ADVANTAGE MULTI®

For Cats

(imidacloprid + moxidectin) Topical Solution

Once-a-month topical solution for the prevention of heartworm disease, kills adult fleas, is indicated for the treatment of flea infestations, as well as the treatment and control of ear mite infestations and intestinal parasite infections in cats and kittens 9 weeks of age and older and that weigh at least 2 lbs.

CAUTION:
Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Advantage Multi® for Cats (10% imidacloprid + 1% moxidectin) is a colorless to yellow ready-to-use solution packaged in single-dose applicator tubes for topical treatment of cats. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/lb (10.0 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin based on body weight.
Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name of imidacloprid is 1-[(6-Chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine. Moxidectin is a semisynthetic macrocyclic lactone endectocide derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus*. The chemical name of moxidectin is [6R, 23E, 25S(E)]-5-O-Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

INDICATIONS:
Advantage Multi for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. *Advantage Multi for Cats* kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. *Advantage Multi for Cats* is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the following intestinal parasites:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma tubaeforme*	X	X	X
Roundworm Species	*Toxocara cati*	X		X

WARNINGS:
Do not use on sick, debilitated, or underweight cats (See ADVERSE REACTIONS). Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight.

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children.
Children should not come in contact with the application site for 30 minutes after application.
Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. **Wash hands thoroughly with soap and warm water after handling.** If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, moxidectin, or imidacloprid should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice. The Material Safety Data Sheet (MSDS) provides additional occupational safety information.
For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

PRECAUTIONS:
Do not dispense dose applicator tubes without complete safety and administration information.
Avoid oral ingestion. Cats may experience hypersalivation, tremors, vomiting and decreased appetite if *Advantage Multi for Cats* is inadvertently administered orally or through grooming/licking of the application site.
The safety of *Advantage Multi for Cats* has not been established in breeding, pregnant, or lactating cats.
Use of this product in geriatric patients with subclinical conditions has not been adequately studied. Several otherwise healthy, thin geriatric cats experienced prolonged lethargy and sleepiness after using this drug.
(**See ADVERSE REACTIONS**).

ADVERSE REACTIONS:
Field Study: Following treatment with *Advantage Multi for Cats* or an active control, cat owners reported the following post-treatment reactions:

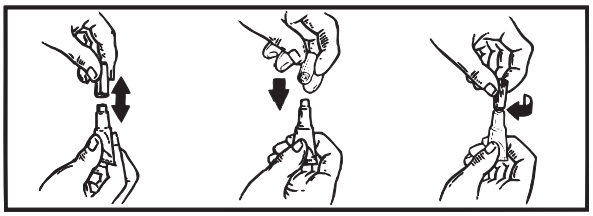
OBSERVATION	*Advantage Multi* n=113	Active Control n=38
Lethargy (protracted sleeping, poorly responsive)	3 cats* (2.7%)	None observed
Behavioral changes (e.g., agitated, excessive grooming, hiding, pacing, spinning)	9 cats (8.0%)	1 cat (2.6%)
Discomfort (e.g., scratching, rubbing, head-shaking)	5 cats (4.4%)	None observed
Hypersalivation (within 1 hour after treatment)	3 cats (2.7%)	None observed
Polydipsia	3 cats (2.7%)	None observed
Coughing and gagging	1 cat (0.9%)	None observed

