

- 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 adductival 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 Large**.
- 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 calipharis (*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 Large 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		Tablet 8,000 mg Fluralaner 1 g
			Fluralaner 125 mg	Fluralaner 250 mg	
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 demodetic, sarcoptic and/or otodectic scabies, administer a single dose. Since demodetic mange 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 acarosis, such as the presence of plaques, scales and crusts; papules and pustules; alopecia and erythema.

Atrevia® XR Large 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 Large** 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 observation¹. The same was observed¹ 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 Large** tablets.
- Do not administer **Atrevia® XR Large** to animals of less weight, approved for dogs of greater body weight.
- Do not administer **Atrevia® XR Large** 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 Large**. 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 Large** 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.
- Agrovét 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, praziquantel, 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 Large is presented in:
Box x 1, 2 or 4 soft chews in sealed aluminized blister x 8,000 mg - Large Dogs.

Reg. SENASA Peru: F.87.31.N.0478; Reg. Nicaragua: MV-14074.

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Atrevia® XR Large

Ectoparasiticida Oral de Acción Inmediata y de 3 Meses de Duración

Tabletas Blandas Masticables (Soft Chews) Altamente Palatables

Controla Pulgas, Garrapatas y Ácaros en Perros

Uso Veterinario



Composición

Perros large (20 a 40 kg)

Cada tableta masticable de 8,000 mg contiene:

Fluralaner..... 1 g
Excipientes y saborizantes c.s.p..... 1tableta

Forma Farmacéutica

Atrevia® XR Large es una tableta blanda, masticable y de muy agradable sabor para los perros. Es de color marrón (de claro a oscuro) en forma de cono trunco. Puede presentar un aspecto marmoleado, moteado, o ambos.

Características

Atrevia® XR Large es un novedoso tratamiento ectoparasitario sistémico contra pulgas, garrapatas y ácaros, en base a **fluralaner**¹, que protege a los perros por 3 meses. Puede utilizarse en animales infestados o como preventivo. Controla la infestación de pulgas en el medio ambiente y áreas donde el perro tratado tiene acceso. Empieza su acción en 90 minutos y mata a las pulgas en 8 horas y a las garrapatas en 12 horas. Existen 4 presentaciones comerciales de acuerdo al peso del perro.

Atrevia® XR Large es altamente efectivo contra pulgas (*Ctenocephalides felis* y *Ctenocephalides canis*), garrapatas de diferentes especies en perros (*Rhipicephalus sanguineus*, *Ixodes hexagonus*, *Ixodes scapularis*, *Ixodes ricinus*, *Ixodes holocyclus*, *Dermacentor reticulatus*, *Dermacentor variabilis*, *Ixodes* spp.: ninfas y larvas) y ácaros de la piel y oído (*Demodex canis*, *Sarcoptes scabiei var. canis* y *Otodectes cynotis*). También se ha observado efectividad contra otros ectoparásitos como piojos (*Linognathus* spp.) y chinches o chinchachas (*Triatoma infestans*), vector que transmite la enfermedad de chagas (tripanosomiasis americana).

Atrevia® XR Large puede utilizarse desde las 8 semanas y 2 kg de peso y puede administrarse sin restricciones en reproductores, hembras en gestación y lactación, lo mismo que en perros de raza Collie. Por su acción sistémica, no requiere de precauciones adicionales para que la mascota tratada entre en contacto con otros animales o seres humanos.

Mecanismo de Acción, Farmacocinética y Farmacodinamia

Atrevia® XR Large contiene **fluralaner**, molécula nueva perteneciente a la clase de las isoxazolinas. Representa una nueva clase de parasiticida potente para el control de pulgas, garrapatas y ácaros en perros. Es un potente bloqueador de canales iónicos que actúa de forma antagónica no competitiva sobre los canales de cloruro de los receptores ionotrópicos (receptores de ácido γ -aminobutírico (GABA) y L-glutamato-) del sistema nervioso de los artrópodos. Es mucho más selectivo para los receptores de artrópodos que de mamíferos, incluidos seres humanos (de allí su gran margen de seguridad). Dicho acople a los canales de cloruro de las células nerviosas y musculares, bloquea la transmisión de los impulsos nerviosos del parásito. Pulgas, garrapatas, ácaros y otros ectoparásitos afectados quedan paralizados y mueren rápidamente.

