midwest veterinary supply

Elanco Paws4Purpose™ Animal Welfare Agreement

Effective: January 1, 2026 - December 31, 2026

PAWS 4 PURPOSE™

TIER 1

$185K Yearly Commitment* | All Brands Eligible

7.5%

- Droncit® (praziquantel)
- Drontal® (praziquantel/pyrantel pamoate)
- Drontal® Plus (praziquantel/pyrantel pamoate/febantel)
- profender® (emodepside/praziquantel)

12.5%

- Bexacat™ (bexagliflozin tablets) — Before using Bexacat, it is important to read the entire package insert including the **boxed warning.**

17.5%

- Advantage® II
- Galliprant® (grapiprant tablets)
- K9 Advantix® II
- Cheristin™ for cats spinetoram
- onsior® (robenacoxib)
- Trifexis® (spinosad+milbemycin oxime)
- Zenrelia™ (ilunocitinib tablets) — Before using Zenrelia, it is important to read the entire package insert including the **boxed warning.**

20%

- Credelio Quattro® (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)
- Credelio® (lotilaner)
- Credelio® CAT (lotilaner)
- INTERCEPTOR® PLUS (milbemycin oxime/praziquantel)

22.5%

- advantage multi® (imidacloprid+moxidectin)

25%

- Seresto®

27.5%

- CLARO® (florfenicol, terbinafine, mometasone furoate) Otic Solution

35%

- Canine Parvovirus Monoclonal Antibody — CPMA is USDA conditionally approved

70%

- Elanco™ ALL ELANCO VACCINES
- truCan™
- truCan™ ultra
- truFel™
- truFel™ ultra
- Rabvac™

TIER 1+

$185K Yearly Commitment | $125K Vaccines and $60KPara/Thera

10%

- Droncit® (praziquantel)
- Drontal® (praziquantel/pyrantel pamoate)
- Drontal® Plus (praziquantel/pyrantel pamoate/febantel)
- profender® (emodepside/praziquantel)

15%

- Bexacat™ (bexagliflozin tablets) — Before using Bexacat, it is important to read the entire package insert including the **boxed warning.**
- Zorbium® (buprenorphine transdermal solution) — Before using Zorbium, it is important to read the entire package insert including the **boxed human warning.**

20%

- Advantage® II
- Galliprant® (grapiprant tablets)
- K9 Advantix® II
- Cheristin™ for cats spinetoram
- onsior® (robenacoxib)
- Trifexis® (spinosad+milbemycin oxime)
- Zenrelia™ (ilunocitinib tablets) — Before using Zenrelia, it is important to read the entire package insert including the **boxed warning.**

25%

- Credelio Quattro® (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)
- Credelio® (lotilaner)
- Credelio® CAT (lotilaner)
- INTERCEPTOR® PLUS (milbemycin oxime/praziquantel)

30%

- advantage multi® (imidacloprid+moxidectin)
- Seresto®
- CLARO® (florfenicol, terbinafine, mometasone furoate) Otic Solution

40%

- Canine Parvovirus Monoclonal Antibody — CPMA is USDA conditionally approved

70%

- Elanco™ ALL ELANCO VACCINES
- truCan™
- truCan™ ultra
- truFel™
- truFel™ ultra
- Rabvac™

BEXACAT INDICATION:
Bexacat is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

BEXACAT IMPORTANT SAFETY INFORMATION:
Before using Bexacat, you must read the entire package insert, including the boxed warning. Call 1-888-545-5973 or visit www.elancolabels.com/us/bexacat for complete safety information.

Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis, both of which may result in death. Development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat. Do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus. The use of Bexacat in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of Bexacat, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death. Sudden onset of hyporexia/anorexia, lethargy, dehydration, diarrhea that is unresponsive to conventional therapy, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level. Bexacat should not be initiated in cats with pancreatitis, anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus, as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis. Due to risk of severe adverse reactions, do not use Bexacat in cats with evidence of hepatic disease or reduced renal function. Consult a physician in case of accidental ingestion by humans.

ZENRELIA INDICATIONS:
Zenrelia is indicated for control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

ZENRELIA IMPORTANT SAFETY INFORMATION:
Read the entire package insert, including the Boxed Warning, before using this drug.
For full prescribing information call 1 888 545 5973 or visit www.elancolabels.com/us/zenrelia.

WARNING: INADEQUATE IMMUNE RESPONSE TO VACCINES. Based on results of the vaccine response study, dogs receiving Zenrelia are at risk of an inadequate immune response to vaccines. Discontinue Zenrelia for at least 28 days to 3 months prior to vaccination and withhold Zenrelia for at least 28 days after vaccination. Dogs should be up to date on vaccinations prior to starting Zenrelia. Do not use in dogs less than 12 months old or dogs with a serious infection. Monitor dogs for infections because Zenrelia may increase susceptibility to infections, including adenoviral hepatitis and pancreatitis. Neoplastic conditions(benign and malignant) were observed during clinical studies. Consider the risks and benefits of treatment in dogs with a history of recurrence of these conditions. The most common adverse reactions were vomiting, diarrhea and lethargy. Zenrelia has not been evaluated in breeding, pregnant, or lactating dogs and concurrent use with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents has not been tested.For full prescribing information see package insert.

ZORBIUM IMPORTANT SAFETY INFORMATION:

Before using ZORBIUM (buprenorphine transdermal solution), read the entire package insert including the Boxed Human Warning. Call 1-888-545- 5973 or visit www.elancolabels.com/us/zorbium for full prescribing information. ZORBIUM is not for use in humans. ZORBIUM contains buprenorphine, an opioid that exposes humans to risks of misuse, abuse, and addiction, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ZORBIUM.

Elanco™

Elanco Paws4Purpose™ Animal Welfare Agreement

Effective: January 1, 2026 - December 31, 2026

Instructions:

Please complete the form below to finalize your participation in the Elanco Paws4Purpose™ Animal Welfare Agreement for the 2026 program. Ensure all fields are filled out accurately. If any information is missing or incorrect, it may delay the processing of your agreement. Once completed, please submit the form to your Elanco Sales Rep.

Account Name: _____

Elanco Account Number: _____

Required Commitment: $ _____

Business Phone #: _____

Business Email: _____

Preferred Distributor: _____

Thank you for your commitment to animal welfare and your participation in the Elanco Paws4Purpose™ program. Together, we're making a positive impact on the health and well-being of animals. We appreciate your partnership and dedication!

If a shelter participating in the Paws 4 Purpose program sells Elanco product(s) to an unauthorized reseller (as solely determined by Elanco), such shelter will be immediately removed from the Paws 4 Purpose program and forfeit all associated pricing.

Elanco™

advantage multi™ for dogs

(imidacloprid+moxidectin)
Topical Solution

Once-a-month topical solution for the prevention of heartworm disease, the treatment of circulating microfilariae, kills adult fleas, is indicated for the treatment of flea infestations, the treatment and control of sarcoptic mange, as well as the treatment and control of intestinal parasite infections in dogs and puppies that are at least 7 weeks of age and that weigh at least 3 lbs.

WARNING
- **DO NOT ADMINISTER THIS PRODUCT ORALLY**
- **For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals.**
- **Children should not come in contact with application sites for two (2) hours after application.**

(See Contraindications, Warnings, Human Warnings, and Adverse Reactions, for more information)

CAUTION:
Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Advantage Multi for Dogs (10 % imidacloprid + 2.5 % moxidectin) is a colorless to yellow ready-to-use solution packaged in single dose applicator tubes for topical treatment of dogs. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin based on body weight.

Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name for 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 for moxidectin is [6R, 23E, 25S(E)]-5-0- Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

INDICATIONS:
Advantage Multi for Dogs is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs. *Advantage Multi for Dogs* kills adult fleas and is indicated for the treatment of flea infestations (*Ctenocephalides felis*). *Advantage Multi for Dogs* is indicated for the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*. *Advantage Multi for Dogs* is also indicated for the treatment and control of the following intestinal parasites:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma caninum*	X	X	X
	Uncinaria stenocephala	X	X	X
Roundworm Species	*Toxocara canis*	X		X
	Toxascaris leonina	X		
Whipworm	*Trichuris vulpis*	X		

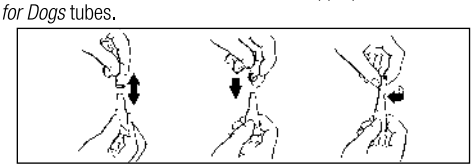
DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin, once a month, by topical administration.

Do not apply to irritated skin.

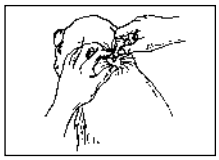
1. Remove one dose applicator tube from the package. As specified in the following table, administer the entire contents of the *Advantage Multi for Dogs* tube that correctly corresponds with the body weight of the dog.

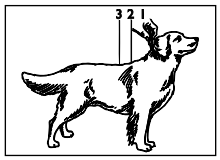
Dog (lbs.)	Advantage Multi For Dogs	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
3–9	*Advantage Multi 9*	0.4	40	10
9.1–20	*Advantage Multi 20*	1.0	100	25
20.1–55	*Advantage Multi 55*	2.5	250	62.5
55.1–88	*Advantage Multi 88*	4.0	400	100
88.1–110*	*Advantage Multi 110*	5.0	500	125

* Dogs over 110 lbs. should be treated with the appropriate combination of *Advantage Multi for Dogs* 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. The dog should be standing for application. Part the hair on the back of the dog between the shoulder blades until the skin is visible. For dogs weighing 20 lbs. or less, place the tip of the tube on the skin and apply the entire contents directly on the exposed skin at one spot between the shoulder blades. For dogs weighing more than 20 lbs., place the tip of the tube on the skin and apply the entire contents directly on the exposed skin at 3 or 4 spots on the top of the backline from the base of the neck to the upper back in an area inaccessible to licking. Do not apply an amount of solution at any one location that could run off the side of the dog.

Do not let this product get in your dog's mouth or eyes. **Do not allow the dog to lick any of the application sites for 30 minutes.** In households with multiple pets, keep each treated dog separated from other treated dogs and other pets for 30 minutes after application to prevent licking the application sites.
(See WARNINGS.) Contact with eyes can lead to eye irritation and corneal ulceration. If contact with eyes occurs, hold the dog's eyelids open, flush thoroughly with water, and contact your veterinarian.

Stiff hair, a damp appearance of the hair, pink skin, or a slight powdery residue may be observed at the application site on some animals. This is temporary and does not affect the safety and effectiveness of the product.

Shampooing 90 minutes after treatment does not reduce the effectiveness of *Advantage Multi for Dogs* in the prevention of heartworm disease. Shampooing or water immersion 4 days after treatment will not reduce the effectiveness of *Advantage Multi for Dogs* in the treatment of flea infestations. However, shampooing as often as once weekly may reduce the effectiveness of the product against fleas.

Heartworm Prevention: For prevention of heartworm disease, *Advantage Multi for Dogs* should be administered at one-month intervals. *Advantage Multi for Dogs* may be administered year-round 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 Dogs* 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 Dogs* should be given within one month of the last dose of the former medication.

Treatment of Circulating Microfilaria: For the treatment of circulating *D. immitis* microfilaria in heartworm-positive dogs, *Advantage Multi for Dogs* should be administered at one-month intervals. Treatment with an approved adulticide therapy is recommended because *Advantage Multi for Dogs* is not effective for the treatment of adult *D. immitis*.
(See PRECAUTIONS.)

Flea Treatment: For the treatment of flea infestations, *Advantage Multi for Dogs* should be administered at one-month intervals. If the dog is already infested with fleas when the first dose of *Advantage Multi for Dogs* is administered, adult fleas on the dog will be killed. However, reinfestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated. Dogs 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 dog.

