

Atrevia® XR Medium

Oral Ectoparasiticide of Immediate Action and 3 months Duration

Highly Palatable Soft Chews

Controls Fleas, Ticks and Mites on Dogs

Veterinary Use



Composition

Medium dogs (10 to 20 kg)

Each 4,000 mg chewable tablet contains:

Fluralaner.....	500 mg
Excipients and flavorings... q.s.ad.....	1 tablet

Pharmaceutical form

Atrevia® XR Medium is a soft, chewable tablet with a very pleasant taste for dogs. It is brown in color (light to dark) in the shape of a truncated cone. It can appear marbled, mottled, or both.

Features

Atrevia® XR Medium is a novel systemic ectoparasitic treatment against fleas, ticks and mites, based on fluralaner[®], which protects dogs for 03 months. You can use it on infested animals or as a preventive. Control flea infestation in the environment and areas where the treated dog has access. It begins its action in 90 minutes and kills fleas in 8 hours and ticks in 12 hours. There are 4 commercial presentations according to the weight of the dog.

Atrevia® XR Medium is highly effective against fleas (*Ctenocephalides felis* and *Ctenocephalides canis*), ticks of different species in dogs (*Rhipicephalus sanguineus*, *Ixodes hexagonus*, *Ixodes scapularis*, *Ixodes ricinus*, *Ixodes holocyclus*, *Dermacentor reticulatus*, and *Dermacentor reticulatus* var. skin and ear (*Demodex canis*, *Sarcoptes scabiei* var. *canis* and *Otodectes cynotis*). Effectiveness has also been observed against other ectoparasites such as lice (*Linognathus* spp.) and bed bugs (*Triatoma infestans*), a vector that transmits Chagas disease (American trypanosomiasis).

Atrevia® XR Medium can be used from 8 weeks old and 2 kg of weight and can be administered without restrictions in young or adult dogs, breeders, pregnant and lactating females, as well as in Collie breed dogs. Due to its systemic action, it does not require additional precautions for the treated pet to come into contact with other animals or humans.

Mechanism of Action, Pharmacokinetics and Pharmacodynamics

Atrevia® XR Medium contains fluralaner[®], a new molecule belonging to the class of isoxazolines. It represents a new class of potent parasiticide for the control of fleas, ticks and mites in dogs. It is a powerful blocker that acts in a non-competitive antagonistic way on the chloride channels of ionotropic receptors (γ-aminobutyric acid (GABA) and L-glutamate receptors) of the arthropod nervous system. It is much more selective for receptors in arthropods than in mammals, including humans (hence its large margin of safety). This coupling to the chloride channels of nerve and muscle cells blocks the transmission of nerve impulses from the parasite. Fleas, ticks, mites and other affected ectoparasites are paralyzed and die quickly.

Fluralaner acts systemically, that is, after ingestion, it is absorbed into the blood, quickly through which it is distributed throughout the body of the treated animal. Thus, ectoparasites are affected and die when exposed to the dog's blood.

The life cycle of the ectoparasite is interrupted because:

- An orally administered dose of fluralaner[®] begins to eliminate fleas (*Ctenocephalides felis*) in the dog from 90 minutes after treatment.
- Oral administration of fluralaner[®] through chewable tablets has been shown to be effective in controlling flea and tick infestations for up to a minimum of 98 days in dogs.
- It has been shown that fluralaner can interfere with oviposition (egg laying), larval development (thus indicating its larvicidal action) and flea (*Ctenocephalides felis*) reproduction in vitro.
- Fluralaner[®] contributes to the control of the environmental population of fleas in areas visited by treated dogs.

Fluralaner has shown significantly higher efficacy than other currently available molecules. In the same way, "in vitro" studies showed that parasites with reduced sensitivity to other molecules did not have any resistance to the action of fluralaner (against amidines, organophosphates, cyclodienes, macrocyclic lactones, phenylpyrazoles, benzophenyl-ureas, pyrethroids or carbamates). To date, there are no reports of resistance to fluralaner by fleas or ticks of dogs. Isoxazolines do not appear to be cross-resistant with other antiparasitics that act on the same receptors.

