

Satisfaction Guarantee Guidelines For Cats and Dogs

If you feel that Revolution[®] (selamectin) or Revolution[®] Plus (selamectin and sarolaner topical solution) is not providing satisfactory protection for the indications for which it is labeled, respectively, please call our medical support team to discuss our Satisfaction Guarantee. Zoetis will work with you to ensure that you are satisfied with the performance of these products or we will refund the purchase price.*

The Satisfaction Guarantee is available to individuals who have purchased Revolution or Revolution Plus from a veterinarian or pharmacy with a valid veterinary prescription.** All claims are evaluated on a case-by-case basis based on the program guidelines and requirements outlined below.



HEARTWORM DISEASE GUIDELINES:

If any dog determined by a licensed veterinarian to be free of heartworm infection at the onset of treatment with Revolution develops heartworm disease, we will provide reimbursement for reasonable and customary costs associated with the diagnosis and treatment of heartworm disease (up to \$1,000 and the acquisition cost of melarsomine dihydrochloride) and provide a year's supply of Revolution. Feline heartworm cases involving Revolution or Revolution Plus will be evaluated on a case-by-case basis.

Canine Heartworm Reimbursement Requirements:

- Revolution was used, at all times, according to its label directions.
- The use of an antigen test will be the standard for determining heartworm status. Knott's or any filter test for the detection of microfilariae is not sufficient evidence for pretreatment heartworm negative status.
- Two separate blood samples using at least two different brands of antigen tests are required to document heartworm positive status.
- Dogs previously treated for heartworm disease must have a negative antigen test prior to starting Revolution.
- Dogs starting or changing heartworm preventatives are required to have two negative antigen tests at least 6 months apart after initiation of Revolution treatment.†



FLEA GUIDELINES:

The affected dog (Revolution) or cat (Revolution or Revolution Plus) must be on the product for 60 days prior to the report. All other pets in the home must also be treated with a flea control product for 60 days prior to the report. We will provide reimbursement up to \$30 for an alternative approved flea treatment or reimburse you for the cost of one dose of Revolution (dogs or cats) or Revolution Plus (cats). This guarantee does not cover any other costs, including, but not limited to, those associated with the control of flea infestations in and around living quarters, medical treatments, and procedures.



TICK GUIDELINES:

Revolution protects against the American Dog Tick (*Dermacentor variabilis*) in dogs. We will reimburse you up to \$30 for an alternative approved tick treatment or provide reimbursement for the cost of one dose of Revolution to be administered 2 weeks after the previous dose as per label directions. While Revolution has not demonstrated efficacy against ticks in cats, Revolution Plus is indicated for the treatment and control of tick infestations in cats caused by black-legged or deer ticks (*Ixodes scapularis*), Gulf Coast ticks (*Amblyomma maculatum*), and American dog ticks (*Dermacentor variabilis*). If a cat receiving Revolution Plus becomes infested with ticks, we will reimburse you the cost of one additional dose of Revolution Plus. This Satisfaction Guarantee does not cover any other tick-related costs, including, but not limited to, those associated with the control of tick infestations in or around living quarters, or medical treatments or procedures.

Satisfaction Guarantee Guidelines For Cats and Dogs



HOOKWORM, ROUNDWORM, WHIPWORM, TAPEWORM GUIDELINES:

Revolution has not demonstrated efficacy against hookworms, roundworms, whipworms or tapeworms in dogs. However, if you are dispensing Revolution to a dog and such dog is found to be positive with *T. canis*, *A. caninum*, *T. vulpis*, *D. caninum*, *T. pisiformis* and/or *Echinococcus spp* eggs demonstrated in the fecal sample, we will provide you Cestex[®] (epsiprantel) dewormer free of charge or provide reimbursement for the reasonable and customary costs up to \$100 for an approved treatment. In cats, both Revolution and Revolution Plus are indicated for the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections. If you are dispensing Revolution or Revolution Plus and a cat is found to be positive with *T. cati* and/or *A. tubaeforme* eggs demonstrated in the fecal sample, we will provide reimbursement for the reasonable and customary costs up to \$100 for an approved treatment. Revolution and Revolution Plus have not demonstrated efficacy against tapeworms in cats. However, if you are dispensing Revolution or Revolution Plus and a cat tests positive for tapeworms, we will provide you Cestex dewormer free of charge or provide reimbursement for the reasonable and customary costs up to \$100 for an approved treatment.



OTHER LABEL RELATED INDICATIONS (SARCOPTIC MANGE IN DOGS AND EAR MITES IN CATS OR DOGS) GUIDELINES:

We will provide reimbursement for reasonable and customary costs up to \$30 for a treatment of approved label indications if you believe Revolution or Revolution Plus is not performing as labeled.