Treatment and Control of Intestinal Nematode Infections: For the treatment and control of intestinal hookworm infections caused by *Ancylostoma caninum* and *Uncinaria stenocephala* (adults, immature adults and fourth stage larvae) and roundworm infections caused by *Toxocara canis* (adults and fourth stage larvae), and *Toxascaris leonina* (adults), and whipworm infections caused by *Trichuris vulpis* (adults), *Advantage Multi for Dogs* should be administered once as a single topical dose.

Treatment and Control of Sarcoptic Mange: For the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*, *Advantage Multi for Dogs* should be administered as a single topical dose. A second monthly dose may be administered if necessary.

CONTRAINDICATIONS:
Do not administer this product orally. (See WARNINGS.)
Do not use this product (containing 2.5 % moxidectin) on cats.

WARNINGS
For the first 30 minutes after application:
Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs, and
Separate treated dogs from one another and from other pets to reduce the risk of accidental ingestion.
Ingestion of this product by dogs may cause serious adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors.
In avermectin sensitive dogs,[a] the signs may be more severe and may include coma and death.[b]

[a] Some dogs are more sensitive to avermectins due to a mutation in the MDR1 gene. Dogs with this mutation may develop signs of severe avermectin toxicity if they ingest this product. The most common breeds associated with this mutation include Collies and Collie crosses.

[b] Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.

HUMAN WARNINGS:

Not for human use. Keep out of the reach of children.
Children should not come in contact with application sites for two (2) hours after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headache; dizziness; and redness, burning, tingling, or numbness of the 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, imidacloprid or moxidectin 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 Safety Data Sheet (SDS) provides additional occupational safety information. For product questions, to report adverse reactions, or for a copy of the Safety Data Sheet (SDS), call Elanco Product & Veterinary Support at 888-545-5973.

PRECAUTIONS:

Do not dispense dose applicator tubes without complete safety and administration information.

Use with caution in sick, debilitated, or underweight animals. The safety of *Advantage Multi for Dogs* has not been established in breeding, pregnant, or lactating dogs. The safe use of *Advantage Multi for Dogs* has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight.

Prior to administration of *Advantage Multi for Dogs*, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of *Advantage Multi for Dogs* has not been evaluated when administered on the same day as an adulticide. *Advantage Multi for Dogs* is not effective against adult *D. immitis*. Although the number of circulating microfilariae is substantially reduced in most dogs following treatment with *Advantage Multi for Dogs*, the microfilaria count in some heartworm-positive dogs may increase or remain unchanged following treatment with *Advantage Multi for Dogs* alone or in a dosing regimen with melarsomine dihydrochloride.
(See ADVERSE REACTIONS and ANIMAL SAFETY – Safety Study in Heartworm-Positive Dogs.)

Advantage Multi for Dogs has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

ADVERSE REACTIONS:

Heartworm-Negative Dogs

Field Studies: Following treatment with *Advantage Multi for Dogs* or an active control, dog owners reported the following post-treatment reactions:

OBSERVATION	Advantage Multi n = 128	Active Control n = 68
Pruritus	19 dogs (14.8%)	7 dogs (10.3%)
Residue	9 dogs (7.0%)	5 dogs (7.4%)
Medicinal Odor	5 dogs (3.9%)	None observed
Lethargy	1 dog (0.8%)	1 dog (1.5%)
Inappetence	1 dog (0.8%)	1 dog (1.5%)
Hyperactivity	1 dog (0.8%)	None observed

During a field study using 61 dogs with pre-existing flea allergy dermatitis, one (1.6 %) dog experienced localized pruritus immediately after imidacloprid application, and one investigator noted hyperkeratosis at the application site of one dog (1.6 %).

In a field safety and effectiveness study, *Advantage Multi for Dogs* was administered to 92 client-owned dogs with sarcoptic mange. The dogs ranged in age from 2 months to 12.5 years and ranged in weight from 3 to 231.5 pounds. Adverse reactions in dogs treated with *Advantage Multi for Dogs* included hematochezia, diarrhea, vomiting, lethargy, inappetence, and pyoderma.

Laboratory Effectiveness Studies: One dog in a laboratory effectiveness study experienced weakness, depression, and unsteadiness between 6 and 9 days after application with *Advantage Multi for Dogs*. The signs resolved without intervention by day 10 post-application. The signs in this dog may have been related to peak serum levels of moxidectin, which vary between dogs, and occur between 1 and 21 days after application of *Advantage Multi for Dogs*.

The following clinical observations also occurred in laboratory effectiveness studies following application with *Advantage Multi for Dogs* and may be directly attributed to the drug or may be secondary to the intestinal parasite burden or other underlying conditions in the dogs: diarrhea, bloody stools, vomiting, anorexia, lethargy, coughing, ocular discharge and nasal discharge. Observations at the application sites included damp, stiff or greasy hair, the appearance of a white deposit on the hair, and mild erythema, which resolved without treatment within 2 to 48 hours.

Heartworm-Positive Dogs

Field Study: A 56-day field safety study was conducted in 214 *D. immitis* heartworm and microfilaria positive dogs with Class 1, 2 or 3 heartworm disease. All dogs received *Advantage Multi for Dogs* on Study Days 0 and 28; 108 dogs also received melarsomine dihydrochloride on Study Days – 14, 14, and 15. All dogs were hospitalized for a minimum of 12 hours following each treatment. Effectiveness against circulating *D. immitis* microfilariae was > 90 % at five of six sites; however, one site had an effectiveness of 73.3 %. The microfilaria count in some heartworm-positive dogs increased or remained unchanged following treatment with *Advantage Multi for Dogs* alone or in a dosing regimen with melarsomine dihydrochloride.

Following treatment with *Advantage Multi for Dogs* alone or in a dosing regimen with melarsomine dihydrochloride, the following adverse reactions were observed:

Adverse Reaction	Dogs Treated with Advantage Multi for Dogs Only n = 106	Dogs Treated with Advantage Multi for Dogs + Melarsomine n = 108
Cough	24 (22.6%)	25 (23.1%)
Lethargy	14 (13.2%)	42 (38.9%)
Vomiting	11 (10.4%)	18 (16.7%)
Diarrhea, including hemorrhagic	10 (9.4%)	22 (20.4%)
Inappetence	7 (6.6%)	19 (17.6%)
Dyspnea	6 (5.7%)	10 (9.3%)
Tachypnea	1 (< 1%)	7 (6.5%)
Pulmonary Hemorrhage	0	1 (< 1%)
Death	0	3 (2.8%)

Three dogs treated with *Advantage Multi for Dogs* in a dosing regimen with melarsomine dihydrochloride died of pulmonary embolism from dead and dying heartworms. One dog, treated with *Advantage Multi for Dogs* and melarsomine dihydrochloride, experienced pulmonary hemorrhage and responded to supportive medical treatment. Following the first treatment with *Advantage Multi for Dogs* alone, two dogs experienced adverse reactions (coughing, vomiting, and dyspnea) that required hospitalization. In both groups, there were more adverse reactions to *Advantage Multi for Dogs* following the first treatment than the second treatment.

To report a suspected adverse reaction, call 888-545-5973.

Post-Approval Experience (2022)

The following adverse events are based on post-approval adverse drug experience reporting for *Advantage Multi for Dogs*. Not all adverse events are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data.

The following adverse events reported in dogs are listed in decreasing order of reporting frequency: depression/lethargy, pruritus, vomiting, diarrhea, anorexia, application site reactions (alopecia, pruritus, erythema, and lesions, including blisters), hyperactivity, ataxia, trembling, seizures, panting, hypersalivation, anaphylaxis/anaphylactic reactions (hives, facial swelling, edema of the head), and corneal ulceration.

Serious reactions, including neurologic signs and death have been reported when cats have been exposed (orally and topically) to this product.

In humans, nausea, numbness or tingling of the mouth/lips and throat, ocular and dermal irritation, pruritus, headache, vomiting, diarrhea, depression and dyspnea have been reported following exposure to this product.

Contact Information:

For product questions, to report adverse drug experiences, or for a copy of the Safety Data Sheet (SDS), call Elanco Product & Veterinary Support at 888-545-5973.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

ANIMAL SAFETY:

Heartworm-Negative Dogs

Field Study: In a controlled, double-masked, field safety study, *Advantage Multi for Dogs* was administered to 128 dogs of various breeds, 3 months to 15 years of age, weighing 4 to 157 pounds. *Advantage Multi for Dogs* was used safely in dogs concomitantly receiving ACE inhibitors, anticonvulsants, antihistamines, antimicrobials, chondroprotectants, corticosteroids, immunotherapeutics, MAO inhibitors, NSAIDs, ophthalmic medications, sympathomimetics, synthetic estrogens, thyroid hormones, and urinary acidifiers. Owners reported the following signs in their dogs after application of *Advantage Multi for Dogs:* pruritus, flaky/greasy residue at the treatment site, medicinal odor, lethargy, inappetence, and hyperactivity.
(See ADVERSE REACTIONS.)

Safety Study in Puppies: *Advantage Multi for Dogs* was applied topically at 1, 3 and 5X the recommended dose to 7-week-old Beagle puppies once every 2 weeks for 6 treatments on days 0, 14, 28, 42, 56, and 70. Loose stools and diarrhea were observed in all groups, including the controls, throughout the study. Vomiting was seen in one puppy from the 1X treatment group (day 57), in two puppies from the 3X treatment group (days 1 and 79), and in one puppy from the 5X treatment group (day 1). Two puppies each in the 1X, 3X, and 5X groups had decreased appetites within 24 hours post-dosing. One puppy in the 1X treatment group had pruritus for one hour following the fifth treatment. A puppy from the 5X treatment group displayed rapid, difficult breathing from 4 to 8 hours following the second treatment.

Dermal Dose Tolerance Study: *Advantage Multi for Dogs* was administered topically to 8-month-old Beagle dogs at 10X the recommended dose once. One dog showed signs of treatment site irritation after application. Two dogs vomited, one at 6 hours and one at 6 days post-treatment. Increased RBC, hemoglobin, activated partial thromboplastin, and direct bilirubin were observed in the treated group. Dogs in the treated group did not gain as much weight as the control group.

Oral Safety Study in Beagles: *Advantage Multi for Dogs* was administered once orally at the recommended topical dose to 12 dogs. Six dogs vomited within 1 hour of receiving the test article, 2 of these dogs vomited again at 2 hours, and 1 dog vomited again up to 18 hours post-dosing. One dog exhibited shaking (nervousness) 1 hour post-dosing. Another dog exhibited abnormal neurological signs (circling, ataxia, generalized muscle tremors, and dilated pupils with a slow pupillary light response) starting at 4 hours post-dosing through 18 hours post-dosing. Without treatment, this dog was neurologically normal at 24 hours and had a normal appetite by 48 hours post-dosing.
(See CONTRAINDICATIONS.)

Dermal Safety Study in Ivermectin-Sensitive Collies: *Advantage Multi for Dogs* was administered topically at 3 and 5X the recommended dose every 28 days for 3 treatments to Collies which had been prescreened for avermectin sensitivity. No clinical abnormalities were observed.

Oral Safety Study in Ivermectin-Sensitive Collies: *Advantage Multi for Dogs* was administered orally to 5 pre-screened ivermectin-sensitive Collies. The Collies were asymptomatic after ingesting 10 % of the minimum labeled dose. At 40 % of the minimum recommended topical dose, 4 of the dogs experienced neurological signs indicative of avermectin toxicity including depression, ataxia, mydriasis, salivation, muscle fasciculation, and coma, and were euthanized.
(See CONTRAINDICATIONS.)

Heartworm-Positive Dogs

Laboratory Safety Study in Heartworm-Positive Dogs: *Advantage Multi for Dogs* was administered topically at 1 and 5X the recommended dose every 14 days for 3 treatments to dogs with adult heartworm infections and circulating microfilaria. At 5X, one dog was observed vomiting three hours after the second treatment. Hypersensitivity reactions were not seen in the 5X treatment group. Microfilaria counts decreased with treatment.