Fluralaner is readily and rapidly absorbed after single-dose oral administration, having a very long residual period. Due to the reduced bioavailability of the drug in the fastest state, fluralaner should be administered with food. Fluralaner is distributed systemically and reaches the highest concentrations in fat tissue, followed by liver, kidney and muscle. It has been shown that single doses of 12.5, 25 and 50 mg/kg bw, resulted in the verification of the maximum concentration (C_{max}) in plasma on day 1 after treatment.

Long-term systemic persistence, slow clearance from plasma (t_{1/2} = 12 days), and lack of extensive metabolism provide effective concentrations of fluralaner during the interval between doses. Individual variation was observed in C_{max} and t_{1/2}. Peak concentrations of fluralaner can be considered to be between 2 hours and 3 days, and the elimination half-life ranges from 9.3 to 16.2 days after oral administration.

Approximately 90% of the dose of fluralaner is excreted unchanged in the faeces, its main route of elimination. The renal route is the minor route of elimination.

Target Species

Dogs.

Indications of use

For the control of infestations of the main ectoparasites in dogs (ticks, fleas and mites) during 12 weeks. Insecticide and systemic acaricide of immediate action.

- Treatment and prevention of flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*). Additionally, it controls the infestation of fleas in the environment and areas where the animal has access.
- Treatment and prevention of infestations by ticks (*Ixodes ricinus*, *Ixodes hexagonus*, *Ixodes scapularis*, *Ixodes holocyclus*, *Dermacentor reticulatus*, *Dermacentor variabilis* and *Rhipicephalus sanguineus* (adults and juveniles)).
- Treatment of skin mite infestations: demodicosis (*Demodex canis*) and sarcoptic mange (*Sarcoptes scabiei* var. *canis*).

- Treatment of infestations by ear mites (*Otodectes cynotis*).
- Treatment of infestations by bed bugs of the *Triatoma infestans* species.
- Treatment and prevention of lice infestations (*Linognathus* spp.) for 7 weeks.
- Control of flea bite allergy dermatitis (FAD), as part of a therapeutic strategy.
- Protection against infections by *Babesia canis* (transmitted by ticks of the genus *Dermacentor reticulatus*).

Additional considerations regarding indications for use:

- The effectiveness of the product is linked to the attachment of fleas and ticks to the host and at the beginning of their feeding in order to be exposed to fluralaner. This effect occurs within 8 hours post fixation in the case of fleas and 12 hours post fixation in the case of ticks.
- The preventive effect against reinfestations is the result of adulticidal activity, a reduction in egg production (fleas die before producing viable eggs), and their non-viability (very low concentrations of fluralaner stop production of viable eggs by fleas) and for its effect against the development of immature stages (ticks) and persists up to 12 weeks after a single administration of **Atrevia® XR Medium**.
- The residual effect of **Atrevia® XR** on flea and tick control, after one application, has been shown to be maintained for a minimum of 98 days.
- **Atrevia® XR** contributes to the control of the environmental population of fleas in areas visited by treated dogs. Indeed, it has been shown that the environmental effect of **Atrevia® XR** is capable of reducing flea infestations in untreated canines living in the same environment as treated canines.
- In laboratory studies, fluralaner has also shown efficacy against mosquito larvae (*Aedes aegypti*) and calipharids (*Lucilia cuprina*), adult female *Rhipicephalus* (*Boophilus*) *microplus*, and nymphs of soft ticks (*Ornithodoros moubata*).

Route of Administration and Dosage, Considerations and Guidelines for its Correct Administration

Atrevia® XR Medium is administered orally, according to the following table (the doses correspond to 25-56 mg of fluralaner/kg of body weight within each weight range):

Atrevia® XR Soft chewable tablets						
Product	Pet's size	Body weight	Tablet 1,000 mg Fluralaner 125 mg	Tablet 2,000 mg Fluralaner 250 mg	Tablet 4,000 mg Fluralaner 500 mg	Tablet 8,000 mg Fluralaner 1 g
Atrevia® XR Mini	Mini dogs	2 - 4.5 kg	△			
Atrevia® XR Small	Small dogs	4.5 - 10 kg	△	△		
Atrevia® XR Medium	Medium dogs	10 - 20 kg		△	△	
Atrevia® XR Large	Large dogs	20 - 40 kg			△	△

* For dogs weighing more than 40 kg, administer an appropriate combination of tablets.