IMPORTANT SAFETY INFORMATION: The safe use of Revolution Plus has not been established in kittens less than 8 weeks old or in breeding, pregnant or lactating cats. Reported side effects in clinical trials included lethargy and anorexia. Use with caution in cats with a history of neurologic disorders. Sarolaner, one of the ingredients in Revolution Plus, is a member of the isoxazoline class, which has been associated with adverse reactions such as tremors, ataxia, and seizures. Reactions have occurred in cats with or without a history of neurologic disorders. In humans, Revolution Plus may be irritating to skin and eyes. See full Prescribing Information, attached.

IMPORTANT SAFETY INFORMATION: Do not use Revolution on sick, weak, or underweight animals. Use only on cats 8 weeks and older. Use only on dogs 6 weeks and older. Prior to administration, dogs should be tested for heartworms. In cats, side effects may include digestive upset and temporary hair loss at application site with possible inflammation. In people, Revolution may be irritating to skin and eyes. Wash hands after use. See full Prescribing Information, attached.

* Subject to program requirements outlined in this document.

** Guarantee applies to current products purchased from a veterinarian or from a pharmacy through fulfillment of a valid veterinary prescription. Revolution or Revolution Plus obtained free of charge is not eligible. All claims via distribution must be accompanied by a valid proof of purchase.

Zoetis reserves the right to modify or discontinue this program at any time for any reason. Call Zoetis Veterinary Medical Information & Product Support with Satisfaction Guarantee questions at 1-888-ZOETIS1.

† Dogs that have not previously received heartworm prevention, or those that have received inconsistent heartworm prevention, prior to starting Revolution may test negative when therapy is initiated despite being infected. This may occur due to very low worm burdens, the inability of antigen heartworm tests to reliably detect infections less than five months post-infection, as well as the potential of macrocyclic lactones to delay the development of heartworms. As such, a single test—or two tests separated by six months after the initiation of a preventative regimen—will miss some infections. At this time, the American Heartworm Society recommends three consecutive “negative” antigen tests six months apart to potentially classify dogs as heartworm disease “negative.”

revolution[®] PLUS

(selamectin and sarolaner topical solution)

CAUTION:

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

REVOLUTION PLUS (selamectin and sarolaner topical solution) for Cats is available as a colorless to yellow, ready to use solution in single dose tubes for topical (dermal) treatment of cats and kittens eight weeks of age and older. The content of each tube is formulated to provide a minimum of 2.7 mg/lb (6 mg/kg) of body weight of selamectin and 0.45 mg/lb (1.0 mg/kg) of body weight of sarolaner. Inactive ingredients: Dipropylene glycol Monomethylether, Isopropyl Alcohol, Butylated Hydroxytoluene.

Selamectin is a member of the macrocyclic lactone class of parasiticides and the chemical name is 25-Cyclohexyl-4'-O-de(2,6-dideoxy-3-O-methyl- α -l-arabino-hexopyranosyl)-5-demethoxy-25-de (1-methylpropyl)-22,23-dihydro-5-(hydroxyimino)-avermectin A1a.

Sarolaner is a member of the isoxazoline class of parasiticides and the chemical name is 1(5'-(5S)-5-(3,5-Dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-3'-H-spiro(azetidine-3,1'-(2)benzofuran)-1-yl)-2-(methylsulfonyl)ethanone.

REVOLUTION PLUS contains the S-enantiomer of sarolaner.

INDICATIONS:

REVOLUTION PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. REVOLUTION PLUS kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, the treatment and control of tick infestations with *Ixodes scapularis* (black-legged tick), *Amblyomma maculatum* (Gulf Coast tick) and *Dermacentor variabilis* (American dog tick), the treatment and control of ear mite (*Otodectes cynotis*) infestations, and the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

DOSAGE AND ADMINISTRATION:

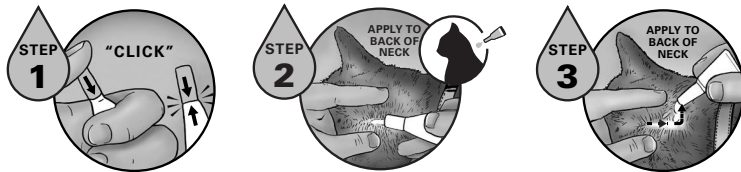
The recommended minimum dosage is 2.7 mg selamectin per pound (6 mg/kg) of body weight and 0.45 mg sarolaner per pound (1 mg/kg) of body weight.