STORAGE INFORMATION:

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

HOW SUPPLIED:

Applications Per Package
6 x 0.4 mL tubes
6 x 1.0 mL tubes
6 x 2.5 mL tubes
6 x 4.0 mL tubes
6 x 5.0 mL tubes

Revised: January 2023

Approved by FDA under NADA # 141-251

Made in Germany

Manufactured for:
Elanco US Inc
Greenfield, IN 46140 U.S.A.

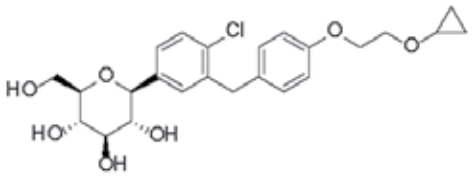
Bexacat™
(bexagliflozin tablets)

15 mg flavored tablets
For oral use in cats only
Sodium-glucose cotransporter 2 (SGLT2) inhibitor

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

WARNING: DIABETIC KETOACIDOSIS/EUGLYCEMIC DIABETIC KETOACIDOSIS
- **Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis (see Adverse Reactions). As diabetic ketoacidosis and euglycemic diabetic ketoacidosis in cats treated with Bexacat may result in death, development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat (see Monitoring).**
- **Due to the risk of developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis, do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus (see Contraindications).**
- **Bexacat should not be initiated in cats with anorexia, dehydration or lethargy at the time of diagnosis of diabetes mellitus or without appropriate screening tests (see Animal Safety Warnings).**

DESCRIPTION
Bexacat (bexagliflozin tablets) are flavored pentagonal, 10 mm, speckled white, brown, or tan biconvex with a characteristic odor. The empirical formula is C24H29ClO7 and the molecular weight is 464.94 g/mol. The chemical name is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
The chemical structure of bexagliflozin is:



INDICATION
Bexacat is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

DOSAGE AND ADMINISTRATION
Always provide the Client Information Sheet with the prescription.

Dosing Instructions
Administer one tablet by mouth to cats weighing 6.6 lbs (3.0 kg) or greater once daily, at approximately the same time each day, with or without food, and regardless of blood glucose level.

Monitoring
- Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level.
- During treatment with Bexacat, blood glucose, fructosamine, serum β-hydroxybutyrate (BHBA), serum feline pancreas-specific lipase (fPL), liver parameters, serum cholesterol and triglycerides; and body weight and clinical signs should be routinely monitored.
  - Increasing or persistently elevated feline pancreas-specific lipase or liver parameters should prompt further evaluation for pancreatitis and/or hepatic disease and consideration for discontinuing Bexacat.
  - BHBA is the predominate ketoacid in diabetic ketoacidosis. Bexacat should be discontinued if a notable reduction in BHBA is not observed after initiation of Bexacat, or if BHBA persistently rises after an initial reduction.
  - Cats with increasing or persistently elevated cholesterol and triglyceride levels may be at an increased risk for developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis.
  - Bexacat should be discontinued if poor glycemic control, as described below, develops.
- During the first 8 weeks after initiation of Bexacat, assessment of glycemic control and clinical improvement should be evaluated.
  - A physical examination, an 8-hour blood glucose curve, serum fructosamine and body weight should be assessed at 2, 4 and 8 weeks.
  - Cats demonstrating poor glycemic control, including weight loss, an average blood glucose concentration from an 8-hour blood glucose curve ≥ 250 mg/dL, and/or a fructosamine indicating poor glycemic control should be closely monitored.
  - Bexacat should be discontinued, and initiation of insulin considered in cats demonstrating poor glycemic control, as described above, at 8 weeks.
- Cats may present with diabetic ketoacidosis and a normal blood glucose concentration (euglycemic diabetic ketoacidosis). Delay in recognition and treatment of diabetic ketoacidosis and euglycemic diabetic ketoacidosis may result in increased morbidity and mortality.
- Development of diabetic ketoacidosis and euglycemic diabetic ketoacidosis requires the following actions:
  - Discontinuation of Bexacat
  - Prompt initiation of insulin therapy
  - Administration of dextrose or other carbohydrate source, regardless of blood glucose concentration
  - Appropriate nutritional support should be promptly initiated to prevent or treat hepatic lipidosis.

For more information refer to **CONTRAINDICATIONS** and **WARNINGS.**

CONTRAINDICATIONS
- Do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus. The use of Bexacat in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of Bexacat, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death.
- Due to risk of severe adverse reactions, do not use Bexacat in cats with evidence of hepatic disease or reduced renal function.

WARNINGS
User Safety Warnings
Not for use in humans. Keep out of reach of children. Consult a physician in case of accidental ingestion by humans.

Animal Safety Warnings
- Bexacat should not be initiated in cats with:
  - Anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus, as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis.
  - An fPL level > 5.3 mcg/L, diagnostic imaging consistent with pancreatitis, a history of pancreatitis, or current clinical signs suggestive of pancreatitis.
  - Laboratory values consistent with diabetic ketoacidosis, including elevated urine or serum ketones, and metabolic acidosis (high anion gap, or decreased bicarbonate, pH, or partial pressure carbon dioxide [PaCO2] levels).
  - A BHBA > 37 mg/dL, or if BHBA is > 25 mg/dL and the cat has a history of renal disease or metabolic acidosis.
- Persistent plasma bexagliflozin concentrations and reduced clearance of Bexacat, represented as the presence of plasma half-lives in excess of 24 hours, may result in prolonged clinical effects such as glucosuria and/or euglycemia despite discontinuation of Bexacat in some cats with hepatic disease and/or reduced renal function, including cats with clinically undetectable disease at the time of Bexacat initiation. Reduced clearance of Bexacat may contribute to persistent glucosuria, resulting in an osmotic diuresis and dehydration that requires appropriate hydration support. These cats may require hospitalization, which may be protracted, for sequalae such as diabetic ketoacidosis, euglycemic diabetic ketoacidosis, or hepatic lipidosis.
- Cats should be screened for urinary tract infections and treated, if indicated, when initiating Bexacat. Treatment with Bexacat may increase the risk for urinary tract infections (see **Adverse Reactions**). Cats treated with Bexacat should be monitored for urinary tract infections and treated promptly. Consider discontinuation of Bexacat in cats with recurrent urinary tract infections.
- Bexacat may cause increased serum calcium concentrations. Bexacat should be discontinued in cats with persistent increases in serum total calcium or ionized calcium because of increased risk of forming calcium containing uroliths (see **Adverse Reactions**).
- Long term use of Bexacat may increase the risk of urothelial carcinoma (see **Adverse Reactions**).
- Keep Bexacat in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS
- Bexacat should be discontinued in cats who develop diarrhea unresponsive to conventional therapy.
- Consider temporary discontinuation of Bexacat in cats during times of decreased caloric intake, such as surgery or decreased appetite, as administration of Bexacat in these cats may increase the risk of diabetic ketoacidosis or hepatic lipidosis.
- The osmotic diuretic effects of Bexacat may contribute to inappropriate urination in some cats (see **Adverse Reactions**).
- Polyphagia as a compensatory response to caloric wasting from glucosuria may persist in up to 80% of cats, despite evidence of adequate glycemic control, and may lead to progressive weight gain.
- Approximately 20-30% of cats may have persistent polyuria and/or polydipsia secondary to Bexacat-induced osmotic diuresis and may be a risk factor for dehydration-associated diabetic ketoacidosis.
- The concurrent use of volume depleting drugs in cats treated with Bexacat has not been evaluated.
- The safety of Bexacat in breeding, pregnant, and lactating cats has not been evaluated.

ADVERSE REACTIONS
Field Study
Eighty-four cats with newly diagnosed diabetes mellitus were enrolled in a 180-day multicenter field effectiveness and safety study. Safety data were evaluated in 84 cats treated with at least one dose of Bexacat. All cats received one tablet, once daily, regardless of body weight or blood glucose level. Seventy-two of the 84 enrolled cats completed the study. The most common adverse reactions included elevated blood urea nitrogen (BUN), vomiting, elevated urine specific gravity (USG), elevated serum fPL, diarrhea, anorexia, lethargy, and dehydration. The adverse reactions seen during the field study are summarized in Table 1 below.

Table 1. Adverse Reactions (n=84)

Adverse Reaction	Number (%)
Elevated BUN*	46 (54.8)
Vomiting	42 (50.0)
Elevated USG†	33 (39.3)
Elevated fPL‡	33 (39.3)
Diarrhea	32 (38.1)
Anorexia	31 (37.0)
Lethargy	17 (20.2)
Dehydration	16 (19.0)
Elevated symmetrical dimethylarginine (SDMA)	13 (15.5)
Weight loss	13 (15.5)
Urinary tract infection	12 (14.3)

Adverse Reaction	Number (%)
Elevated ALT and/or AST§	11 (13.1)
Hypercalcemia	8 (9.5)
Behavioral changes**	6 (7.1)
Proteinuria	5 (6.0)
Elevated creatinine	4 (4.8)
Elevated creatine kinase	4 (4.8)
Inappropriate urination	4 (4.8)
Death	3 (3.6)
Diabetic ketoacidosis	3 (3.6)
Pancreatitis	3 (3.6)
Euglycemic diabetic ketoacidosis	2 (2.4)
Hepatic lipidosis	2 (2.4)
Elevated alkaline phosphatase	2 (2.4)
Elevated total bilirubin	2 (2.4)
Constipation	2 (2.4)

* Most cats had elevations < 1.5 times the upper limit of normal (ULN).
† Elevations were predominantly attributable to dehydration and/or glucosuria.
‡ Most cats had one or more isolated elevations, followed by a return to previous values.
§ Of nine cats with elevations ≥ 1.5X ULN, 2 cats developed diabetic ketoacidosis and were transitioned to insulin. One cat developed diabetic ketoacidosis and hepatic lipidosis resulting in death (euthanasia). One cat developed anemia, progressive weight loss and fPL elevations resulting in death.
** Observations included hiding, agitation, aggression, vocalization, and anxious behavior.

Nine serious adverse reactions associated with Bexacat administration occurred during the study, including three cats who died or were euthanized. Of the three cats who died or were euthanized, two cats became clinically ill within 5 doses of Bexacat administration (range 3 to 5 doses). One cat with euglycemic diabetic ketoacidosis and hepatic lipidosis was euthanized due to further deterioration of its clinical condition, despite supportive treatment. One cat demonstrating anorexia, lethargy, dehydration, azotemia, and hypokalemia was euthanized without supportive treatment. One cat, who demonstrated a lack of effectiveness, anemia and hepatic lipidosis died on Day 77 despite supportive treatment and additional diagnostics. Six of the nine cats had serious adverse reactions that did not result in death or euthanasia. Five cats were treated for their clinical conditions and transitioned to insulin. Serious adverse reactions in these cats were associated with the following conditions (number of cats): euglycemic diabetic ketoacidosis (1); lack of effectiveness, diabetic ketoacidosis, elevated liver parameters (1); diabetic ketoacidosis (1); diabetic ketoacidosis and pyelonephritis (1); and lack of effectiveness, weight loss, dehydration (1). One cat with constipation and pancreatitis received supportive treatment and remained on Bexacat (bexagliflozin tablets).

Pilot Field Study

Eighty-nine cats with newly diagnosed diabetes mellitus were enrolled in a 56-day multicenter pilot field effectiveness and safety study, with continued use for up to 180 days. All cats received one tablet, once daily, regardless of body weight or blood glucose level. Safety data were evaluated for all 89 cats treated with at least one dose of bexagliflozin. The most common adverse reactions included elevated blood urea nitrogen (BUN), elevated urine specific gravity (USG), elevated serum feline pancreas-specific lipase, vomiting, diarrhea/loose stool, hyporexia/anorexia, lethargy, elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and urinary tract infections. The adverse reactions seen in the pilot study are summarized in Table 2 below.