Dosage frequency:

- Administer one **Atrevia® XR** tablet every 3 months. The product can be administered throughout the year. **Atrevia® XR** should be administered with food or immediately before or after eating. Do not divide the tablets.
- For the treatment of demodicosis, sarcoptic and/or otodectid scabies, administer a single dose. Since demodicosis is multifactorial, it is advisable to diagnose and treat any underlying disease. The need and frequency of retreatment should follow the advice of the veterinarian.
- The absence of mites can be confirmed by two consecutive scrapings every 15-30 days. If the mite infestation recurs, consult your veterinarian. For ear mite infestations, a veterinary check is necessary 28 days after treatment. The vet will decide if any additional treatment is necessary.
- The application of **Atrevia® XR** helped to significantly reduce the clinical signs related to acroasis, such as the presence of plaques, scales and crusts; papules and pustules; alopecia and erythema.

Atrevia® XR Medium is a highly palatable, soft and chewable tablet, which facilitates its administration. Alternatively, if applicable, it can be administered with food or by opening the animal's mouth and placing the tablet in the deep back of the tongue like any other medicine.

Treatment with **Atrevia® XR Medium** can be started at any time of the year, preferably starting one month before the fleas become active and then continuously according to the previously mentioned time interval. In areas where fleas are present throughout the year, treatment should be extended throughout the year, without interruption. To eradicate the possibility of flea reinfestation, it is recommended to treat all the animals in the house at the same time.

In dogs older than 8 weeks, treatment every 2 months has been shown to be well tolerated. Puppies should be weighed regularly. Rapidly growing puppies that exceed the initial weight band during the re-treatment interval can be re-treated for fleas and ticks at 2-month intervals. Treatment can be tailored by the veterinarian to suit individual weight changes.

Studies carried out did not show statistical differences between treatment with **Atrevia® XR** and another commercial product based on fluralaner.

Tolerance and Safety

Studies have shown that **Atrevia® XR** is completely safe for use in the treatment and control of the main ectoparasites in naturally infested canines.

Fluralaner has been shown to be safe in:

- *Breeding, pregnant or lactating females.* In a reproductive study, adult Beagle dogs were treated up to 3 times the recommended dose, 3 treatments at 8 week intervals, starting 12 weeks (males) and 4 weeks (females) prior to anticipated copulation. Treatment continued in males until the females were delivered, and in females until the offspring were weaning. No adverse effects were observed either in the adults, nor in their reproductive performance, nor in the number of puppies born or survivors.
- *Puppies from 8 weeks of age or over 2 kg.* Indeed, during three treatments with intervals shorter (8 weeks) than those recommended, Beagle puppies treated at 1, 3 and 5 times the maximum recommended dose (for effect at 120 days: = 25 to ~ 60 mg/kg), tolerated the treatment very well. No dose-dependent effects related to the product were observed on food consumption, body weight, clinical parameters, physical variables, or clinical pathology.
- *Collie breed dogs and dogs lacking multi-drug resistance protein 1 (MDR1).* The safety and tolerance of fluralaner has been measured in Collie dogs with a proven mutation of the MDR1 gene (multidrug resistant gene), treating them with 168 mg/kg of b.w. (3 times the recommended dose for the effect at 120 days), showing that fluralaner is very safe in dogs with this genetic condition, since no clinical signs associated with neurotoxicity were observed, in addition, no adverse reaction was observed during the 112 days of post-treatment observation). The same was observed in healthy Beagle breed dogs, administering doses of up to 280 mg/kg (5 times the recommended dose for the effect at 120 days), at intervals of 8 weeks, not giving rise to any findings related to the treatments, that could be contrasted by clinical and pathological observation or in the macro and microscopic post-mortem examination.

From the foregoing, it follows that, according to the maximum dose used in the studies with fluralaner -280 mg/kg (more than 11 times the clinical dose for the effect at 120 days) - it presents a safety dose of up to 8 times, higher than that of other isoxazolines.

