IN PARTNERSHIP WITH VIRBAC

TVC

February Issue 2021

The TVC Veterinary Cooperative SM

Breakthrough Cancer Treatment

Virbac's soon-to-be-released cancer fighting drug could be a paradigm shift for veterinarians and the pets they treat. **pg. 10**

NEW!

C.E.T.®
IntelliDent™
Cat Bites
Support Healthy Teeth and Gums

So smart they could only be for cats.

3-in-1 dental support in just 3 healthy bites per day

- Cleans teeth
- Freshens breath
- Supports gums

Crunchy and flavorful C.E.T.® IntelliDent™ Cat Bites work with a cat's natural chewing action to help reduce the plaque and tartar buildup associated with periodontal disease, and feature beneficial ingredients to help maintain healthy gums.

- ✔ One size for all patients
- ✔ <8 Calories per day
- ✔ Low fat content
- ✔ No artificial preservatives
- ✔ Natural flavoring

C.E.T.® HOME DENTAL CARE

For these and other easy-to-use, client-friendly dental care solutions, contact your Virbac representative or call 1-844-4-VIRBAC (1-844-484-7222).

dental.virbac.com

Shaping the future of animal health

Virbac

Contents

Building Better Bridges

Chad Clark, Senior Owner Success Advocate, TVC

- **We believe that each vendor we bring into the TVC community** can help you build better bridges, whether that be the way your clinic communicates with clients or builds better outcomes for pets.

One constant challenge for clinics has been time, even more so now. When COVID hit, almost overnight, practices had to scramble for ways to keep their patient volume afloat with social distancing restrictions in place. Thus, any amount of time to trim off appointments became crucial because that was another entire appointment, and another couple hundred dollars-worth of revenue during an economic downturn.

Enter SnoutID. This new TVC vendor has several features that have helped practices streamline their operations. For instance, the SnoutID system offers a touch-less check-in system that allows clients to check-in remotely from their own device. Other benefits include:

- Accessing standardized and verified medical records from any practice in North America.
- E-signatures and digital forms to avoid face-to-face contact and physical paperwork.
- Freeing up telephone lines and staff time.
- Fully customized with a practice's own branding.

Other recent vendor partner additions include:

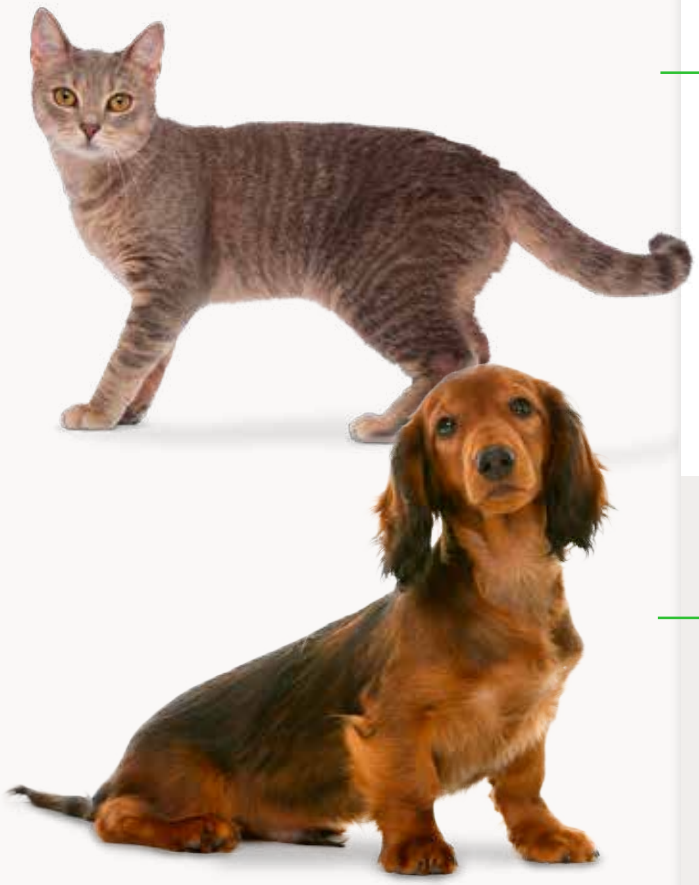
- **Scrubin –** Scrubin Uniforms aims to provide veterinary professionals with top-of-the-line pet care vet scrubs
- **Terumo –** A valuable vendor that can offer savings on needles, catheters, syringes.
- **MWI –** Office Supplies.
- **Talkatoo –** Talkatoo is giving veterinarians back their day by simplifying the documentation process. It can save staff about 50% of their medical charting time.

From a touchless check-in process, to office supplies, to even the uniforms a veterinary team wears, TVC's vendor partner offerings can help improve your business. For more information, visit the member website. ■

Flexadin® Advanced with UC-II®

BUY 10, GET 2 FREE

Flexadin® Advanced with UC-II® 60 Count Chews



PRODUCT

Flexadin® Advanced with UC-II® is made from a breakthrough formula that supports healthy joints and flexibility in dogs and cats of all ages and sizes. One chew daily - for any size cat or dog - can help ease joint stiffness and help support a healthy immune system. No loading administration period.