Table 2. Adverse Reactions (n=89)

Adverse Reaction	Number (%)
Elevated BUN*	51 (57.3)
Elevated USG†	43 (48.3)
Elevated fPL‡	39 (43.8)
Vomiting	39 (43.8)
Diarrhea/Loose Stool	29 (32.6)
Hyporexia/Anorexia	28 (31.4)
Lethargy	16 (18.0)
Elevated ALT and/or AST§	13 (14.6)
Urinary tract infection	13 (14.6)
Dehydration	10 (11.2)
Elevated symmetrical dimethylarginine (SDMA)	10 (11.2)
Behavioral changes**	9 (10.1)
Ketosis/Ketonuria	8 (9.0)
Weight loss	8 (9.0)
Proteinuria	8 (9.0)
Pancreatitis	7 (7.9)
Death	6 (6.7)
Anemia	6 (6.7)
Hepatopathy	6 (6.7)
Hypercalcemia	4 (4.5)
Elevated creatine kinase	4 (4.5)
Inappropriate urination	4 (4.5)
Peritonitis	3 (3.4)
Constipation	3 (3.4)
Elevated creatinine	2 (2.2)
Euglycemic diabetic ketoacidosis	2 (2.2)
Diabetic ketoacidosis	2 (2.2)
Hemolytic anemia	2 (2.2)
Elevated total bilirubin	2 (2.2)

* Most cats had elevations ≤ 1.5X upper limit of normal (ULN).
† Elevations were predominantly attributable to dehydration and/or glucosuria.
‡ Most cats had one or more isolated elevations, followed by a return to previous values.
§ Most elevations were ≤ 2X ULN. One cat had marked ALT and AST (9X and 6X upper limit of normal, respectively) elevations on Day 28. Following discontinuation of bexagliflozin, the liver enzymes decreased within 24 hours and returned to within reference range in 10 days.
** Observations included hiding, hyperactivity, vocalization, and abnormal behavior.

Twenty cats (22%) had at least one blood glucose value < 65 mg/dL recorded during 8-hour blood glucose curves. No clinical signs of hypoglycemia were observed and bexagliflozin dosing was not adjusted in any cat due to documented hypoglycemia. Nine serious adverse reactions associated with bexagliflozin administration occurred during the study, including six cats who died or were euthanized. Of the six cats who died or were euthanized, five became clinically ill within receiving 5 doses of bexagliflozin (range 1 to 5 doses). Four of the cats were euthanized due to further deterioration of their clinical condition despite supportive treatment. One cat died despite supportive treatment. Deaths were associated with the following conditions (number of cats): necrotizing pancreatitis and pancreatic abscess (1), pancreatitis and hepatic lipidosis (1), euglycemic diabetic ketoacidosis and severe hepatic lipidosis (1), pancreatitis and hepatic abscesses (1), diabetic ketoacidosis (1), and persistent polyuria and polydipsia and quality of life concerns (1).

Three of nine serious adverse reactions that did not result in death or euthanasia included the following (number of cats): acute hepatocellular injury (1), immune-mediated hemolytic anemia (1), and euglycemic diabetic ketoacidosis with concurrent pancreatitis and hepatopathy (1). Two cats with serious adverse reactions demonstrated persistent bexagliflozin blood plasma levels and elimination half-lives after discontinuation of bexagliflozin. One cat with renal and liver values within the reference range at screening was euthanized due to a continued decline in clinical condition despite treatment for euglycemic diabetic ketoacidosis and severe hepatic lipidosis. The second cat, noted to have IRIS (International Renal Interest Society) stage II renal disease and liver values within the reference range at screening, recovered following treatment for marked liver enzyme elevations above the reference range on Day 28.

Extended Use Field Study

One hundred twenty-five cats with diabetes mellitus that had previously completed a bexagliflozin field study were enrolled in a multicenter extended use field study. Cats were enrolled in the study for a range of 7 to 1064 days, with a mean of 329 days. Safety data were evaluated for all 125 cats treated with at least one dose of Bexacat (bexagliflozin tablets). All cats received one tablet, once daily, regardless of body weight or blood glucose level. Forty-nine of the 125 enrolled cats were withdrawn from the study due to adverse reactions, serious adverse reactions, death/euthanasia, lack of effectiveness, suspected diabetic remission, withdrawal of owner consent, or lost to follow up. The most common adverse reactions were similar to those noted in the previous field studies and included elevated USG (35.2%), vomiting (27.2%), elevated fPL (26.4%), anorexia (24.0%), diarrhea (22.4%), urinary tract infections (17.6%), lethargy (16.8%), and death (16.0%).

Twenty serious adverse reactions associated with Bexacat administration occurred during the study, all resulting in death or euthanasia. Clinical signs of hypoglycemia were observed in two of these cats. Deaths were associated with the following conditions (number of cats), with some cats experiencing multiple comorbidities (necropsy was not granted in all cases): euglycemic diabetic ketoacidosis (8); diabetic ketoacidosis (4); hepatic lipidosis (5); pancreatic necrosis/peripancreatic fat saponification (3); urothelial carcinoma (2); hypercalcemia, recurrent calcium containing cystic calculi (1); lack of effectiveness, weight loss, anorexia (1); lethargy, weight loss, pallor (1); chronic renal disease, glomerulonephritis (1); chronic enteropathy (1); hypoglycemia, possible pancreatitis (1).

CONTACT INFORMATION

To report suspected adverse events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc at 1-888-545-5973.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

INFORMATION FOR CAT OWNERS

Owners should be given the Client Information Sheet to read before Bexacat is administered. Owners should be advised to discontinue Bexacat and contact a veterinarian immediately if their cat develops anorexia, lethargy, vomiting, diarrhea, or weakness.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bexagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT2), the renal transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.

Pharmacokinetics

In a laboratory pilot study conducted to determine the prandial state of maximum exposure, systemic exposure for bexagliflozin was greater in the fasted state than in the fed state by 82% for the mean maximum observed plasma concentration (C_{max}), and by 54% for the mean area under the plasma concentration versus time curve (AUC) from dosing (time 0) to the last quantifiable concentration ($AUC_{0\text{-last}}$), respectively.

In a well-controlled margin of safety study (see **Target Animal Safety**), mean C_{max} was approximately dose-proportional over a dosage range of 5 mg/kg (1X) to 25 mg/kg (5X). Mean AUC from time 0 to 24 hours exposure was approximately dose-proportional over a dosage range of 5 to 15 mg/kg, but more than dose-proportional at 15 to 25 mg/kg. An increase in exposure (AUC_{0-24} and C_{max}), was observed in female cats compared to male cats on all evaluation days. Median time to reach peak plasma concentration (T_{max}) was approximately 0.5 hours (range 0.5 to 2 hours) and mean half-life ($T_{1/2}$) was approximately 5 hours across all dose groups. There was no accumulation of bexagliflozin following daily dosing of 5, 15, and 25 mg/kg in healthy non-diabetic cats. However, field studies showed that some diabetic cats had persistent bexagliflozin blood levels after discontinuation of the drug, which may be related to a decrease in liver function in some cats (see **Animal Safety Warnings**).

EFFECTIVENESS

Field Study

Eighty-four cats diagnosed with diabetes mellitus were enrolled in a 180-day multicenter field effectiveness and safety study. Enrolled cats included purebreds and mixed breeds, ranging in age from 3 to 19 years, and weighing between 7.3 to 24.3 lbs (3.3 to 11.3 kg). Cats received one tablet, once daily, regardless of body weight or blood glucose level. Treatment success was defined as improvement in at least one blood glucose variable (blood glucose curve mean or fructosamine) and improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, polyphagia, or body weight [weight gain or no weight loss]).

Of 77 cats included in the effectiveness-evaluable population:

- 64 cats (83.1%) were considered a treatment success on Day 56.
- The lower bound two-sided 90% confidence interval was 74.5%. Effectiveness was demonstrated if the lower bound of the confidence interval was > 66%.
- Mean blood glucose curve mean decreased from 284 mg/dL on Day 0 to 143 mg/dL on Day 56.
- Mean fructosamine levels decreased from 544 µmol/L prior to Day 0 to 295 µmol/L on Day 56.
- Improvements in the clinical signs of polyuria, polydipsia, polyphagia, and body weight on Day 56 were observed in 53 (68.8%), 57 (74.0%), 44 (57.1%), and 42 (54.6%) cats, respectively.
- 66 cats (85.7%) completed the 180-day study.

Pilot Field Study

Eighty-nine cats diagnosed with diabetes mellitus were enrolled in a 56-day, multicenter pilot field effectiveness and safety study with continued use for up to 180 days. Enrolled cats included purebreds and mixed breeds, ranging in age from 3 to 17 years and weighing 6.4 to 22.9 lbs (2.9 to 10.4 kg). Cats received one tablet, once daily, regardless of weight. Treatment success was defined as improvement in at least one blood glucose variable (blood glucose curve mean or fructosamine) and improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, polyphagia, or body weight [weight gain or no weight loss]). Of the 72 cats included in the effectiveness-evaluable population, 58 (80.6%) were considered treatment successes on Day 56.

TARGET ANIMAL SAFETY

In a well-controlled laboratory margin of safety study, Bexacat was administered orally to 28 fasted, healthy, lean, intact adult cats at doses of at least 1X (8 cats), 3X (8 cats), and 5X (12 cats) the maximum exposure dose (5 mg/kg) once daily for 26 weeks. The control group (8 cats) was sham dosed. The maximum exposure dose (5 mg/kg) was based on the assessment that the minimum weight of an eligible cat with diabetes mellitus is approximately 3 kg. Polyuria, glucosuria (with a corresponding increase in food consumption), loose stools and diarrhea, and ketonuria were reported more frequently in cats that received Bexacat than in control cats. There were drug-related clinically insignificant increases in calcium, magnesium, and cholesterol levels, and decreases in creatinine and amylase levels, and blood pressure and heart rate values. Gross necropsy demonstrated treatment-related observations of mild, diffuse zonal patterns in the liver. One cat with the observed zonal pattern had mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and a histopathological observation of minimal, multifocal necrosis in the liver. The histopathological finding did not correspond to the zonal patterns observed grossly. There were no clinically relevant, drug-related effects on hematology and coagulation parameters and organ weight values.

STORAGE CONDITIONS Bexacat should be stored at room temperature 68 to 77 °F (20 to 25 °C).

HOW SUPPLIED

Flavored tablet each containing 15 mg bexagliflozin; 30 or 90 tablets per bottle.

Approved by FDA under NADA # 141-566
Manufactured for: Elanco US Inc, Greenfield, IN 46140

September 2022

Zenrelia™
(ilunocitinib tablets)

Immunosuppressive
For oral use in dogs only

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

> **WARNING: INADEQUATE IMMUNE RESPONSE TO VACCINES**
>
> **Based on results of the vaccine response study, dogs receiving Zenrelia are at risk of an inadequate immune response to vaccines. Discontinue Zenrelia for at least 28 days to 3 months prior to vaccination and withhold Zenrelia for at least 28 days after vaccination (see Warnings and Target Animal Safety).**

DESCRIPTION
Zenrelia is a synthetic Janus kinase (JAK) inhibitor. Zenrelia is a member of the pyrrolidine class of JAK inhibitors and its chemical name is 2-[1-cyclopropylsulfonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetonitrile.

INDICATIONS
Zenrelia is indicated for control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

DOSAGE AND ADMINISTRATION
The dose of Zenrelia (ilunocitinib tablets) is 0.27 to 0.36 mg ilunocitinib/lb (0.6 to 0.8 mg ilunocitinib/kg) body weight, administered orally, once daily, with or without food.