Safety data collected on fluralaner during field studies in Europe and the USA showed that treated animals generally tolerate the product well at the recommended dose. In European studies, mild and transient diarrhea, vomiting, poor appetite and excessive salivation were

observed in 1.6% of dogs in the first few days after treatment. Studies have shown that **Atrevia® XR** is very well tolerated, reporting adverse effects in only 1.36% of cases.

Regarding the safety of the owner, as fluralaner is administered orally and acts systemically, no chemical residues are found on the dog's coat after treatment. For this reason, unlike products for topical administration, there is no risk of contamination or toxicity in other animals, humans (especially children) by direct contact with treated animals.

Finally, taking into account its action mechanism, fluralaner is extremely selective for arthropod receptors over those of mammals, including humans, further extending its large margin of safety.

Adverse reactions

- Tolerance and safety studies with **Atrevia® XR** reported unwanted reactions in 1.36% of the treated animals, being vomiting (0.54%) diarrhea, lethargy and polydipsia (0.27% each) the only ones found.
- Despite the fact that there are reports of neurological reactions due to individual causes after the application of fluralaner, in studies carried out with **Atrevia® XR** no case could be evidenced. However, if any are reported, an immediate visit to the veterinarian should be made to evaluate the animal.
- In general, dogs tolerate fluralaner very well at the therapeutic dose apart from the possible adverse reactions mentioned.
- A potential mistake when treating dogs that can cause overdose and therefore should be avoided is the administration to small dogs of tablets approved only for larger dogs.
- If you observe or suspect any serious reaction or others not mentioned, contact your veterinarian immediately.

Contraindications

- Do not use in case of known hypersensitivity to any of the active substances or to any excipient.
- There are no known contraindications to the use of the product.
- Do not use in dogs with severe liver disease or severe hypoproteinemia.

Precautions

- Do not use in dogs less than 8 weeks old or less than 2 kg in weight.
- Do not split or divide the **Atrevia® XR Medium** tablets.
- Do not administer **Atrevia® XR Medium** to animals of less weight, approved for dogs of greater body weight.
- Do not administer **Atrevia® XR Medium** at intervals of less than 8 weeks.
- When starting treatment, the risk of transmission of diseases mediated by ectoparasites is greatly reduced due to the rapid onset of action of **Atrevia® XR Medium**. However, as the parasites must initiate feeding in the pet to be exposed to fluralaner, the risk of the transmission of these diseases cannot be excluded.
- To help control the flea population, it is recommended to treat all the animals in the house with **Atrevia® XR Medium** at the same time.
- Fleas frequently infest the animal's basket, bedding, and usual resting areas, such as carpets and textiles, which should be treated with a suitable insecticide and vacuumed in case of massive infestation at the beginning of treatment.
- Fluralaner is a member of the isoxazoline class. This class has been associated with neurological adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class medications, even in dogs without a history of seizures. Use cautiously in dogs with a history of seizures or neurological disorders.
- Keep the product in the aluminum blister until use.
- Do not eat, drink or smoke while handling the tablets.
- Wash your hands after handling the tablets.
- Agrovect Market S.A. is not responsible for the consequences derived from the use (of the product) different from that indicated in this insert.

Interactions with other drugs and other forms of interaction

- None known.
- Due to its high binding to plasma proteins, fluralaner could act competitively with other drugs with similar pharmacological characteristics, including non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, etc. Incubation of fluralaner in the presence of carprofen or warfarin in dog plasma at expected maximum plasma concentrations did not reduce the binding of fluralaner, carprofen, or warfarin proteins.
- The safety of fluralaner in combination with other active substances such as deltamethrin, milbemycin oxime, moxidectin, pyrantel, ivermectin or praziquantel has been documented.

Storage

Store in a cool and dry place, in its original container, protected from light between 15 °C and 30 °C. Keep out of the reach of children and pets.

Commercial presentation

Atrevia® XR Medium is presented in:
Box x 1, 2 or 4 soft chews in sealed aluminized blister x 4,000 mg - Medium Dogs.

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¹ The chemical name for fluralaner is (±)-4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl] benzamide.

² Atrevia® XR