*These three cats were from the same household and included one 13-yr-old cat in good health, one 15-yr-old FIV positive cat in good health, and one 15-yr-old, underweight cat in fair health. Lethargy was noted for 24 to 36 hrs after the first treatment only; one cat was unsteady at 48 hrs. These cats were not on other medications.
During another field study, a 16-year-old cat with renal disease slept in the same place without moving for two days following application. (**See PRECAUTIONS**).
Laboratory Effectiveness Studies: *Advantage Multi for Cats* was administered at the recommended dose to 215 cats in 20 effectiveness studies. One random-sourced cat exhibited signs consistent with either moxidectin toxicity or viral respiratory disease and died 26 hours after product application; necropsy findings were inconclusive as to the cause of death. A second cat that became ill 3 days after application of *Advantage Multi for Cats* responded to treatment for respiratory infection and completed the study. A third cat became ill on day 3 and died with signs and lesions attributable to panleukopenia on day 7 after moxidectin application.
Foreign Market Experience: Because the following events were reported voluntarily during post-approval use of the product in foreign markets, it is not always possible to reliably establish a causal relationship to drug exposure. Adverse events reported in cats topically treated with imidacloprid + moxidectin for cats included: application site reaction (dermatitis, pyoderma, erythema, alopecia), facial edema, attempts to rub product off, pruritus, lethargy, recumbency, ataxia, dyspnea, vomiting, loss of appetite, and death due to concurrent heartworm disease. One 15-year-old cat salivated after application and over a week's time, became lethargic then dull and lifeless and was euthanized. No necropsy was done to determine cause of illness. One 11-week-old kitten with respiratory illness died of signs of moxidectin toxicity (depression, disorientation, mydriasis, and tremors) after receiving an overdose. Accidental oral ingestion caused salivation, agitation, muscle fasciculations, lethargy, staggering and oral mucosal ulceration.
To report a suspected adverse event, call 1-800-422-9874.

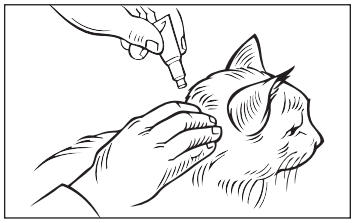
DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 4.5 mg/lb (10.0 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin, once a month, by topical administration.
Do not apply to irritated skin.
1. Remove one dose applicator tube (tube) from the package. As specified in the following table, administer the entire contents of the *Advantage Multi® for Cats* tube that correctly corresponds with the body weight of the cat.

Cat (lbs.)	*Advantage Multi for Cats*	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2-5	*Advantage Multi 5*	0.23	23	2.3
5.1-9	*Advantage Multi 9*	0.4	40	4
9.1-18*	*Advantage Multi 18*	0.8	80	8

* Cats over 18 lbs. should be treated with the appropriate combination of *Advantage Multi for Cats* tubes



2. While holding the tube in an upright position, remove the cap from the tube.
3. Turn the cap over and push the other end of cap onto the tip of the tube.
4. Twist the cap to break the seal and then remove cap from the tube.



5. Part the hair on the back of the cat's neck at the base of the head, until the skin is visible. Place the tip of the tube on the skin and apply the entire contents directly on the exposed skin. Lift tube away from skin before releasing pressure on tube.

Do not get this product in the cat's mouth or eyes or allow the cat to lick the application site for 30 minutes. Treatment at the base of the head will minimize the opportunity for ingestion by grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.
Stiff, matted hair or a damp, oily appearance of the hair may be observed at the application site on some cats. This is temporary and does not affect the safety and effectiveness of the product.
Heartworm Prevention: For prevention of heartworm disease, *Advantage Multi for Cats* should be administered at one-month intervals. *Advantage Multi for Cats* may be administered year-around or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer *Advantage Multi for Cats* immediately and resume the monthly dosing schedule. When replacing another heartworm preventative product in a heartworm prevention program, the first treatment with *Advantage Multi for Cats* should be given within one month of the last dose of the former medication. At the discretion of the veterinarian, cats older than 6 months of age may be tested to determine the presence of existing heartworm infection before treatment with *Advantage Multi for Cats* **(See ADVERSE REACTIONS - Foreign Market Experience).**
Flea Treatment: For the treatment of flea infestations, *Advantage Multi for Cats* should be administered at one-month intervals. If the cat is already infested with fleas when the first dose of *Advantage Multi for Cats* is administered, adult fleas on the cat will be killed. However, re-infestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated.
Cats treated with imidacloprid, including those with pre-existing flea allergy dermatitis have shown clinical improvement as a direct result of elimination of fleas from the cat.
Ear Mite Treatment: For the treatment of ear mites (*Otodectes cynotis*), *Advantage Multi for Cats* should be administered once as a single topical dose. Monthly use of *Advantage Multi for Cats* will control any subsequent ear mite infestations.
Intestinal Nematode Treatment: For the treatment and control of intestinal hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults and fourth stage larvae) and roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), *Advantage Multi for Cats* should be administered once as a single topical dose.