Dosing Chart

Weight Range (in lb)	Weight Range (in kg)	Number of Tablets to be Administered			
		4.8 mg tablets	6.4 mg tablets	8.5 mg tablets	15 mg tablets
6.6 – 8.8	3.0 - 4.0	0.5			
8.9 – 11.8	4.1 – 5.3		0.5		
11.9 – 14.3	5.4 – 6.5			0.5	
14.4 – 17.7	6.6 – 8.0	1			
17.8 – 23.6	8.1 – 10.6		1		
23.7 – 31.1	10.7 – 14.1			1	
31.2 – 35.4	14.2 – 16.0		1.5		
35.5 – 43.1	16.1 – 19.5			1.5	
43.2 – 55.0	19.6 – 24.9				1
55.1 – 62.5	25.0 – 28.3			2	
62.6 – 82.5	28.4 – 37.4				1.5
82.6 – 110.0	37.5 – 49.9				2
110.1 – 137.5	50.0 – 62.4				2.5
137.6 – 165.0	62.5 – 74.9				3
≥ 165.1	≥ 75	Administer the appropriate combination of tablet strengths			

WARNINGS
User Safety Warnings
Not for use in humans. Keep this drug out of the reach of children. Wash hands immediately after handling tablets. In case of accidental ingestion, seek medical attention immediately.

Animal Safety Warnings
Due to the risk of infections, dogs should be up to date on vaccinations prior to starting Zenrelia (see Target Animal Safety).

Due to the risk of an inadequate immune response to vaccines, do not administer vaccines to a dog receiving Zenrelia. Discontinue Zenrelia for at least 28 days to 3 months prior to vaccination and withhold Zenrelia for at least 28 days after vaccination (see Target Animal Safety).

Dogs should be monitored for the development of infections because Zenrelia may increase susceptibility to infections, including bacterial hepatitis and pancreatitis, demodicosis, interdigital furunculosis, coccidiosis, and pneumonia, and exacerbation of established or uncomplicated infections (see Target Animal Safety and Adverse Reactions).

Zenrelia is not for use in dogs with serious infections.

Zenrelia may cause a progressive or persistently decreased hematocrit, hemoglobin, and/or red blood cell count without a corresponding increase in absolute reticulocyte count (see Target Animal Safety).

New neoplastic conditions (benign and malignant) were observed in dogs treated with Zenrelia during clinical studies (see Adverse Reactions).

Consider the risks and benefits of treatment prior to initiating Zenrelia in dogs with a history of recurrent serious infections or recurrent demodicosis or neoplasia (see Adverse Reactions and Target Animal Safety).

Zenrelia modulates the immune system.

Zenrelia is not for use in dogs less than 12 months of age (see Target Animal Safety).

Keep Zenrelia in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS
The safe use of Zenrelia has not been evaluated in breeding, pregnant, or lactating dogs.

Decreased prostate gland weights in intact male dogs were observed in a laboratory safety study (see Target Animal Safety).

The safe use of Zenrelia has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents.

ADVERSE REACTIONS
Control of Atopic Dermatitis
In a masked field study assessing effectiveness and safety of Zenrelia for the control of atopic dermatitis in dogs, 181 Zenrelia-treated dogs and 87 placebo-treated dogs diagnosed with atopic dermatitis were evaluated for safety up to 112 days. By Day 112, 88.7% of placebo-treated dogs and 22.1% of Zenrelia-treated dogs exited the study. Adverse reactions seen during the field study are summarized in Table 1 below.

Table 1. Adverse Reactions through Day 112

Adverse Reaction	Zenrelia N = 181 Number of Dogs (%)	Placebo N = 87 Number of Dogs (%)
Vomiting or nausea	40 (22.1 %)	14 (16.1 %)
Diarrhea	35 (19.3 %)	9 (10.3 %)
Lethargy	22 (12.2 %)	9 (10.3 %)
Otitis externa	19 (10.5 %)	20 (23.0 %)
Anorexia	17 (9.4 %)	7 (8.0 %)
Dermal growth (e.g., cyst, papilloma)	16 (8.8 %)	4 (4.6 %)
Epiphora or ocular discharge	14 (7.7 %)	1 (1.1 %)
Coughing or sneezing, including respiratory infections	12 (6.6 %)	2 (2.3 %)
Bacterial skin infection	10 (5.5 %)	9 (10.3 %)
Elevated liver enzyme(s)	10 (5.5 %)	2 (2.3 %)
Urinary tract infection	10 (5.5 %)	2 (2.3 %)
Upset stomach, including flatulence and abdominal pain	10 (5.5 %)	0
Leukopenia	9 (4.9 %)	1 (1.1 %)
Scooting	8 (4.4 %)	1 (1.1 %)
Lipoma	7 (3.9 %)	1 (1.1 %)
Weight gain	7 (3.9 %)	0
Increased water intake	4 (2.2 %)	2 (2.3 %)
Gingivitis (recurrence or worsening)	4 (2.2 %)	0
Blood in stool	4 (2.2 %)	0
Elevated total bilirubin	4 (2.2 %)	0
Elevated triglycerides	4 (2.2 %)	0
Histiocytoma	3 (1.7 %)	0
Increased appetite	3 (1.7 %)	0
Fungal skin infection	3 (1.7 %)	2 (2.3 %)
Weight loss	2 (1.1 %)	1 (1.1 %)
Metastatic neoplasia (i.e., hemangiosarcoma)	1 (0.6 %)	0
Systemic fungal infection	1 (0.6 %)	0
Mast cell tumor	1 (0.6 %)	0

N – number of dogs

Abnormal hematology results likely related to Zenrelia treatment included thrombocytopenia, leukopenia, neutropenia, lymphopenia, eosinopenia, monocytopenia, and decreased red blood cell count.

Abnormal serum chemistry results likely related to Zenrelia treatment included increased hepatobiliary parameters (alanine transaminase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and total bilirubin), increased blood urea nitrogen (concurrently with an increase in creatinine for one dog), hypertriglyceridemia, hypercholesterolemia, hypoalbuminemia (without a concurrent hypoglobulinemia), and hypoglobulinemia (with or without a decrease in total protein).

Twelve Zenrelia-treated dogs withdrew from the study early due to an adverse reaction, nine of which were considered likely related to Zenrelia treatment. These reactions included repeated episodes of vomiting, leukopenia, neutropenia, worsening of pre-existing lymphocytosis, enlargement of a non-resolving histiocytoma, eyelid mass with bacterial blepharitis, otitis interna with vestibular disease, urinary tract infection, and upper respiratory infection. Five placebo dogs withdrew from the study early due to an adverse reaction (i.e., lethargy, worsening of pre-existing lymphocytosis, occurrence of pyoderma, skin infection, and foot infection).

One Zenrelia-treated dog was diagnosed with splenic and liver masses on Day 112. Histopathologic diagnosis after euthanasia one month later confirmed metastatic splenic and hepatic hemangiosarcoma. Another Zenrelia-treated dog experienced traumatic lacerations and a puncture wound four days prior to study completion, which progressed to a serious infection. The owner elected amputation after study completion. A third Zenrelia-treated dog experienced a moderate neutropenia on Day 28 associated with a pre-existing subclinical urinary tract infection (UTI) that had progressed into a clinical UTI. The neutrophil count normalized seven days later while still receiving Zenrelia, prior to exiting the study to receive antibiotics.

Control of Pruritus Associated with Allergic Dermatitis
In a masked field study assessing effectiveness and safety of Zenrelia for the control of pruritus associated with allergic dermatitis in dogs, 206 Zenrelia-treated dogs and 100 placebo-treated dogs diagnosed with allergic dermatitis were evaluated for safety up to 112 days. By Day 112, 64% of placebo-treated dogs and 46.6% of Zenrelia-treated dogs exited the study. Adverse reactions seen during the field study are summarized in Table 2 below.

Table 2. Adverse Reactions through Day 112

Adverse Reaction	Zenrelia N = 206 Number of Dogs (%)	Placebo N = 100 Number of Dogs (%)
Vomiting or nausea	32 (15.5%)	11 (11.0 %)
Diarrhea	25 (12.2 %)	6 (6.0 %)
Lethargy	25 (12.1 %)	7 (7.0 %)
Urinary tract infection	13 (6.3 %)	2 (2.0 %)
Anorexia	10 (4.9 %)	3 (3.0 %)
Coughing, wheezing, or difficulty breathing	9 (4.4 %)	0
Elevated liver enzyme(s)	8 (3.9 %)	0
Otitis externa	8 (3.9 %)	5 (5.0 %)
Increased water intake	7 (3.4 %)	2 (2.0 %)
Upset stomach, including flatulence, retching, and abdominal pain	5 (2.4 %)	4 (4.0 %)
Ocular discharge	5 (2.4 %)	1 (1.0 %)
Elevated triglycerides	5 (2.4 %)	0
Dermal or subcutaneous growth (e.g., cyst, nodule)	3 (1.5 %)	2 (2.0 %)
Sneezing	3 (1.5 %)	0
Blood in stool	3 (1.5 %)	0
Increased urination	3 (1.5 %)	0
Bacterial skin infection	2 (1.0 %)	4 (4.0 %)
Weight gain	2 (1.0 %)	0
Neurological disorder (e.g. tremors, ataxia)	2 (1.0 %)	0
Increased appetite	1 (0.5 %)	0
Fungal skin infection	1 (0.5 %)	0
Fever	1 (0.5 %)	0
Hematuria (without urinary tract infection)	1 (0.5 %)	0

N = number of dogs

Abnormal hematology results likely related to Zenrelia treatment included thrombocytosis, leukopenia, neutropenia, eosinopenia, and monocytopenia.

Abnormal serum chemistry results likely related to Zenrelia treatment included increased hepatobiliary parameters (alanine transaminase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and total bilirubin), increased blood urea nitrogen, increased creatinine, hypertriglyceridemia, hypercholesterolemia, hypoproteinemia, and hypoglobulinemia (with or without a decrease in total protein).

Seven Zenrelia-treated dogs withdrew from the study early due to an adverse reaction, four of which were considered likely related to Zenrelia treatment. These reactions included vomiting, lethargy, soft stool, neutropenia, increased liver enzymes, fever, abdominal discomfort, coughing, and wheezing. Four placebo treated dogs also withdrew from the study early due to an adverse reaction (i.e., splenic hemangiosarcoma, melanoma, abdominal pain, lethargy, and vomiting).

CONTACT INFORMATION
To report suspected adverse events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc at 1-888-545-5973.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY
Mechanism of Action
Ilunocitinib is a non-selective JAK inhibitor which inhibits the function of a variety of pruritogenic, pro-inflammatory and allergy related cytokines that are dependent upon JAK enzymes. Ilunocitinib has a high potency for JAK1, JAK2, and tyrosine kinase 2 (TYK2) inhibition. Ilunocitinib is not a corticosteroid or an antihistamine.

Pharmacokinetics
Ilunocitinib is rapidly and well absorbed and excreted via the biliary/fecal route after oral administration in dogs. Following a single oral or intravenous administration of ilunocitinib at 0.8 mg/kg, the oral bioavailability based on area under the curve from the time of dosing to the last quantifiable plasma concentration (AUC_{last}) was 80% in the fed state and 58% in the fasted state. The systemic clearance following intravenous administration was 389 mL/hour/kg with a terminal half-life of 3.6 h. The volume of distribution was 1280 mL/kg (n=8). The maximum plasma concentration (C_{max}) and AUC_{last} were 128% and 45% higher, respectively, in the fed state as compared to the fasted state (n=16).

In a laboratory margin of safety study, healthy adult dogs (see Target Animal Safety) received daily oral administration of Zenrelia at 0.8 mg/kg, 1.6 mg/kg, 2.4 mg/kg, or 4.0 mg/kg for 182 consecutive days. Dogs were dosed in the fed state, the expected state of maximum bioavailability. At 0.8 mg/kg, the ilunocitinib mean (coefficient of variation %) C_{max} was 318 ng/mL (24.6%) with a median time to C_{max} of 2 h (range 1 – 2 h), and the AUC_{last} and half-life were 1360 h*ng/mL (35.1%) and 3.3 h (11.9%), respectively. Minimal accumulation was observed between Days 1 and 182 with geometric mean accumulation ratios for C_{max} and AUC_{last} between 1.1 and 1.8. After the first dose, C_{max} increased in a linear but less than proportional manner where a 5-fold increase in dose resulted in a 3.4-fold (90% confidence limit: 2.8 – 4.0) increase in C_{max}. There was a non-linear relationship between dose and AUC_{last} where a 5-fold increase in dose resulted in a 4.2-fold (90% confidence limit: 3.4 – 5.1) increase in AUC_{last}. Pharmacokinetic parameters are presented as geometric means.