Fluralaner actúa de modo sistémico, es decir, tras la ingestión, se absorbe a la sangre, rápidamente a través de la cual se distribuye por todo el cuerpo del animal tratado. Es así que los ectoparásitos se afectan y mueren cuando se exponen a la sangre del perro.

El ciclo de vida del ectoparásito se ve interrumpido porque:

- Una dosis administrada vía oral de **fluralaner**² comienza a eliminar pulgas (*Ctenocephalides felis*) en el perro desde los 90 minutos posteriores al tratamiento.
- La administración oral de **fluralaner**² a través de tabletas masticables ha demostrado efectividad en el control de infestaciones de pulgas y garrapatas hasta por un mínimo de 98 días en perros.
- Se ha demostrado que **fluralaner** puede interferir con la oviposición (puesta de huevos), el desarrollo larvario (indicado así su acción larvicida) y la reproducción de pulgas (*Ctenocephalides felis*) in vitro.
- **Fluralaner**² contribuye al control de la población medio ambiental de pulgas en áreas visitadas por los perros tratados.

Fluralaner ha demostrado una eficacia significativamente superior a otras moléculas actualmente disponibles. De la misma manera, estudios "in vitro" demostraron que los parásitos con sensibilidad reducida a otras moléculas no poseían ninguna resistencia a la acción de **fluralaner** (frente a amidinas, organofosforados, cicloclonos, lactonas macrocíclicas, fenilpirazoles, benzofenil-ureas, piretroides ni carbamatos). A la fecha, no hay reportes de resistencia al **fluralaner** por parte de pulgas o garrapatas de los perros. Al parecer las isoxazolinas no tienen resistencia cruzada con otros antiparasitarios que actúan sobre los mismos receptores.

Fluralaner se absorbe fácil y rápidamente después de la administración oral a dosis única, teniendo un periodo residual muy amplio. Debido a la reducida biodisponibilidad del fármaco en ayunos, **fluralaner** debe administrarse con alimentos. **Fluralaner** se distribuye sistemáticamente y alcanza las concentraciones más altas en tejido graso, seguido por el hígado, riñón y músculo. Se ha demostrado que dosis únicas de 12.5, 25 y 50 mg/kg de p.v., resultaron en la verificación de la concentración máxima (C_{max}) en plasma en el día 1 pos tratamiento.

La persistencia prolongada sistémica, su eliminación lenta desde el plasma (t_{1/2} = 12 días) y la falta de un metabolismo extenso, proporciona concentraciones efectivas de **fluralaner** durante el intervalo entre dosis (siendo aún cuantificable, >10 ng/mL, en el día 84 de tratamiento). Concentraciones cuantificables del fármaco pueden permanecer (menos de lo necesario para la efectividad) hasta por 112 días. Se observó variación individual en la C_{max} y t_{1/2}. Se puede considerar que las concentraciones máximas de fluralaner se alcanzan entre 2 horas y 3 días y la vida media de eliminación oscila entre 9,3 y 16,2 días después de su administración oral.

Aproximadamente, el 90% de la dosis de **fluralaner** se elimina sin alteración excretado con las heces, su principal vía de eliminación. La vía renal es la menor vía de eliminación.

Especies de Destino

Caninos.

Indicaciones de Uso

Para el control de infestaciones de los principales ectoparásitos en perros (garrapatas, pulgas y ácaros) durante 12 semanas. Insecticida y acaricida sistémico de acción inmediata y larga duración.

- Tratamiento y prevención de las infestaciones por pulgas (*Ctenocephalides felis* y *Ctenocephalides canis*). Adicionalmente controla la infestación de pulgas en el medio ambiente y áreas donde el animal tiene acceso.
- Tratamiento y prevención de las infestaciones por garrapatas (*Ixodes ricinus*, *Ixodes hexagonus*, *Ixodes scapularis*, *Ixodes holocyclus*, *Dermacentor reticulatus*, *Dermacentor variabilis* y *Rhipicephalus sanguineus* (adultas y juveniles).

¹ El nombre químico de fluralaner es (4)-4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-metil-N-[2-oxo-2-(2,2,2-trifluoroetilamino)etil] benzamida

² Atrevia® XR