ANIMAL SAFETY:
Studies in Kittens: *Advantage Multi for Cats* was topically applied at 0, 1, 3, and 5X the maximum dose to 48 healthy 9-week-old kittens on days 0, 28, and 56. Lethargy was observed in 1 kitten from the 3X group and 1 from the 5X group on the day after initial treatment; the kitten from the 3X group was also disoriented and ataxic. One kitten from the 3X group had a slow pupillary light response two days after treatment and one had tremors the day after treatment. Hypersalivation was seen in one kitten from the 5X group approximately six hours post-treatment. One kitten from the 3X group was scratching at the treatment site 2 days after treatment. Slight cough was noted in 7 different kittens (2-0X, 2-1X, and 3-5X) during the 13-day period following the first treatment. Histopathology showed granulomatous inflammation at the treatment site in three 1X kittens. Causal relationship to the drug could not be determined. Pulmonary inflammation (1-5X) and lymphoid hyperplasia (2-1X, 4-3X) were seen in treated kittens.
In a second study, *Advantage Multi for Cats* was topically applied at 0, 1.7, 5.2 and 8.7X the maximum dose to 48 healthy 9-week-old kittens every two weeks for 6 doses. One kitten in the 8.7X group apparently ingested an unknown amount of the drug and developed the following clinical signs prior to euthanasia: mydriasis, salivation, depression, vomiting, unsteadiness, rapid to slow to difficult breathing, poor pupillary response, generalized tremors, inability to move, and nystagmus. Two kittens in the 5.2X group developed mydriasis, salivation, depression, squinting, and poor appetite. A kitten in the 1.7X group developed mydriasis.
Dose Tolerance Study: Eight healthy juvenile cats were topically dosed with a single application of *Advantage Multi for Cats* at 10 times the recommended dose volume. Mild, transient hypersalivation occurred in two of the cats.
Oral Study in Cats: The oral safety of *Advantage Multi for Cats* was tested in case of accidental oral ingestion. The maximum topical dose was orally administered to twelve healthy 9-week-old kittens. Hypersalivation (8 of 12 kittens) and vomiting (12 of 12 kittens) were observed immediately post-treatment. Tremors developed in one kitten within 1 hour, resolving without treatment within the next hour. All 12 kittens were either anorexic or had decreased appetite for at least 1 day following treatment. In 3 kittens, the anorexia or decreased appetite continued into the second week following treatment. There was a post-treatment loss of body weight in treated kittens compared to control kittens. In a pilot safety study using kittens younger in age and lighter in weight than allowed by product labeling, an 8-week old kitten weighing 0.6 kg orally received 2X of the label topical dose (0.46 mL/kg). Immediately after dosing, it vomited, had labored breathing and slight tremors. Within 4 hours, it was normal, but was found dead on day 6. Necropsy could not determine the cause of death.
Study in Heartworm Positive Cats: Young adult cats were inoculated subcutaneously with third-stage *D. immitis* larvae. At 243-245 days post-infection, immunoserology and echocardiography were performed to identify cats with adult heartworm burdens similar to naturally-acquired infections. Two groups were treated topically with either *Advantage Multi for Cats* at the label dose or placebo, once every 28 days, for three consecutive treatments. A third group was treated topically, once, with *Advantage Multi for Cats* at 5X the label dose. Sporadic vomiting and labored breathing related to heartworm burden were observed in the treatment and control groups. There was no difference between treatment groups in the numbers of adult *D. immitis* recovered at study conclusion. No adverse reactions were associated with the topical application of *Advantage Multi for Cats* to experimentally heartworm-infected cats.

STORAGE INFORMATION:
Store at temperatures between 4°C (39°F) and 25°C (77°F), avoiding excess heat or cold.

HOW SUPPLIED:

Code	Applications Per Package
08890342	3 x 0.23 mL tubes
08891438	6 x 0.4 mL tubes
08891446	6 x 0.8 mL tubes

Advantage Multi is protected by one or more of the following U.S. patents: 6,232,328 and 6,001,858.

08944663, R.3 February 2009, R.1
79827768 GHG050912
NADA # 141-254, Approved by FDA

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