Lufenuron
Technical Profile
Lufenuron

Virbac is proud to have the insect growth regulator (IGR) lufenuron as part of its parasiticide portfolio. Lufenuron is also referred to as an insect development inhibitor (IDI) because of its unique inhibition of the maturation process in fleas and other insects.

**HOW LUFENURON WORKS**

**INDICATIONS**

Lufenuron is indicated for the prevention and control of flea populations. It does this by preventing the development of flea eggs; it does not kill adult fleas. The adult female flea is exposed to the drug when feeding on a treated pet. The drug, which has no deleterious effect on the adult flea, acts to inhibit the development of flea eggs. The mode of action is interference with the synthesis, polymerization, and deposition of chitin, the major supportive component of the flea egg case and cuticle that forms the exoskeleton of larval stages.\(^1\,^2\) Breaking the flea life cycle at the egg stage helps prevent flea populations from infesting both pets and their environments.

An application of an adulticide can be added as needed for adequate control of adult fleas, especially if a pet has repeated exposure to flea-infested animals or environments.
TARGET: FLEAS

Dogs and cats are primary hosts for the most common species, *Ctenocephalides felis*, the cat flea, and for the less common dog flea, *C. canis*. The flea life cycle has 4 stages: egg, larva, pupa, and adult. The female flea lays eggs on the dog. These eggs then fall off the pet into the environment; eggs hatch in 2 to 5 days; larvae feed on organic matter and flea feces for 8 to 15 days, then pupate. Pupae can remain in their cocoons up to 12 months before emerging as adults. Unlike most other flea species, the cat flea remains on its host to feed, mate, and lay eggs. The life cycle can take a few weeks to 12 months. By the time a pet owner sees fleas on a pet, immature stages have been in the environment for 1 to 2 months. The majority of the life cycle (95%) occurs off the dog; adult fleas represent only 5% of the flea population.

>Ctenocephalides felis, the cat flea, is the most common flea infesting dogs.

*Image courtesy of Companion Animal Parasite Council.*
**PHARMACOKINETICS**

Oral administration of lufenuron with a meal is necessary for absorption with maximum concentrations achieved in around 6 hours. Because lufenuron is lipophilic, it accumulates in adipose tissue and is slowly released into the bloodstream. Lufenuron is excreted unchanged in the feces.

Lufenuron is the only systemic IGR available for pets. In contrast to topical products, it provides systemic coverage, is not degraded by sunlight, and is not washed off by water.*

*Individual characteristics may vary by product.

**MODE OF ACTION**

Adult fleas ingest lufenuron when they feed on the blood of their hosts. The drug is passed transovarially to flea eggs, which then fail to hatch. Although the exact mechanism is unknown, lufenuron halts the formation of the exoskeleton by inhibiting chitin synthesis and deposition. Chitin is a polysaccharide that forms the tough exoskeleton of fleas and other arthropods. Microscopic examination of unhatched larvae from eggs of treated fleas revealed that the cuticle, epidermal cells, chorion, and vitelline membrane were affected by lufenuron treatment. Structural defects to these structures are due to the cytotoxic effects of lufenuron. Larval hatching was prevented by ruptures in the cuticle, which tear during the hatching process, resulting in the loss of hemolymph and desiccation of the larva. Tearing of the cuticle was caused by cuticular expansion and muscular movement of the larva within the eggshell.

Lufenuron is toxic to flea eggs, causing structural defects that affect hatching and survival.
EFFICACY

LABORATORY STUDIES

Lufenuron has undergone extensive laboratory testing to evaluate its ability to control flea infestations.

In one study, adult fleas were fed on lufenuron-treated cats. Drug levels in the host blood, flea feces, and flea eggs were measured. Flea egg hatch and larval development were also measured. The level of lufenuron in the host’s blood was strongly correlated with the amount found in the flea eggs and flea feces. The level of lufenuron in the flea eggs was strongly correlated with egg mortality. There was also a direct relationship between the amount of lufenuron in flea feces and the mortality of larvae feeding on the feces. This study demonstrated the efficacy of lufenuron in causing mortality in flea eggs directly and in the free-living flea larvae by ingestion of lufenuron-containing feces distributed in the environment.

In a second study, two groups of 12 dogs were housed in a combination indoor-outdoor habitat. All dogs were infested initially with adult fleas and one group was treated orally with lufenuron every 30 days. Dogs were housed for 3 months and fleas counted throughout the study. The percentage of reduction of fleas recovered from treated dogs compared to control dogs exceeded 90% by study day 35 and 95% by study day 56 (Fig 1).