EFFECTIVENESS
Control of Atopic Dermatitis
A masked, placebo-controlled field study was conducted at 26 veterinary clinics in the US and Canada, enrolling 268 client-owned dogs diagnosed with atopic dermatitis and having at least moderate pruritus and mild skin lesions. Dogs were randomized to once daily treatment with Zenrelia at 0.6 – 0.8 mg/kg or placebo, at a ratio of 2:1 respectively. Other medications that could affect the evaluation of effectiveness were not allowed during the study, such as corticosteroids, antihistamines, and cyclosporine. Treatment success for each dog was defined as a ≥ 50% reduction from baseline in owner-assessed pruritus scores on the Pruritus Visual Analog Scale (PVAS) or a ≥ 50% reduction from baseline in veterinarian-assessed skin lesion scores on the Canine Atopic Dermatitis Extent and Severity Index version 4 (CADESI-4) on Day 28. The proportion of dogs in the Zenrelia group that were treatment successes was greater than and significantly different from the placebo group on Day 28 (Table 3, below).

Table 3. Estimated Proportion of Dogs Achieving Treatment Success

Treatment Group	Estimated Proportion of Success*
Zenrelia (N = 172)	0.83
Placebo (N = 77)	0.31†

* Based on back-transformed least square means.
† Placebo vs. Zenrelia p < 0.001
N = Number of dogs

The Zenrelia group had a higher proportion of dogs with a ≥ 50% reduction from baseline in both owner-assessed PVAS and veterinarian-assessed CADESI-4 scores, compared to placebo, at all time points. The mean owner-assessed PVAS and veterinarian-assessed CADESI-4 scores were also lower for the Zenrelia group compared to the placebo group at all time points.

Control of Pruritus Associated with Allergic Dermatitis
A masked, placebo-controlled field study was conducted at 15 veterinary clinics in the US, enrolling 306 client-owned dogs diagnosed with allergic dermatitis and having at least moderate pruritus. The allergic dermatitis was attributed to one or more of the following conditions: atopic dermatitis, contact dermatitis, flea allergy dermatitis, food hypersensitivity, or other. Dogs were randomized to once daily treatment with Zenrelia at 0.6 – 0.8 mg/kg or placebo, at a ratio of 2:1 respectively. Other medications that could affect the evaluation of effectiveness were not allowed during the study, such as corticosteroids, antihistamines, and cyclosporine. Treatment success for each dog was defined as a ≥ 50% reduction from baseline in owner-assessed pruritus scores on the Pruritus Visual Analog Scale (PVAS) on at least 5 out of the first 7 days of treatment. The proportion of dogs in the Zenrelia group that were treatment successes was greater than and significantly different compared to the placebo group on Day 7 (Table 4, below).

Table 4. Estimated Proportion of Dogs Achieving Treatment Success

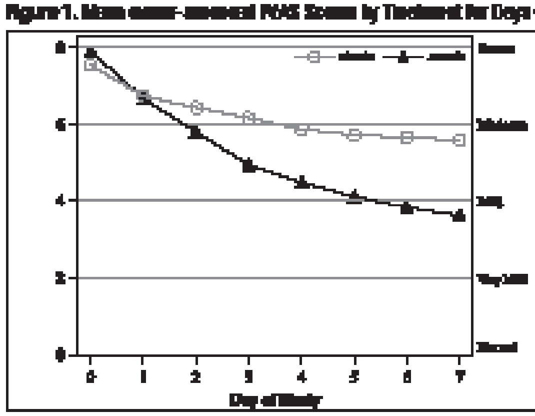
Treatment Group	Estimated Proportion of Success*
Zenrelia (N = 198)	0.25
Placebo (N = 91)	0.09†

* Based on back-transformed least square means.
† Placebo vs. Zenrelia p = 0.008
N = number of dogs

The Zenrelia group had a higher proportion of dogs with a ≥ 50% reduction from baseline in owner-assessed PVAS, compared to placebo, on Days 2 through 7.

After Day 1, mean owner-assessed PVAS scores were lower in the Zenrelia group (Figure 1, below).

Figure 1. Mean owner-assessed PVAS Scores by Treatment for Days 0-7



Veterinarians used a dermatitis visual analog scale (DVAS) to assess each dog's dermatitis. Veterinarian-assessed DVAS scores were lower for the Zenrelia group compared to the placebo group at all time points through Day 28.

TARGET ANIMAL SAFETY
Margin of Safety Study:
Zenrelia was administered to 40 (8 dogs per group) healthy, 11 to 12-month-old, lab Beagle dogs, once daily at 0X, 1X, 2X, 3X and 5X the maximum exposure dose of 0.8 mg/kg for 6 months. Control dogs were sham-dosed. Zenrelia-related clinical observations included a dose-dependent increase in the frequency and severity of interdigital furunculosis (cysts), with or without discharge on one or more paws, swollen and/or reddened paws, and paw skin thickening and/or discoloration. Zenrelia-related hemogram findings included a dose-dependent minimal to moderate decrease in hematocrit (HCT), hemoglobin (HGB), and red blood cell (RBC) count without a corresponding increase in absolute reticulocyte count. Other Zenrelia-related findings included a minimal to mild decrease in mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin

concentrations (MCHC), and eosinophil counts. Abnormal clinical pathology observations considered secondary to the interdigital furunculosis, included minimal to moderate increases in fibrinogen concentrations, total protein, C-reactive protein, and globulins, and decreases in albumin, albumin/globulin ratio and calcium levels. There were no Zenrelia-related effects on lymphocytes, monocytes, and basophils. Two dogs in the 5X group had minimally lower myeloid:erythroid ratios consistent with a physiological bone marrow response to the lower red blood cell mass despite no apparent effect on absolute reticulocytes. Zenrelia-related pathology changes included decreased prostate gland weights in the 5X group males and interdigital papillomas and/or demodectic furunculosis, predominantly in the 5X group. One dog in the 5X group had enlarged and mildly reactive draining lymph nodes associated with interdigital furunculosis. One dog in the 3X group had a papilloma on each paw with fragments of *Demodex canis*, and a follicular cyst within the markedly inflamed dermis.

Vaccine Response Study:

Zenrelia was administered to 16 (8 dogs per group) healthy, 10-month-old, vaccine naïve Beagle dogs, once daily at 0 and 3X the maximum exposure dose of 0.6 mg/kg for 89 days. Control dogs were placebo dosed. An 84-day recovery period followed in which no drug was administered. Dogs were administered a multivalent modified live virus (MLV) vaccine, including canine adenovirus type-2 (CAV-2), canine parvovirus (CPV), and canine distemper virus (CDV), on Days 28 and 56 and a killed rabies virus (RV) vaccine on Day 56. The primary endpoint was achievement on Day 85 of post-defined serum titer thresholds considered adequate for protective immunity. Serum titers were also evaluated 27 days (RV only) and 83 days after discontinuing drug administration (Days 118 and 172, respectively).

On Day 62, one dog administered Zenrelia was euthanized due to lethargy, depression, poor body condition, and weakness. Necropsy revealed findings consistent with a catarrhal intussusception, potentially related to a clinical *Cystoisospora canis* infection secondary to Zenrelia-induced immunosuppression.

On Day 64, another dog administered Zenrelia was euthanized due to lethargy, depression, poor body condition, and weakness. Histopathology evaluation revealed marked necrotizing hepatitis and pancreatitis and evidence of systemic coagulopathy. Prominent intranuclear inclusion bodies were found in the liver and pancreas, consistent with adenoviral infection. Polymerase chain reaction (PCR) analysis and DNA sequencing conducted post-mortem on preserved liver tissues from both euthanized dogs were positive for the presence of canine adenovirus type 1 (CAV-1) and canine adenovirus type 2 (CAV-2) DNA. Although the presence of live virus could not be confirmed, the presence of another adenovirus suggests that the fatal adenoviral hepatitis and pancreatitis was not vaccine induced and may have been due to a natural adenoviral infection, such as infectious canine hepatitis.

Clinical signs observed in Zenrelia-treated dogs included poor body condition, pale mucous membranes, lethargy, diarrhea, vomiting, weight loss, decreased appetite, and depression likely due to a clinical *C. canis* infection secondary to Zenrelia-induced immunosuppression in seven of the eight dogs. No dogs in the control group were diagnosed with a *C. canis* infection. One dog in the control group had diarrhea. Zenrelia-related clinical observations also included interdigital cysts, lameness, and thickening and crusting of the ear margins. Clinical pathology findings in Zenrelia-treated dogs included decreases in hematocrit, hemoglobin, and red blood cell counts with a corresponding increase in absolute reticulocyte count, and decreases in total serum protein, albumin, and globulins, likely due to the *C. canis* infection.

On Day 85, all eight control dogs demonstrated an adequate immune response to CAV-2, CPV, CDV, and RV vaccination and all six remaining dogs receiving Zenrelia demonstrated an adequate immune response to CAV-2 and CPV vaccination. Four (of six) Zenrelia-treated dogs failed to demonstrate an adequate immune response to RV vaccination, and one (of six) Zenrelia-treated dogs failed to demonstrate an adequate immune response to CDV vaccination on Day 85.

During the recovery period, on Day 118 (27 days after discontinuing treatment), one (of eight) control dogs and one (of six) Zenrelia-treated dogs failed to demonstrate an adequate immune response to RV vaccination. On Day 172 (83 days after discontinuing treatment), all eight control dogs demonstrated an adequate immune response to CAV-2, CPV, and CDV vaccination, all six remaining Zenrelia-treated dogs demonstrated an adequate immune response to CAV-2 and CPV vaccination, one (of six) Zenrelia-treated dogs failed to demonstrate an adequate immune response to CDV vaccination, and one (of eight) control dogs and three (of six) Zenrelia-treated dogs failed to demonstrate an adequate immune response to RV vaccination.

Potential recovery from drug-induced immunosuppression 27 days after discontinuing Zenrelia is evidenced by the observed adequate immune response to RV vaccination on Day 118 in three of the four dogs in the Zenrelia group that failed to achieve an adequate RV titer while receiving Zenrelia on Day 85. However, one of these four dogs did not achieve adequate RV titers after Zenrelia was discontinued for 83 days. A 3-month washout period prior to vaccination is supported by the 2024 World Small Animal Veterinary Association and 2023 Center for Disease Control and Prevention vaccination guidelines. The 28-day time period to withhold Zenrelia after vaccination is based on published and unpublished data evaluating the duration of MLV vaccine virus shedding.

Pilot Margin of Safety Study:

A non-final formulation of ilunocitinib (oral suspension) was administered via gavage to 32 (8 dogs per group) healthy, 9-month-old, Beagle dogs, once daily at 0X, 1X, 3X, and 4.5X the maximum exposure dose of 0.8 mg/kg through Day 64. Due to serious adverse reactions in the 3X and 4.5X groups, on Day 65, the 4.5X group was decreased to 2X through Day 185. Control dogs were sham dosed. One dog in the 4.5X group and two dogs in the 3X group were prematurely euthanized (on Days 52, 57, and 124, respectively) due to an acute onset of lethargy, labored breathing, fever, tremors, and pale gums, starting within four hours of dosing via oral gavage. Microscopic pathology findings in the three dogs included necrotic hemorrhagic pneumonia, considered secondary to ilunocitinib-induced immunosuppression and gavage administration. Two of these three dogs developed severe leukopenia and neutropenia and one dog had severe weight loss in the two weeks prior to euthanasia. Twelve dogs administered ilunocitinib, including the three dogs prematurely euthanized, had a decrease in at least one RBC parameter (HCT, HGB, or RBC count), without a corresponding increase in absolute reticulocyte count, at one or more timepoints during the study. Additional ilunocitinib-related microscopic pathology changes included minimal to mild increased erythrophagia and pigment in the spleen, minimal to mild pigmented macrophages in the liver, and minimal adipocyte accumulation in the bone marrow.