Administer the entire contents of a single tube (or two tubes in combination for cats weighing over 22 pounds) of REVOLUTION PLUS topically in accordance with the following table.

Body Weight (lbs)	Tube Cap Color	Tube Volume (mL)	Tube Contents	
			Selamectin (mg/tube)	Sarolaner (mg/tube)
2.8 - 5.5	gold	0.25	15	2.5
5.6 - 11	orange	0.5	30	5
11.1 - 22*	green	1	60	10

* Cats over 22 lbs should be treated with the appropriate combination of tubes. Recommended for use in cats and kittens 8 weeks of age or older.

A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying REVOLUTION PLUS topically to cats and kittens prior to first use.



Firmly press the cap down to puncture the seal on the REVOLUTION PLUS tube; a clicking sound will confirm that the cap has successfully punctured the seal. Remove the cap and check to ensure that the tip of the tube is open. To administer the product, part the hair on the back of the animal at the base of the neck in front of the shoulder blades until the skin is visible. Place the tip of the tube on the skin and squeeze the tube 3 or 4 times to empty its entire contents directly on to the skin in one spot. Keeping the tube squeezed, drag it away from the liquid and lift to remove. Check the tube to ensure that it is empty.

Do not massage the product into the skin. Due to alcohol content, do not apply to broken skin. Avoid contact between the product and fingers. Do not apply when the hair coat is wet. Stiff hair, clumping of hair, hair discoloration, or a slight powdery residue may be observed at the treatment site in some cats. These effects are temporary and do not affect the safety or effectiveness of the product. Discard empty tubes in your ordinary household refuse.

The effectiveness of REVOLUTION PLUS against *D. immitis* after bathing has not been evaluated. Bathing or shampooing the cat 24 hours after treatment does not reduce the effectiveness of topical selamectin, one of the ingredients of REVOLUTION PLUS, against *D. immitis*.

Flea Treatment and Prevention

For the treatment and prevention of flea infestations, REVOLUTION PLUS may begin at any time of year. REVOLUTION PLUS should be administered year-round at monthly intervals or begin at least one month before fleas become active. If a cat is already

infested with fleas when the first dose of REVOLUTION PLUS is administered, adult fleas on the animal are killed before they can lay eggs. However, an environmental infestation may persist for a short time after beginning treatment with REVOLUTION PLUS because of the development of adult fleas from eggs that were laid prior to the initiation of treatment.

Tick Treatment and Control

For the treatment and control of infestations with *Ixodes scapularis*, *Amblyomma maculatum* and *Dermacentor variabilis*, REVOLUTION PLUS may begin at any time of year. REVOLUTION PLUS should be administered year-round at monthly intervals or begin at least one month before the ticks become active.

Heartworm Prevention

For the prevention of heartworm disease, REVOLUTION PLUS must be administered on a monthly basis. REVOLUTION PLUS should be administered year-round or at least within one month after the animal's first exposure to mosquitoes and monthly thereafter until the end of the mosquito season. The final dose must be given within one month after the last exposure to mosquitoes. If a dose is missed and a monthly interval between dosing is exceeded then immediate administration of REVOLUTION PLUS and resumption of monthly dosing will minimize the opportunity for the development of adult heartworms. When replacing another monthly heartworm preventive product in a heartworm disease prevention program, the first dose of REVOLUTION PLUS must be given within a month of the last dose of the former medication.

Selamectin, one of the active ingredients in REVOLUTION PLUS, is a macrocyclic lactone compound. These compounds effectively prevent the development of adult heartworms when administered to cats within one month of exposure to infective (L_3) *Dirofilaria immitis* larvae. This product effectively eliminates the tissue stage of heartworm larvae for a month after infection. Cats with unknown heartworm history that test negative prior to the initiation of REVOLUTION PLUS may be harboring pre-patent infections at the time REVOLUTION PLUS was started. Testing such animals 3-4 months after initiation of REVOLUTION PLUS would be necessary to confirm their negative heartworm status.

At the discretion of the veterinarian, cats \geq 6 months of age may be tested to determine the presence of existing heartworm infections before beginning treatment with REVOLUTION PLUS. Cats already infected with adult heartworms can be given REVOLUTION PLUS monthly to prevent further infections.

Ear Mite Treatment and Control

For the treatment of ear mite (*Otodectes cynotis*) infestations, REVOLUTION PLUS should be administered once as a single topical dose. Do not administer into the ear canal. Monthly use of REVOLUTION PLUS will control any subsequent ear mite infestations. Cleansing of the infested ears is recommended to remove debris.

