

Atrevia® One Large

Oral Ectoparasiticide of Immediate Action and Monthly Application

Highly Palatable Soft Chews

Controls Fleas, Ticks and Mites on Dogs

Veterinary Use

petmedica[®]

Composition

Large dogs (20 to 40 kg)

Each soft chew of 8,000 mg contains:

Fluralaner..... 400 mg
Excipients and flavorings q.s.ad..... 1 tablet

Pharmaceutical form

Atrevia® One Large 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® One Large is a novel systemic ectoparasitic treatment against fleas, ticks and mites, based on *fluralaner*¹, which protects dogs up to 30 days. 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® One Large 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® One Large can be used from 8 weeks age 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.

Atrevia® One Large can be used on dogs of any age and is particularly suitable for dogs in the early stages of their life, starting with a monthly flea and tick protection regimen; thus, owners can enjoy their puppies' early life experience with monthly dosing and then easily switch to the longer lasting **Atrevia® XR Large** as the dog reaches six months of age, helping to ensure treatment and consistent compliance. It is an ideal start for dogs in the early stages of their life.

Mechanism of Action, Pharmacokinetics and Pharmacodynamics

Atrevia® One Large 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*² begins to eliminate fleas (*Ctenocephalides felis*) in the dog from 90 minutes after treatment.
- The oral administration of *fluralaner*² through chewable tablets, at the doses present in **Atrevia® One Large**, has shown effectiveness in the control of flea and tick infestations in dogs, for a minimum of 98 days, after 3 applications every 28 days.
- 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, cycloclenens, 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 fasted 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.

Target Species

Dogs.

Indications of use

For the control of infestations of the main ectoparasites in dogs (ticks, fleas and mites) when protection is required for a month, whether in young dogs (e.g. in early stages between 2 to 6 months) or adults. 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 (DAPP), 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, the reduction in egg production (fleas die before producing viable eggs), their non-viability (very low fecundity) and of fluralaner stop production of viable eggs by fleas) and of its effect against the development of immature stages (ticks) and persists up to 4 weeks after a single administration.
- It has been shown that the residual effect of **Atrevia® One** on the control of fleas and ticks, after 3 applications every 28 days, is maintained for up to a minimum of 98 days.
- **Atrevia® One Large** 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® One** is capable of reducing flea infestations in untreated canines that live in the same environment as treated canines.
- In laboratory studies, fluralaner has also shown efficacy against mosquito larvae (*Aedes aegypti*) and caliphards (*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® One Large is administered orally, according to the following table (the doses correspond to 10-22 mg of fluralaner/ kg of body weight within each weight range):

Product	Pet's size	Atrevia® One Soft chewable tablets				
		Body weight	Tablet 1,000 mg Fluralaner 50 mg	Tablet 2,000 mg Fluralaner 100 mg	Tablet 4,000 mg Fluralaner 200 mg	Tablet 8,000 mg Fluralaner 400 mg
Atrevia® One Mini	Mini dogs	2 - 4.5 kg	☐			
Atrevia® One Small	Small dogs	4.5 - 10 kg		☐		
Atrevia® One Medium	Medium dogs	10 - 20 kg			☐	
Atrevia® One Large	Large dogs	20 - 40 kg				☐

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

Dosage frequency

- Administer one **Atrevia® One Large** tablet every 30 days. The product can be administered throughout the year. **Atrevia® One Large** should be administered with food or immediately before or after eating. Do not divide the tablets.
- For the treatment of demodectic, sarcoptic and/or otodectic scabies, administer one dose every 30 days for one to three consecutive months³. **Atrevia® One** has shown 100% effectiveness for the resolution of cases of acarosis (demodicosis, scabies or mixed scabies) after 3 consecutive treatments every 4 weeks. However, since demodectic 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® One** helped to significantly reduce the clinical signs related to acarosis, such as the presence of plaques, scales and crusts; comedones, papules and pustules; alopecia and erythema.

Atrevia® One 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® One 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, monthly treatment has been shown to be well tolerated. Puppies should be weighed regularly. Treatment can be tailored by the veterinarian to suit individual weight changes.

Studies carried out did not show statistical differences between the monthly treatment of **Atrevia® One** and a monthly application based on sarolaner.

Tolerance and Safety

Studies have shown that **Atrevia® One** 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.

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® One** is very well tolerated, reporting adverse effects in only 0.85% 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.

³ Studies have shown that, depending on the severity of the cases of acarosis in canines, 1, 2 or 3 applications of **Atrevia® One** may be necessary every 28 days.

Adverse reactions

- Tolerance and safety studies with **Atrevia® One** reported unwanted reactions in 0.85% of the treated animals, being diarrhea (0.28%), lethargy (0.28%) and polydipsia (0.28%) 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® One** 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 hypoproteinaemia.

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® One Large** tablets.
- Do not administer **Atrevia® One Large** to animals of less weight, approved for dogs of greater body weight.
- Do not administer **Atrevia® One Large** at intervals of less than 30 days.
- When starting treatment, the risk of transmission of diseases mediated by ectoparasites is greatly reduced due to the rapid onset of action of **Atrevia® One 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® One 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.
- Agrovet 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® One Large is presented in:

Box x 1, 2 or 4 soft chews in sealed aluminized blister x 8,000 mg - Large Dogs.

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Strengthening bonds

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¹ The chemical name for fluralaner is (±)-4-[15-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]benzamide.

² **Atrevia® One**