STORAGE CONDITIONS:

Store at room temperature between 15 to 25°C (59 to 77°F), excursions permitted between 5 to 40°C (41 to 104°F).

HOW SUPPLIED:

Zenrelia (ilunocitinib tablets) is available in scored tablets in four strengths: 4.8 mg, 6.4 mg, 8.5 mg, and 15 mg. Each tablet strength is available in 10 and 30 count blister packages and 90 count bottles.

Manufactured for: Elanco US Inc. Greenfield, IN 46140

Approved by FDA under NADA # 141-585

July 2025

For use in cats only

Zorbium® CT

(buprenorphine transdermal solution)

20 mg/mL

For topical application in cats
Opioid analgesic
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

HUMAN SAFETY WARNINGS

Abuse Potential

ZORBIUM contains buprenorphine, an opioid that exposes humans to risks of addiction, abuse, and misuse, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. The risk of abuse by humans should be considered when ordering, administering, and dispensing of ZORBIUM. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drugs or alcohol) or mental illness (e.g. depression).

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ZORBIUM. Monitor for respiratory depression if human exposure to buprenorphine occurs. Misuse or abuse of buprenorphine by swallowing, snorting, or injecting poses a significant risk of overdose and death.

Accidental Exposure

Because of the potential for adverse reactions associated with accidental exposure, ZORBIUM should only be administered by veterinarians or veterinary technicians who are trained in the handling of potent opioids. Accidental exposure to even one tube of ZORBIUM, especially in children, can result in a fatal overdose of buprenorphine.

Risks From Concurrent Misuse or Abuse with Benzodiazepines or Other CNS Depressants

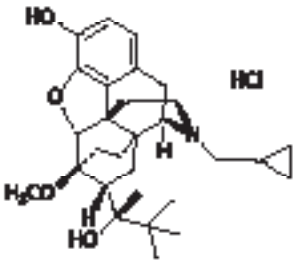
Concurrent misuse or abuse of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

See Human Safety Warnings for detailed information.

DESCRIPTION:

ZORBIUM is a viscous liquid transdermal solution intended for topical application that provides continuous, systemic delivery of the opioid analgesic, buprenorphine. Buprenorphine belongs to the opioid class of drugs and is a narcotic under the Controlled Substances Act due to its structural derivation from thebaine. Once ZORBIUM is applied to the skin, rapid drying results in dermal absorption and sequestration of buprenorphine into the stratum corneum. Each mL of ZORBIUM contains 20 mg buprenorphine (administered as 21.39 mg of buprenorphine hydrochloride). The inactive ingredients are diisobutyl adipate, palmitic 0, butylated hydroxytoluene, and butylated hydroxyanisole.

Buprenorphine hydrochloride has an empirical formula of $C_{29}H_{41}NO_4$•HCl and a molecular weight of 504.10. The chemical structure of buprenorphine HCl is:



INDICATION:

ZORBIUM is indicated for the control of postoperative pain associated with surgical procedures in cats.

DOSAGE AND ADMINISTRATION:

This product should only be administered by veterinary personnel.

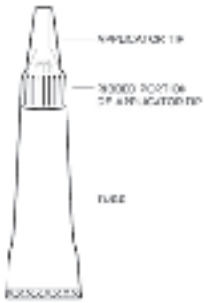
ZORBIUM is for administration only once for the surgical procedure. ZORBIUM should be applied 1 to 2 hours before surgery. A single application provides analgesia for 4 days. ZORBIUM should only be applied topically to the dorsal cervical area, at the base of the skull. Do not apply if dorsal cervical skin is diseased or injured. The dosage of ZORBIUM is 1.2 – 3.1 mg/kg (0.7 – 0.7 mg/lb) administered topically as the entire tube contents according to the following dosing table:

Pounds of Body Weight	Kilograms of Body Weight	Dose of ZORBIUM
2.8 to 6.6	1.2 to 3	0.4 mL (8 mg) pink tube
>6.6 to 16.5	>3 to 7.5	1 mL (20 mg) green tube

Dose Application

Wear impermeable latex or nitrile gloves, protective glasses, and a laboratory coat to prevent direct solution contact with human skin, eyes, or mucous when handling and applying the solution. Do not dispense ZORBIUM for administration at home by the pet owner (see HUMAN SAFETY WARNINGS).

Figure 1 - Diagram of tube components.



Pierce applicator tip to open.
Applicator tip is not removable.

Figure 2 – Proper grasp of the applicator tube: To prepare to open the tube for application, the tube must be held in an upright position to avoid spilling contents. Grasp the tube just beneath the ribbed portion of the tip.

Figure 3 – Opening the applicator tube: Keeping the tube upright, grasp the ribbed portion of the tip, and turn the applicator tip in either direction at least 180° to open the tube. The applicator tip is designed to stay on the tube and should not be removed. The tube is ready for application when a breaking of the seal is felt.

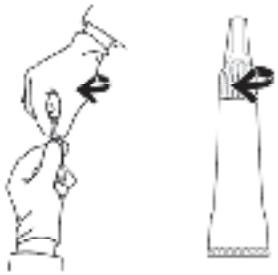


Figure 4 – Solution application: Fur should not be clipped. Do not apply to injured or diseased skin. Gently hold the cat both before and after application to prevent the cat from shaking or rubbing. Part the fur and apply the tip of the tube directly onto the skin at the base of the head. Squeeze the tube 2 – 3 times to empty the contents without moving the tube or the tip. Lift the tube directly away from the skin, avoiding contact of the tip with the cat's fur.

CONTRAINDICATIONS:

ZORBIUM is contraindicated in cats with known hypersensitivity to buprenorphine hydrochloride, any of the inactive ingredients of ZORBIUM, or known intolerance to opioids.

WARNINGS:

HUMAN SAFETY WARNINGS:

Not for use in humans. Keep this and all medications out of reach of children and pets.

Human User Safety Risks Associated With ZORBIUM in the Hospital:

Protective Covering: Do not cause tube direct contact with ZORBIUM. Wear impermeable latex or nitrile gloves, protective glasses, and a laboratory coat when applying ZORBIUM.

Human Membrane or Eye Contact During Application:

Direct contact of ZORBIUM with the eyes, oral, or other mucous membranes could result in absorption of buprenorphine and the potential for adverse reactions. If accidental eye, oral, or other mucous membrane contact is made during application, flush the area with water and contact a physician immediately. If wearing contact lenses, flush the eye first and then remove the contact lens.

Skin Contact During Application:

Following application to the cat, allow a minimum drying time of 30 minutes before direct contact with the application site. If human skin is accidentally exposed to ZORBIUM, wash the exposed area immediately with soap and water and contact a physician. Accidental exposure could result in absorption of buprenorphine and the potential for adverse reactions.

Drug Abuse, Addiction, and Diversion of Opioids:
Controlled Substance:
ZORBIUM contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids.

Abuse:
ZORBIUM contains buprenorphine, an opioid substance, that can be abused and is subject to misuse, abuse, and addiction, which may lead to overdose and death. This risk is increased with concurrent use of alcohol and other central nervous system depressants, including other opioids and benzodiazepines.
ZORBIUM should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.
Prescription drug abuse is the intentional, non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse.

Storage and Disposal:
ZORBIUM is a Schedule III opioid. Store in a locked cabinet according to federal and state controlled substance requirements/guidelines. Any unused or expired tubes must be destroyed by a reverse distributor; for further information, contact your local DEA field office or call Elanco US Inc. at 1-888-545-5973.

Information for Physician:
ZORBIUM transdermal solution contains a mu opioid partial agonist (20 mg buprenorphine/mL). In the case of an emergency, provide the physician with this package insert. Naloxone may not be effective in reversing respiratory depression produced by buprenorphine. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride has also been used as a respiratory stimulant.

ANIMAL SAFETY WARNINGS:
For topical use in cats only. This product should only be administered by veterinary personnel.
Do not apply ZORBIUM if the application site of the dorsal cervical area has diseased or injured skin.
Do not apply ZORBIUM to anatomic areas other than the dorsal cervical area because absorption characteristics may be different.

PRECAUTIONS:
Following anesthesia and opioid analgesia, body temperature should be monitored postoperatively for immediate hypothermia and subsequent hyperthermia. Hyperthermia can occur and persist after the hypothermic effects of anesthesia have resolved.
The safe use of ZORBIUM has not been evaluated in debilitated cats or cats with renal, hepatic, cardiac, or respiratory disease.
The safe use of ZORBIUM has not been evaluated in cats that are pregnant, lactating, or intended for breeding.
The safe use of ZORBIUM has not been evaluated in cats younger than four months old.
The safe use of ZORBIUM has not been evaluated in cats weighing less than 2.6 pounds or more than 12.5 pounds.

ADVERSE REACTIONS:
In a randomized, multi-centered, double-masked, field study, ZORBIUM™ (buprenorphine transdermal solution) (N=113) or vehicle control (N=109) was administered to cats prior to elective surgical reproductive sterilization (castration/ovariohysterectomy) in conjunction with forelimb onychectomy. Cats enrolled in the study were 4 months to 5 years of age and weighed 1.1 to 5.7 kg (2.6 to 12.5 lb). Clinical observations and physiological parameters were monitored prior to, during, and after surgery for 96 hours after sternal recumbency. Supplemental heat and fluids were allowed. There were no deaths during the study and no cats received an opioid reversal agent. Three ZORBIUM and 2 vehicle control cats were removed due to hyperthermia suspected to be treatment related. One ZORBIUM cat was removed due to fractious behavior 30 minutes following surgery. Adverse reactions were defined as any single excursion outside the normal range, as defined: 100.5 – 102.5 °F body temperature; 60 – 120 mmHg mean arterial pressure; 80 – 180 beats per minute for heart rate; 24 – 44 breaths per minute for respiratory rate. A summary of adverse reactions during anesthesia (from anesthetic induction through recovery defined as sternal recumbency) is provided in Table 1.

Table 1. Adverse Reactions During Anesthesia:

Adverse Reaction*	ZORBIUM (N=113)	Vehicle Control (N=109)
Hypothermia	37 (32.7%)	33 (30.3%)
Hypotension	31 (27.4%)	28 (25.7%)
Hypertension	27 (23.9%)	18 (16.5%)
Tachycardia	14 (12.4%)	14 (12.8%)
Sedation	12 (10.6%)	7 (6.4%)
Oxygen saturation ≤ 90%	6 (5.3%)	2 (1.8%)
Bradycardia	4 (3.5%)	2 (1.8%)
Hyperthermia	3 (2.7%)	4 (3.7%)

*Physiological adverse reactions were defined as any single excursion outside the normal range at any 10 minute interval during the entire duration of anesthesia.
After recovery, cats were observed in the hospital and underwent physiological assessments that included indirect mean arterial blood pressure, heart rate, respiratory rate, body temperature, lung auscultation, heart auscultation, and assessments of urination, defecation, and appetite. A summary of adverse reactions after anesthetic recovery (sternal recumbency) in all cats is reported in Table 2.

Table 2. Adverse Reactions After Anesthetic Recovery:

Adverse Reaction*	ZORBIUM (N=113)	Vehicle Control (N=109)
Hypothermia	107 (94.7%)	105 (96.3%)
Hyperthermia	84 (74.3%)	42 (38.5%)
Sedation	64 (56.6%)	48 (44.0%)
Tachypnea	55 (48.7%)	70 (64.2%)
Hypotension	50 (44.2%)	51 (46.8%)
Hypertension	42 (37.2%)	34 (31.2%)
Bradycardia	34 (30.1%)	45 (41.3%)
Tachycardia	32 (28.3%)	39 (35.8%)
Anorexia	25 (22.1%)	32 (29.4%)
Dysphoria	20 (17.7%)	28 (25.7%)
Diarrhea	11 (9.7%)	11 (10.1%)
Bradypnea	11 (9.7%)	7 (6.4%)
Leukocytosis	6 (5.3%)	4 (3.7%)
Hyperactivity	2 (1.8%)	6 (5.5%)

*Physiological adverse reactions were defined as any single excursion outside the normal range following anesthetic recovery (sternal recumbency) through 4 days postoperatively.
Hyperthermia was the only adverse event observed in more than 10% of cats in the ZORBIUM group after the day of surgery (24 – 96 hours). The percentage of cats in the ZORBIUM group with hyperthermia decreased over time from 66.4% on Day 0 to 28.3% on Day 1, and to 6.2% by Day 4. A summary of adverse reactions (from anesthetic recovery through 96 hours after recovery) in cats in the ZORBIUM group by study day is reported in Table 3.