Nematode Treatment and Control

For the treatment of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections, REVOLUTION PLUS should be applied once as a single topical dose. Monthly use of REVOLUTION PLUS will control any subsequent roundworm and intestinal hookworm infections.

CONTRAINDICATIONS:

There are no known contraindications for the use of REVOLUTION PLUS.

WARNINGS:

Human warnings:

Not for human use. Keep this and all drugs out of the reach of children.

In humans, REVOLUTION PLUS may be irritating to skin and eyes. REVOLUTION PLUS and selamectin topical solution contain isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Reactions such as hives, itching and skin redness have been reported in humans in rare instances after accidental dermal contact with selamectin topical solution. Individuals with known hypersensitivity to selamectin topical solution should use caution or consult a health care professional before applying this product on a cat. Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water; if wearing contact lenses, rinse the eyes first then remove contact lenses and continue to rinse for 5 – 10 minutes and seek medical attention. In case of ingestion by a human, contact a physician immediately. The safety data sheet (SDS) provides more detailed occupational safety information. For a copy of the SDS or to report a suspected adverse reaction, call Zoetis at 1-888-963-8471.

Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

PRECAUTIONS:

Sarolaner, one of the ingredients in REVOLUTION PLUS, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Neurologic adverse reactions have been reported in cats receiving isoxazoline class drugs, even in cats without a history of neurologic disorders. Use with caution in cats with a history of neurologic disorders.

The safe use of REVOLUTION PLUS has not been evaluated in kittens less than 8 weeks of age. The safe use of REVOLUTION PLUS has not been evaluated in breeding, pregnant, or lactating cats.

ADVERSE REACTIONS:

In a field safety and effectiveness study, REVOLUTION PLUS was administered to cats with fleas. The study included a total of 430 cats (282 treated with REVOLUTION PLUS and 148 treated with imidacloprid + moxidectin once monthly for three treatments). Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions reported in the REVOLUTION PLUS group included those presented in the following table.

Adverse Reactions by Treatment Group

Adverse Reaction	REVOLUTION PLUS (n = 282)	Imidacloprid + moxidectin (n = 148)
Lethargy	12 (4.3%)	1 (0.7%)
Skin lesions*	10 (3.5%)	3 (2.0%)
Anorexia	9 (3.2%)	3 (2.0%)
Pruritus	7 (2.5%)	3 (2.0%)
Conjunctivitis	7 (2.5%)	1 (0.7%)
Sneezing	6 (2.1%)	1 (0.7%)
Administration site hair changes (alopecia)	5 (1.8%)	0 (0.0%)
Administration site lesions (scabbing)	2 (0.7%)	0 (0.0%)

*Lesions not associated with application site.

In a second field safety and effectiveness study, REVOLUTION PLUS was administered to 124 cats with ear mites. Adverse reactions in cats treated with REVOLUTION PLUS included emesis, dermatitis and eczema, and pruritus.

In a third field safety and effectiveness study, REVOLUTION PLUS was administered to 70 cats with hookworms. Adverse reactions in cats treated with REVOLUTION PLUS included diarrhea, anorexia, emesis, and lethargy.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in cats in foreign markets: ataxia, seizures, and tremors.

To report adverse reactions call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

CLINICAL PHARMACOLOGY:

Following topical administration of REVOLUTION PLUS both selamectin and sarolaner are well absorbed with mean absolute bioavailability of 40.5% and 57.9%, respectively, and distribute systemically. In cats, selamectin and sarolaner are low clearance compounds with a long half-life of 12.5 days and 41.5 days following topical administration, respectively. Following IV dose, the total body clearance for selamectin was 10.2 mL/kg/hr and for sarolaner was 3.41 mL/kg/hr. The volume of distribution at steady state was 1.26 L/kg for selamectin and 3.87 L/kg for sarolaner. The primary route of elimination for both drugs is hepatobiliary excretion (approximately 50% of dose excreted in feces).

Following repeated monthly doses of REVOLUTION PLUS, there was a less than dose proportional increase in the C_{max} and AUC of sarolaner and selamectin. The accumulation of both sarolaner and selamectin was observed with C_{max} plateauing after the 6th dose for sarolaner and the 3rd dose for selamectin.

