up to 5 times the maximum dose in healthy adult dogs (treated up to 3 times at monthly intervals) and in puppies (aged 8 weeks treated once). Known side-effects may consist of mild neurological signs, emesis (vomiting) and diarrhea. These are transitory and generally resolve without treatment within 1-2 days.

The risk of experiencing adverse reactions (see section 4.6) may increase with overdosing, so animals should always be treated with the correct pipette size according to bodyweight.

4.11 Withdrawal period

Not applicable

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Ectoparasiticides for topical use, ATCvet code: QP53AX65 (fipronil, combination).

5.1 Pharmacodynamic properties

Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. Fipronil and its metabolite fipronil sulfone act at ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA) as well as desensitising (D) and non-desensitising (N) channels gated by glutamate (Glu, unique invertebrate ligand-gated chloride channels), 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 arthropods.
Permethrin belongs to the Type I class of pyrethroids, which are acaricides and insecticides with repellent activity.

Pyrethroids affect the voltage-gated sodium channels in vertebrates and non-vertebrates. Pyrethroids are so-called “open channel blockers” affecting the sodium channel by slowing both the activation and the inactivation properties, thus leading to hyper-excitability and death of the parasite. Permethrin in the product provides repellent activity (anti-feeding activity) against sandflies (> 80% for 4 weeks), mosquitoes and ticks.
In one experimental study, the product had a faster onset on flea adulticidal activity than fipronil alone at 7 and 14 days after treatment administration.

Speed of kill
The product kills new infesting fleas (*C. canis, C. felis*) within 6 hours from 2 days after treatment and for a full month. *C. felis* fleas already present on dogs when the treatment is applied are killed in 24 hours. Speed of kill against pre-existing *C. canis* has not been evaluated.
The product kills new infesting ticks (*R. sanguineus* and *I. ricinus*) within 6 hours from 2 days after treatment and for a full month. Ticks (*R. sanguineus, I. ricinus, D. reticulatus*) already present on dogs when the treatment is applied are killed in 48 hours.

In one experimental study, the product was shown to indirectly reduce the risk of transmission of *Babesia canis* from infected *Dermacentor reticulatus* ticks from 7 days after application up to 4 weeks, thereby reducing the risk of canine babesiosis in treated dogs in this study.
In one experimental study, the product was shown to indirectly reduce the risk of transmission of *Ehrlichia canis* from infected *Rhipicephalus sanguineus* ticks, from 7 days after application up to 4 weeks, thereby reducing the risk of ehrlichiosis in treated dogs in this study.
However, the effectiveness of the product at reducing the transmission of infectious agents following natural exposure under field conditions has not been investigated.

5.2 Pharmacokinetic particulars

The pharmacokinetic profiles of fipronil and permethrin in combination were studied after topical application in dogs by measuring plasma and hair concentrations for 58 days following treatment. Both permethrin and fipronil, together with its major metabolite, fipronil sulfone, are well- distributed on the haircoat of a dog during the first day after application. The concentrations of fipronil, fipronil sulfone and permethrin in the hair coat decrease with time and are detectable for at least 58 days after dosing.
Fipronil and permethrin act topically upon contact with external parasites and the low systemic absorption of fipronil and permethrin is not relevant for the clinical efficacy.
The spot-on application resulted in negligible systemic absorption of permethrin with sporadic measureable concentrations of cis-permethrin between 11.4 ng/mL and 33.9 ng/mL observed 5 to 48 hours following treatment.
Mean maximum plasma concentrations (Cmax) of 30.1 ± 10.3 ng/ml fipronil and 58.5 ± 20.7 ng/ml of fipronil sulfone were observed between Day 2 and 5 (Tmax) following application. Fipronil plasma concentrations then decline with a mean terminal half-life of 4.8 ± 1.4 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-methyl pyrrolidone
Butylhydroxytoluene (E321)
Medium-chain triglycerides

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

Store in the original blister.
Do not store above 25°C.

6.5 Nature and composition of immediate packaging

The primary packaging is a heat-formed film of polyethylene-ethylvinyl alcohol-polyethylene/polypropylene.
The secondary packaging consists of a plastic/aluminium blister with a plastic/aluminium backing.

Plastic card of 1 pipette containing 2 ml.
Carton box of 3 or 6 pipettes containing 02 ml each.
One size only per box.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
The product may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty container.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

Vm 08327/4283

9. DATE OF FIRST AUTHORISATION

02 July 2018

10. DATE OF REVISION OF THE TEXT

September 2023

Approved 28 September 2023