Table 3. Adverse Reactions in ZORBIUM Cats (N=113) by Day:

Adverse Reaction*	Day 0	Day 1	Day 2	Day 3	Day 4
Hypothermia	105 (92.9%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
Hyperthermia	75 (66.4%)	32 (28.3%)	18 (15.9%)	14 (12.4%)	7 (6.2%)
Sedation	64 (56.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachypnea	51 (45.1%)	5 (4.4%)	2 (1.8%)	3 (2.7%)	4 (3.5%)
Hypotension	42 (37.2%)	2 (1.8%)	1 (0.9%)	4 (3.5%)	2 (1.8%)
Hypertension	28 (24.8%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Anorexia	25 (22.1%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Bradycardia	24 (21.2%)	3 (2.7%)	2 (1.8%)	3 (2.7%)	5 (4.4%)
Tachycardia	24 (21.2%)	4 (3.5%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Dysphoria	20 (17.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bradypnea	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperactivity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

*Physiological adverse reactions were defined as any single excursion outside the normal range following anesthetic recovery (sternal recumbency) through 96 hours postoperatively.

CONTACT INFORMATION:
To report suspected adverse events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc. at 1-888-545-5973.
For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY:
Mechanism of Action: Buprenorphine exerts its analgesic effect via high affinity binding to various subclasses of opioid receptors, particularly mu, in the central nervous system. Buprenorphine analgesic and adverse reactions are mediated by mu opioid receptor agonism. Due to its partial agonist activity, buprenorphine exhibits a ceiling effect to its actions and thus has a greater therapeutic index compared to full mu opioid receptor agonists such as morphine. Buprenorphine binds tightly to and dissociates slowly from the opioid receptor. Therefore, the pharmacological effects of buprenorphine are not directly related to plasma concentrations.
Pharmacokinetics: Following application of ZORBIUM, solvent evaporation coupled with the permeation enhancer action results in rapid absorption and sequestration of the buprenorphine into the skin. ZORBIUM provides analgesia within 1 – 2 hours following administration and continuously releases buprenorphine from the skin into the systemic circulation over a period of days. The mean (range) time to reach peak concentration (T_{max}) was 7.33 (1 – 24) hours. Due to buprenorphine elimination being faster than absorption from the skin, ZORBIUM exhibits flip-flop pharmacokinetics where the absorption determines its terminal half-life (mean 84.9 hours (range 38.1 – 85.7 hours)). The estimated absolute bioavailability (F) of transdermal administration was in the order of 10% (90% confidence interval (CI) –11.3% – 21.7%).
Buprenorphine is extensively metabolized by the liver in humans, the primary route being N-dealkylation to norbuprenorphine by cytochrome P450 enzymes. Both buprenorphine and norbuprenorphine form inactive glucuronide conjugates and are excreted by the bile into the gastrointestinal tract. The cat is devoid of uridine diphosphate glucuronosyltransferase enzymes (UGT1A6 and UGT1A9) responsible for conjugation and therefore conjugated metabolites may be absent. Norbuprenorphine is considered an active metabolite of buprenorphine, though it has one-fiftieth the analgesic activity of buprenorphine in rats. Buprenorphine extensively binds (89 – 96%) to plasma proteins.

EFFECTIVENESS:
The effectiveness of ZORBIUM was demonstrated in cats that underwent elective reproductive sterilization in conjunction with forelimb onychectomy surgery in a randomized, multi-centered, double-masked, vehicle-controlled, field study across 12 investigative sites. Enrolled cats were between 4 months to 5 years of age and weighed 2.6 to 12.6 pounds (1.1 – 5.7 kg).
Cats in the ZORBIUM group received a single dose of 8 mg or 20 mg of buprenorphine according to body weight (see DOSAGE AND ADMINISTRATION). Cats in the vehicle control group received a

transdermal solution of 20 mg/mL posture D in ethanol. The dose was administered topically onto the dorsal cervical skin 1 – 2 hours prior to anesthetic induction for surgery. For intraoperative analgesia, all cats in the study received a single intramuscular injection of an alpha$_2$-agonist 30 minutes prior to anesthetic induction, and a 4-point metacarpal ring block with lidocaine after induction. The adequacy of pain control was scored through 96 hours after surgery. If pain control was considered inadequate at any time following treatment, rescue analgesia was provided immediately. Treatment success was defined as a cat that did not require rescue analgesia, need opioid reversal, or experience an adverse event suspected to be related to treatment through the entire 96-hour post-recovery period. A cat was considered a treatment failure if it had inadequate pain control, required opioid reversal, or experienced an adverse event suspected to be related to treatment.

A total of 19 ZORBIUM and 63 vehicle control cats were removed from the study due to inadequate pain control. Most of these failures occurred on the day of surgery in both groups; however, there were 4 ZORBIUM group cats and 8 vehicle control cats removed due to inadequate pain control between 1 and 3 days after surgery.

Effectiveness was evaluated in 219 cats (112 in the ZORBIUM group and 107 cats in the vehicle control group), and field safety was evaluated in 222 cats (113 cats in the ZORBIUM group and 109 cats in the vehicle control group). Of the 112 cats in the ZORBIUM group, 83 were treatment successes; of the 107 vehicle control cats, 42 were treatment successes. Comparison of the ZORBIUM group and the vehicle control group demonstrated a statistically significant difference in the treatment success rates (p = 0.0001).

Hypothermia was common in both groups during surgery. The overall mean postoperative body temperature was higher in the ZORBIUM group than in the vehicle control group. Mean postoperative body temperatures in the ZORBIUM group were above the normal range at 4 and 8 hours postoperatively (mean±SD of 102.7°±1.2 °F and 102.6°±1.0 °F, respectively [normal range: 100.5 – 102.5 °F]). Mean indirect arterial blood pressure (MAP) was similar between the 2 treatment groups over time. Urination, defecation, appetite, and daily body weights after surgery were not affected by ZORBIUM administration. Fifteen cats in the ZORBIUM group had an increased temperature at discharge, compared to 2 cats in the vehicle control group.

Fluid administration (intravenous and subcutaneous) and supplemental heat support after surgery were the most common concomitant treatments and were used similarly in both groups.

TARGET ANIMAL SAFETY:

Twelve Day Target Animal Safety Study: In a 12-day laboratory study, ZORBIUM was administered to 32 healthy four-month-old domestic cats (8 cats per group) at 0 mg/kg (vehicle control), 6.7 mg/kg (1X), 13.3 mg/kg (2X), and 20 mg/kg (3X) as a topical application to the dorsal cervical area every 4 days for a total of 3 doses. Dose-independent euphoria, mild dysphoria, and mydriasis were observed after ZORBIUM administration. Maximum scores (for euphoria, dysphoria, and mydriasis) in the ZORBIUM groups reached 3 (mildly dysphoric) between 1 – 2 hours after the first dose. On the other 2 dosing days (Days 4 and 8), maximum scores were 2 (euphoric). Euphoria in some cats persisted from 36 to 72 hours.

On dosing day 1, mydriasis was observed in approximately half the cats administered ZORBIUM by 24 hours after dosing (peaked in all ZORBIUM groups at 8 hours) and was not observed between 48 – 96 hours. After the day 8 dose (third dose), it was rarely observed (1 cat in 1X group; 2 cats in 3X at 48 hours; 1 cat in 3X at 72 hours).

Cats administered ZORBIUM had higher body temperatures compared to the vehicle control group throughout the study. Following the initial dose, the mean temperatures in cats administered ZORBIUM increased above normal and were up to 1.8 °F greater than the vehicle control group. Increased body temperature primarily occurred during the first 8 hours after the initial dose and was observed in the majority of cats administered ZORBIUM. Elevated temperatures ranged from 102.6 °F to 104.5 °F. The highest temperatures occurred at 2 hours after the first dose, gradually decreasing by 24 hours. By 3 days after dose administration, body temperatures in cats administered ZORBIUM had returned to levels observed in the vehicle control group. After the second and third doses (days 4 and 8), mean temperatures in all ZORBIUM groups were again higher than in the vehicle control group, but not higher than the normal reference range.

Constipation was recorded for 20 cats (1 vehicle control; 5 in 1X; 4 in 2X; 6 in 3X groups) after the first dose. The constipation was mild and transient. Three cats (2 in the 1X group and 1 in the 3X group) were administered a laxative. ZORBIUM had no clinically significant effects on heart rate or respiratory rate. There were no clinically relevant changes to serum chemistry, hematology, or urinalysis outcomes. Histopathology evaluations revealed mild inflammation of skin at the application site.

Seven Day Target Animal Safety Study: In a 7-day laboratory study, ZORBIUM was administered once topically to the dorsal cervical area of 24 healthy adult domestic cats (6 cats/group) at 0 mg/kg (0X; vehicle control), 3.3 (0.5X), 10 (1.5X), or 30 mg/kg (4.5X the maximal dose of 6.7 mg/kg). Cats were observed for 7 days after the single dose. Clinical results were similar to the 12-day margin of safety study, even at the higher dose of 30 mg/kg, except for transient increases in heart rate in the ZORBIUM groups compared to the vehicle control group. Mean heart rates in ZORBIUM groups were higher than in the vehicle control group from 2 hours through approximately 48 hours after dose administration. Tachycardia (>240 beats per minute) occurred in two cats in the 0.5X group and two cats in the 4.5X group for at least one timepoint after dose administration. The highest heart rate was 288 (in the 0.5X group) and no dose relationship was evident. Dose-independent euphoria, mild dysphoria, and mydriasis were noted in the ZORBIUM groups. Mild constipation and/or abdominal distension were observed with ZORBIUM administration. Transient increases in plasma chloride and sodium concentrations in the ZORBIUM groups compared to vehicle control group indicated mild dehydration.

Cardiovascular Safety Study: In a 12-day cardiovascular laboratory safety study, ZORBIUM was administered to 8 healthy adult cats (4 cats per group) at 0 mg/kg (vehicle control) and 6.7 mg/kg (1X) as a topical application to the dorsal cervical region every 4 days for a total of 3 doses. Continuous, direct physiological monitoring (telemetry) was conducted from 2 hours prior to the first dose through 4 days following the third (final) dose. Body temperature increases averaged <0.4 °F in ZORBIUM group cats over vehicle control cats. In the vehicle control group, 102.6 °F was the maximum temperature, observed at 83 hours after the first dose. In the ZORBIUM group, 103.4 °F was the maximum temperature, observed at 20 hours after the first dose. Heart rate (HR) increased an average of 16.2 beats/minute in the ZORBIUM group cats compared to vehicle control cats. The maximum heart rate in the ZORBIUM group reached 231 beats/minute. In the vehicle control group, the maximum heart rate was 219 beats/minute. Blood pressure (arterial systolic, diastolic, and mean) in the ZORBIUM group cats was not significantly different from the vehicle control cats. There were no clinically significant effects of ZORBIUM on qualitative electrocardiogram results.

STORAGE INFORMATION:

Store at or below 25 °C (77 °F). Excursions permitted to 30 °C (86 °F).

HOW SUPPLIED:

ZORBIUM is available in applicator tubes that deliver a dose volume of 0.4 mL or 1 mL (20 mg/mL buprenorphine) in multi-packs of 10 tubes.

Approved by FDA under NADA # 141-547

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140 USA

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