MODE OF ACTION:

REVOLUTION PLUS contains two active pharmaceutical ingredients, selamectin and sarolaner. Selamectin is a semi-synthetic compound of the avermectin class. Selamectin paralyzes and/or kills a wide range of invertebrate parasites through interference with their chloride channel conductance causing disruption of normal neurotransmission. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods leading to their paralysis and/or death. Sarolaner is an acaricide and insecticide belonging to the isoxazoline family. The primary target of action of sarolaner in insects and acarines is functional blockade of ligand-gated chloride channels (GABA-receptors and glutamate-receptors). Sarolaner blocks GABA- and glutamate-gated chloride channels in the nervous system of insects and acarines. Disruption of these receptors by sarolaner prevents the uptake of chloride ions by GABA and glutamate ion channels, thus resulting in increased nerve stimulation and death of the target parasite. Sarolaner exhibits higher functional potency to block insect/acarine receptors compared to mammalian receptors.

EFFECTIVENESS:

Flea Treatment and Prevention

In a well-controlled laboratory study, REVOLUTION PLUS started to kill fleas within 12 hours of treatment and killed >98% of fleas within 24 hours. During subsequent weekly infestations, REVOLUTION PLUS started to kill fleas within 6 hours and killed ≥93.8% of fleas within 12 hours through Day 28.

In a 90-day multi-center field study in the United States, conducted in households with existing flea infestations, the effectiveness of REVOLUTION PLUS against fleas was 97.2%, 99.5%, and 99.8% when assessed on Days 30, 60, and 90, respectively. Cats with signs of flea allergy dermatitis showed improvement in alopecia, dermatitis/pyodermitis, pruritus, erythema, and papules, and scaling, as a direct result of eliminating fleas.

In two additional well-controlled laboratory studies, there was a 100% reduction in adult flea count against an existing infestation and weekly re-infestation for at least 35 days. In one of these studies in which flea egg laying was examined, no flea eggs were recovered from cats treated with REVOLUTION PLUS through Day 22, and on Day 36. Four flea eggs were recovered from one cat on Day 29, but none of these four eggs hatched and developed into adult fleas. Fleas on control cats continued to produce eggs throughout the study, with counts ranging from 110 - 1,256 eggs per cat. Collectively, the data from the four studies (three laboratory and one field) demonstrate that REVOLUTION PLUS kills fleas before they can lay eggs, thus preventing further flea infestations from developing once treatment of the existing flea infestation has been initiated.

Tick Treatment and Control

In well-controlled laboratory studies, REVOLUTION PLUS began to kill *Ixodes scapularis* ticks within 24 hours of administration and demonstrated ≥93.3% effectiveness 48 hours post re-infestation for a month. REVOLUTION PLUS demonstrated ≥91.6% effectiveness against *Amblyomma maculatum* 48 hours post-infestation for a month. At 72 hours post-infestation, REVOLUTION PLUS demonstrated ≥93.5% effectiveness against *Dermacentor variabilis* for a month.

Heartworm Prevention

In two well-controlled laboratory studies, a single topical dose of REVOLUTION PLUS was 100% effective in preventing the development of heartworms in cats inoculated with infective larvae of *Dirofilaria immitis* 30 days prior to treatment.

Ear Mite Treatment and Control

In a well-controlled laboratory study, a single topical dose of REVOLUTION PLUS resulted in > 99% effectiveness against an existing *Otodectes cynotis* infestation at 30 days post treatment.

In a multi-center field study conducted in households with existing *Otodectes cynotis* infestations, 94.4% of cats in the group treated with REVOLUTION PLUS were negative for ear mites at Day 30.

Nematode Treatment and Control

Elimination of intestinal hookworm (*Ancylostoma tubaeforme*) and roundworm (*Toxocara cati*) infections was demonstrated in well-controlled laboratory studies.

In a 60-day multi-center field study, the effectiveness of REVOLUTION PLUS in reducing *Ancylostoma tubaeforme* fecal egg counts was 99.4% and 99.7% on Days 30 and 60, respectively.

ANIMAL SAFETY:

Margin of Safety Studies: One exploratory and two pivotal margin of safety studies were conducted with REVOLUTION PLUS. In the first study, REVOLUTION PLUS was applied topically to kittens eight weeks of age at doses of 12/2 (selamectin/sarolaner) mg/kg (1X), 36/6 mg/kg (3X), 45/7.5 mg/kg (3.75X), and 60/10 mg/kg (5X) every 28 days for eight consecutive doses. One female cat in the 3.75X group was found dead on study day 115. The cause was determined to be hemorrhage in multiple tissues secondary to a low platelet count. The role of the drug in contributing to this event is undetermined. No significant changes related to REVOLUTION PLUS were observed among the remaining cats for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry), gross pathology, histopathology or organ weights.