Figure 1: Percentage of reduction of adult fleas on treated dogs compared to control dogs.

Dogs were experimentally infested on days 0 and 2 and treated on days 7, 37, 68, and 98.

>>> Laboratory studies confirm that lufenuron is effective at inhibiting the development of flea eggs.
Another way to prove the efficacy of lufenuron is by extensively testing it in field studies. The following studies corroborate the excellent results achieved with lufenuron in the laboratory.

In a double-blind study, 213 client-owned dogs with few or no fleas received either lufenuron or a placebo administered orally each month. No other flea treatments were permitted. Flea counts were performed monthly. After 2 months of treatment, the lufenuron-treated dogs showed significantly fewer fleas than the control dogs ($P<.05$). The difference remained significant throughout the 6 months of the study (Fig 2). No adverse effects were noted.

Figure 2. The effect of lufenuron on prevention of flea infestations.
<table>
<thead>
<tr>
<th>Study Purpose</th>
<th>Study Description and Results</th>
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<tbody>
<tr>
<td>A 3-year study evaluating the ability of lufenuron to protect households against flea infestation&lt;br&gt;• Pets in 15 treatment households received oral lufenuron and pets in 13 controlled households received a placebo yeast tablet monthly for 3 years&lt;br&gt;No flea infestations developed in any of the lufenuron treated households. All of the control households developed active flea infestations.&lt;br&gt;• In control households, after documentation of a flea infestation, each pet in the household was treated with an adulticide and placed on oral lufenuron&lt;br&gt;All infestations were eliminated within 30 to 60 days and there were no recurrences during the 3-year duration of the study.</td>
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<td>A 3-month study evaluating the efficacy of a combination oral treatment with lufenuron and nitenpyram in 18 flea-infested households&lt;br&gt;• All pets in all households were treated orally with lufenuron every 28 to 30 days for 3 months&lt;br&gt;• 10 households: nitenpyram once every 48 hours&lt;br&gt;• In 8 households: nitenpyram as needed&lt;br&gt;In all households, flea populations on pets were reduced by at least 97.3% within 7 days and by as much as 100% at 84 to 90 days.&lt;br&gt;Premise flea counts were reduced by as much as 89.5% by day 28 and by as much as 100% at 84 to 90 days.</td>
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<td>A 1-year study evaluating the combined use of lufenuron and nitenpyram compared to topical treatment with imidacloprid in 45 flea-infested households&lt;br&gt;Households were randomly assigned to 1 of 3 treatments:&lt;br&gt;1. Lufenuron administered orally once a month and nitenpyram administered orally once weekly for 6 weeks to all pets.&lt;br&gt;2. Lufenuron administered orally once a month and nitenpyram administered orally twice weekly to all pets.&lt;br&gt;3. Imidacloprid administered topically once monthly to all pets.&lt;br&gt;Most homes treated with lufenuron and nitenpyram achieved 79.8% to 100% reduction in flea counts; control with imidacloprid achieved 35.2% to 92.8% reduction in flea counts (Fig 3).&lt;br&gt;Environmental flea counts were reduced to 0 (with 1 exception) from weeks 8 through 52 for lufenuron/nitenpyram households.&lt;br&gt;Fleas were found at various times throughout the 52-week period in all imidacloprid households.</td>
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A 57-day study evaluating the efficacy of lufenuron in combination with nitenpyram in 3 dogs living on a heavily infested horse farm\textsuperscript{10}

- Dogs were previously treated topically with imidacloprid every month prior to the use of lufenuron and nitenpyram
- Dogs were treated orally with lufenuron once monthly and treated orally once daily with nitenpyram for the first 30 days and then as needed

Within 57 days of starting treatment, fleas found on the 3 dogs were eliminated and the premises were flea-free. The premise has remained flea-free for more than 5 years (Fig 4).