In the second study, REVOLUTION PLUS was applied topically to cats 9 months of age at doses of 1X, 3X, and 5X every 28 days for six consecutive doses. Cosmetic changes at the application site occurred sporadically in all treatment groups and included wet appearance and dried white material. Hair loss at the dose site was also noted in two cats in the 1X group and one cat in the 5X group within 1-8 days after the fourth dose administered on day 84. No significant changes related to REVOLUTION PLUS were observed for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry).

During an exploratory margin of safety study, one cat in the 60 mg/kg/ 10 mg/kg (selamectin/sarolaner) group (5X dose group) experienced piloerection, tremors, and mydriasis approximately 24 hours after receiving the third monthly dose of the combination. Signs resolved without treatment within 2 hours. This cat completed the study, receiving 3 subsequent 5X doses with no abnormal observations.

Oral safety study: The safety of REVOLUTION PLUS administered orally to kittens was tested in case of accidental oral ingestion. Oral administration of the highest recommended topical dose of REVOLUTION PLUS to kittens resulted in transient lower food consumption and clinical findings of emesis, soft feces, and salivation. In one male, mild tremor was observed and resolved within 3 hours after dosing; the same cat demonstrated reduced activity approximately 6 hours after dosing.

Heartworm Positive Cat Safety of Selamectin: Selamectin is the active ingredient in REVOLUTION PLUS that prevents heartworm disease in cats; it has been shown that the addition of sarolaner does not interfere with this activity. In a safety study in which selamectin topical solution was applied at 4 times the recommended dose to patent heartworm infected cats, no adverse reactions were observed.

Field safety: In three well-controlled field studies, REVOLUTION PLUS was used concurrently with other medications, such as vaccines, cestocidal anthelmintics, antibacterials, sedatives, anesthetics, opioid analgesics, corticosteroids, and non-steroidal anti-inflammatories. No adverse reactions were associated with the concurrent use of REVOLUTION PLUS and other medications.

STORAGE CONDITIONS:

Store at or below 30°C (86°F).

HOW SUPPLIED:

Available in three separate dose strengths for cats of different weights (see **DOSE AND ADMINISTRATION**). REVOLUTION PLUS is available in cartons containing one, three, or six single dose tubes. The amount of liquid in tube varies for each weight range (2.8 - 5.5 lbs, 5.6 - 11 lbs, 11.1 - 22 lbs). Tubes are never completely filled.

Approved by FDA under NADA 141-502

October 2018

zoetis

Distributed by: Zoetis, Kalamazoo, MI 49007

40020180A&P

NADA 141-152, Approved by FDA

REVOLUTION® (selamectin)
Topical Parasiticide For Dogs and Cats

CAUTION:

US Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

Revolution (selamectin) Topical Parasiticide is available as a colorless to yellow, ready to use solution in single dose tubes for topical (dermal) treatment of dogs six weeks of age and older and cats eight weeks of age and older. The content of each tube is formulated to provide a minimum of 2.7 mg/lb (6 mg/kg) of body weight of selamectin. The chemical composition of selamectin is (5Z,25S)-25-cyclohexyl-4'-O-de(2,6-dideoxy-3-O-methyl- α -L-arabino-hexopyranosyl)-5-demethoxy-25-de(1-methylpropyl)-22,23-dihydro-5-hydroxyiminoavermectin A₁.

INDICATIONS:

Revolution is recommended for use in dogs six weeks of age or older and cats eight weeks of age and older for the following parasites and indications:

Dogs:

Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Revolution also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) and for the control of tick infestations due to *Dermacentor variabilis*.

Cats:

Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Revolution is also indicated for the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections in cats.

WARNINGS:

Not for human use. Keep out of the reach of children.

In humans, Revolution may be irritating to skin and eyes. Reactions such as hives, itching and skin redness have been reported in humans in rare instances. Individuals with known hypersensitivity to Revolution should use the product with caution or consult a health care professional. Revolution contains isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water. In case of ingestion by a human, contact a physician immediately. The material safety data sheet (MSDS) provides more detailed occupational safety information. For a copy of the MSDS or to report adverse reactions attributable to exposure to this product, call 1-888-963-8471.

Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

Do not use in sick, debilitated or underweight animals (see SAFETY).

PRECAUTIONS:

Prior to administration of Revolution, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infested dogs should be treated to remove adult heartworms. Revolution is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, Revolution is not effective for microfilariae clearance.

Hypersensitivity reactions have not been observed in dogs with patent heartworm infections administered three times the recommended dose of Revolution. Higher doses were not tested.

ADVERSE REACTIONS:

Pre-approval clinical trials:

Following treatment with Revolution, transient localized alopecia with or without inflammation at or near the site of application was observed in approximately 1% of 691 treated cats. Other signs observed rarely ($\leq 0.5\%$ of 1743 treated cats and dogs) included vomiting, loose stool or diarrhea with or without blood, anorexia, lethargy, salivation, tachypnea, and muscle tremors.

Post-approval experience:

In addition to the aforementioned clinical signs that were reported in pre-approval clinical trials, there have been reports of pruritus, urticaria, erythema, ataxia, fever, and rare reports of death. There have also been rare reports of seizures in dogs (see **WARNINGS**).

DOSAGE:

The recommended minimum dose is 2.7 mg selamectin per pound (6 mg/kg) of body weight.

Administer the entire contents of a single dose tube (or two tubes used in combination for dogs weighing over 130 pounds) of Revolution topically in accordance with the following tables. (See **ADMINISTRATION** for the recommended treatment intervals.)

Cats (lb)	Package color	mg per tube	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1-15	Blue	45 mg	60	0.75
15.1-22	Taupe	60 mg	60	1.0

For cats over 22 lbs use the appropriate combination of tubes.

Dogs (lb)	Package color	mg per tube	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1-10	Purple	30 mg	120	0.25
10.1-20	Brown	60 mg	120	0.5
20.1-40	Red	120 mg	120	1.0
40.1-85	Teal	240 mg	120	2.0
85.1-130	Plum	360 mg	120	3.0

For dogs over 130 lbs use the appropriate combination of tubes.

Recommended for use in dogs 6 weeks of age and older and in cats 8 weeks of age and older.

ADMINISTRATION:

A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying Revolution topically to dogs and cats prior to first use.

Firmly press the cap down to puncture the seal on the Revolution tube; a clicking sound will confirm that the cap has successfully punctured the seal. Remove the cap and check to ensure that the tip of the tube is open. To administer the product, part the hair on the back of the animal at the base of the neck in front of the shoulder blades until the skin is visible. Place the tip of the tube on the skin and squeeze the tube 3 or 4 times to empty its entire contents directly onto the skin in one spot. Keeping the tube squeezed, drag it away from the liquid and lift to remove. Check the tube to ensure that it is empty. Do not massage the product into the skin. Due to alcohol content, do not apply to broken skin. Avoid contact between the product and fingers. Do not apply when the haircoat is wet. Bathing or shampooing the dog 2 or more hours after treatment will not reduce the effectiveness of Revolution against fleas or heartworm. Bathing or shampooing the cat 2 hours after treatment will not reduce the effectiveness of Revolution against fleas. Bathing or shampooing the cat

24 hours after treatment will not reduce the effectiveness of Revolution against heartworm. Stiff hair, clumping of hair, hair discoloration, or a slight powdery residue may be observed at the treatment site in some animals. These effects are temporary and do not affect the safety or effectiveness of the product. Discard empty tubes in your ordinary household refuse.

Flea Control in Dogs and Cats

For the prevention and control of flea infestations, Revolution should be administered at monthly intervals throughout the flea season, starting one month before fleas become active. In controlled laboratory studies >98% of fleas were killed within 36 hours. Results of clinical field studies using Revolution monthly demonstrated >90% control of flea infestations within 30 days of the first dose. Dogs and cats treated with Revolution, including those with pre-existing flea allergy dermatitis, showed improvement in clinical signs associated with fleas as a direct result of eliminating the fleas from the animals and their environment.

If the dog or cat is already infested with fleas when the first dose of Revolution is administered, adult fleas on the animal are killed and no viable fleas hatch from eggs after the first administration. However, an environmental infestation of fleas may persist for a short time after beginning treatment with Revolution because of the emergence of adult fleas from pupae.

Heartworm Prevention in Dogs and Cats

For the prevention of heartworm disease, Revolution must be administered on a monthly basis. Revolution may be administered year-round or at least within one month after the animal's first exposure to mosquitoes and monthly thereafter until the end of the mosquito season. The final dose must be given within one month after the last exposure to mosquitoes. If a dose is missed and a monthly interval between dosing is exceeded then immediate administration of Revolution and resumption of monthly dosing will minimize the opportunity for the development of adult heartworms. When replacing another heartworm preventive product in a heartworm disease prevention program, the first dose of Revolution must be given within a month of the last dose of the former medication.