**Figure 3.** Percentage of flea reduction on pets in households using lufenuron and nitenpyram vs imidacloprid for integrated flea control.
SAFETY

Lufenuron is one of several insecticides specifically designed to take advantage of the physiological differences between mammals and insects. Because there is no chitin in plants and mammals, lufenuron can be used to selectively target fleas, yet provide a wide margin of safety for dogs.¹¹,¹²

**LD₅₀ Studies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Result</th>
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<tbody>
<tr>
<td>Acute oral dose LD₅₀ in mice</td>
<td>No deaths observed at highest dose tested (&gt;2000 mg/kg)</td>
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<tr>
<td>Acute oral dose LD₅₀ in rats</td>
<td>No deaths observed at highest dose tested (&gt;2000 mg/kg)</td>
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<tr>
<td>Acute dermal dose LD₅₀ in rats</td>
<td>No deaths observed at highest dose tested (&gt;2000 mg/kg)</td>
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*Tests performed by Ciba-Geigy, Stein, Switzerland.*

Figure 4. Reduction of flea burden in 3 dogs treated with lufenuron in combination with nitenpyram.
Oral Toxicity in Growing Dogs

A number of studies were conducted to evaluate the toxicity of lufenuron in growing dogs.

<table>
<thead>
<tr>
<th>Lufenuron Dose</th>
<th>Study Description and Results</th>
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<tr>
<td><strong>3-month study</strong></td>
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<td>1X, 3X, 5X</td>
<td>1X, 3X, or 5X the recommended dose (10 mg/kg) was administered to 6-week-old (or younger) puppies for 3 consecutive days per month for 3 months. Increased incidence of certain clinical signs, eg, dehydration and emesis, but all puppies grew at a normal rate and were healthy at study’s end.</td>
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<td><strong>7-month study</strong></td>
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<td>2X</td>
<td>5-month-old puppies were given 2X the recommended dose on 3 consecutive days per month for 7 months. No adverse effects.</td>
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<tr>
<td>6X or 10X</td>
<td>5-month-old puppies were dosed at 6X or 10X the recommended dose on 3 consecutive days per month for 7 months. No overt signs of toxicity. Decreased food consumption in female dogs, but little effect on mean body weight of dogs at study’s end.</td>
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<td><strong>Months 1–3</strong></td>
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<tr>
<td>0, 1X, 3X, 5X</td>
<td>8-week-old puppies were dosed orally on 3 consecutive days per month at a rate of 0, 1X, 3X, or 5X the recommended dose for 3 months, then their doses were doubled to 2X, 6X, or 10X for 7 months. No consistent or meaningful differences between controls and treated dogs in any evaluation criteria. No deaths reported.</td>
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<tr>
<td><strong>Months 4–10</strong></td>
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<tr>
<td>0, 2X, 6X, 10X</td>
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<tr>
<td><strong>One time dose of 20X</strong></td>
<td>7- to 8-month-old puppies were dosed once at 20X the recommended monthly use rate. No marked toxic effects. Reduced body weights in both males and females.</td>
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Oral Toxicity in Reproducing Dogs

A number of studies were conducted to evaluate the effect of lufenuron on reproduction in adult dogs.

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| **5-month study**<br>0 or 3X | Daily 0 or 3X the recommended dose was given to male and female dogs starting an average of 13 weeks prior to mating. Dosing continued for 6 weeks after whelping in females.  
*No significant treatment-related effects in stud sperm quality, general health, body weight, or pup viability.*  
*Average litter size of treated group was 6.5 vs 4.4 for the control group. Similar growth rates for pups between the two groups. No congenital abnormalities noted.* |
| Small breeds<br>1X or 5X | Small-breed males were given 1X or 5X the recommended lufenuron dose or placebo monthly until all females in their group were bred. Small-breed females were dosed at 1X monthly or 5X every other week (lufenuron or placebo) until whelping.  
*No adverse effects in breeding males or females noted.*  
*No differences in pup viability or survival between treatment and placebo groups detected.* |
| Large breeds<br>1X or 5X | Large-breed males were dosed at 1X or 5X the recommended dose monthly until all females in their group were bred. Females received either 1X the recommended dose monthly until weaning or 5X the recommended dose until whelping.  
*No adverse effects in breeding males or females noted.*  
*No differences in pup viability or survival detected between treatment and placebo groups.* |

Lufenuron has undergone numerous trials to test its safety in dogs and shows a **high margin of safety** in adult dogs, puppies, and pregnant and lactating dogs.
CONCLUSION

Lufenuron is the only systemic IGR available for pets. If administered appropriately and used on a monthly basis, it has been proven to break the flea life cycle at the egg stage and help prevent flea populations from infesting both pets and their environments. Lufenuron has a wide safety margin for dogs with safety demonstrated both in experimental studies and in the millions of doses administered in the field.

REFERENCES

10. Dryden MW, Payne PA, McCoy CM. Flea circus in a horse arena. Proceedings of the 7th International Symposium on Ectoparasites of Pets, April 2003; League City, TX.