Selamectin, the active ingredient in Revolution, is a macrocyclic lactone compound. These compounds effectively prevent the development of adult heartworms when administered to dogs and cats within one month of exposure to infective (*L*₃) *Dirofilaria immitis* larvae. Efficacy of macrocyclic lactones decreases below 100% in dogs, however, if first administered >2 months after exposure to infective larvae. Thus, in heartworm endemic regions, delaying initiation of heartworm prevention using Revolution beyond 2 months of first exposure to infective larvae (e.g., starting puppies and kittens at >8 weeks of age), or gaps of >2 months in the administration of Revolution during periods of heartworm transmission, increases the risk of the animal acquiring heartworms. Animals with unknown heartworm history that test negative for heartworms prior to the initiation of Revolution may be harboring pre-patent infections at the time Revolution was started. Testing such animals 3-4 months after initiation of Revolution would be necessary to confirm their negative heartworm status.

At the discretion of the veterinarian, cats ≥ 6 months of age may be tested to determine the presence of existing heartworm infections before beginning treatment with Revolution. Cats already infected with adult heartworms can be given Revolution monthly to prevent further infections.

Ear Mite Treatment in Dogs and Cats

For the treatment of ear mite (*O. cynotis*) infestations in dogs and cats, Revolution should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of Revolution will control any subsequent ear mite infestations. In the clinical field trials ears were not cleaned, and many animals still had debris in their ears after the second dose. Cleansing of the infested ears is recommended to remove the debris.

Sarcoptic Mange Treatment in Dogs

For the treatment of sarcoptic mange (*S. scabiei*) in dogs, Revolution should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of Revolution will control any subsequent sarcoptic mange mite infestations. Because of the difficulty in finding sarcoptic mange mites on skin scrapings, effectiveness assessments also were based on resolution of clinical signs. Resolution of the pruritus associated with the mite infestations was observed in approximately 50% of the dogs 30 days after the first treatment and in approximately 90% of the dogs 30 days after the second monthly treatment.

Tick Control in Dogs

For the control of tick (*Dermacentor variabilis*) infestations in dogs, Revolution should be administered on a monthly basis. In heavy tick infestations, complete efficacy may not be achieved after the first dose. In these cases, one additional dose may be administered two weeks after the previous dose, with monthly dosing continued thereafter.

Nematode Treatment in Cats

For the treatment and control of intestinal hookworm (*A. tubaeforme*) and roundworm (*T. cati*) infections, Revolution should be applied once as a single topical dose.

SAFETY:

Revolution has been tested safe in over 100 different pure and mixed breeds of healthy dogs and over 15 different pure and mixed breeds of healthy cats, including pregnant and lactating females, breeding males and females, puppies six weeks of age and older, kittens eight weeks of age and older, and avermectin-sensitive collies. A kitten, estimated to be 5-6 weeks old (0.3 kg), died 8 1/2 hours after receiving a single treatment of Revolution at the recommended dosage. The kitten displayed clinical signs which included muscle spasms, salivation and neurological signs. The kitten was a stray with an unknown history and was malnourished and underweight (see **WARNINGS**).

DOGS: In safety studies, Revolution was administered at 1, 3, 5, and 10 times the recommended dose to six-week-old puppies, and no adverse reactions were observed. The safety of Revolution administered orally also was tested in case of accidental oral ingestion. Oral administration of Revolution at the recommended topical dose in 5- to 8-month-old beagles did not cause any adverse reactions. In a pre-clinical study selamectin was dosed orally to ivermectin-sensitive collies. Oral administration of 2.5, 10, and 15 mg/kg in this dose escalating study did not cause any adverse reactions; however, eight hours after receiving 5 mg/kg orally, one avermectin-sensitive collie became ataxic for several hours, but did not show any other adverse reactions after receiving subsequent doses of 10 and 15 mg/kg orally. In a topical safety study conducted with avermectin-sensitive collies at 1, 3 and 5 times the recommended dose of Revolution, salivation was observed in all treatment groups, including the vehicle control. Revolution also was administered at 3 times the recommended dose to heartworm infected dogs, and no adverse effects were observed.

CATS: In safety studies, Revolution was applied at 1, 3, 5, and 10 times the recommended dose to six-week-old kittens. No adverse reactions were observed. The safety of Revolution administered orally also was tested in case of accidental oral ingestion. Oral administration of the recommended topical dose of Revolution to cats caused salivation and intermittent vomiting. Revolution also was applied at 4 times the recommended dose to patent heartworm infected cats, and no adverse reactions were observed.

In well-controlled clinical studies, Revolution was used safely in animals receiving other frequently used veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, steroids, collars, shampoos and dips.

STORAGE CONDITIONS: Store below 30°C (86°F).

HOW SUPPLIED: Available in eight separate dose strengths for dogs and cats of different weights (see **DOSAGE**). Revolution for puppies and kittens is available in cartons containing 3 single dose tubes. Revolution for cats and dogs is available in cartons containing 3 or 6 single dose tubes.

revolution®
(selamectin)

zoetis

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