OFFER VALID FOR PURCHASES DATED
February 1, 2021 — March 31, 2021

DETAILS

- Invoices must be dated **February 1 – March 31, 2021**
- Cannot be combined with any other Vetoquinol promotional offer
- Distributor to ship free goods
- Order must be placed with the GPO's preferred distributor(s)

DISTRIBUTORS

- All purchased and free products must be on the same invoice
- All free goods requests must reference code: **FAQ1**
- Vetoquinol USA reserves the right to change, cancel or refuse this program at any time

EXCLUSIVELY FOR: The TVC Veterinary Cooperative

Sold to practicing veterinarians only. This promotion is for practicing veterinarians who use and dispense Vetoquinol USA products under their care, within a valid Veterinarian Client Patient Relationship as defined by AVMA.

This promotion applies to practices/organizations with licensed veterinarians on staff who are not currently listed on the Vetoquinol Do Not Sell list. Vetoquinol USA reserves the right to deny sale to any organization that does not comply with sales and marketing terms

1.800.267.5707
vetoquinolusa.com

vetoquinol
ACHIEVE MORE TOGETHER

TVC News

TVC announces partnership with SnoutID

TVC has reaffirmed their commitment to providing business solutions for partnered hospitals, and through that mission is eager to announce a partnership with SnoutID. SnoutID is a vet-based tech solution that enables the practice support team to focus on the client experience and patient care, not paperwork. With contactless pre-appointment prep and communications, as well as digitization of patient records and forms, SnoutID simplifies the practice workflow and takes the pain out of preparing for the next appointment. Read more on SnoutID here.

TVC adds Terumo to product lineup

Rounding out a plethora of new vendor additions, TVC is pleased to be partnering with Terumo. Terumo fills a much-needed space for needles, syringes, and catheters for our TVC partnered hospitals. Many shareholders already use their products and can now enjoy extra cost savings on these trusted hospital mainstays. Click here for more information.

TVC launches partnership with Talkatoo

January 2021 brought many new additions to the TVC vendor offerings, including Talkatoo – a desktop dictation solution that augments your current workflow by using speech-to-text capability with specialized vocabularies. Users have been blown away by the ease of use and added efficiency that the product creates. Learn more about the Talkatoo & TVC program here.

New partnership with MWI Office Supply unveiled

TVC is also adding a much-needed office supply vendor to our list of partnerships. MWI Office Supply has 26 warehouses nationwide, offers one- or two-day shipping to most locations, and offers free shipping regardless of order size. This is on-top of everyday low prizes and the ability to earn a TVC rebate. Learn more about MWI Office Supply here.

TVC Annual Shareholder Meeting

The virtual TVC Annual Shareholder Meeting was conducted on Saturday, January 30 and drew more than 1,400 TVC partnered hospital from across the country. Clinics gathered together to hear TVC's vision for a future and were detailed on TVC's new 5STARvet initiatives which aims to give support in the areas of practice management, employee recruitment, transition planning and more. To learn more about TVC 5STARvet fill out this interest form. A recorded version of the meeting will be made available.

2x THE DURATION OF MONTHLY PRODUCTS

Ease feline stress with protection that lasts twice as long as REVOLUTION® PLUS (selamectin and sarolaner topical solution) for Cats

- Longer duration means **less stress** on cat and owner
- Extended duration can help **increase compliance**[1,2]
- 2-month **flea and tick protection**
- 2-month prevention of **heartworm disease**
- 2-month treatment of **roundworms and hookworms**

SUGGESTED VET RETAIL PRICE (all SKUs)	PRICE PER DOSE
$256.00	$25.60

197671 178956 197685

FLURALANER
2-month flea and tick protection

+

MOXIDECTIN
2-month broad-spectrum coverage

Extended Duration PLUS Broad Spectrum

fleas ticks heartworm roundworms hookworms

1Lavan RP et al. *Parasites & Vectors*. 2017;10:284.
2Lavan RP et al. *Parasites & Vectors*. 2018;11:581.

IMPORTANT SAFETY INFORMATION:
The most commonly reported adverse reactions include vomiting, hair loss, itching, diarrhea, lethargy, dry skin, elevated ALT, and hypersalivation. BRAVECTO PLUS has not been shown to be effective for 2 months duration in kittens less than 6 months of age. For topical use only. Avoid oral ingestion. The safety of BRAVECTO PLUS has not been established in breeding, pregnant and lactating cats. Fluralaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Neurologic adverse reactions have been reported in cats receiving isoxazoline class drugs, even in cats without a history of neurologic disorders. Use with caution in cats with a history of neurologic disorders. Use with caution in cats that are heartworm positive. The effectiveness of BRAVECTO PLUS to prevent heartworm disease after bathing or water immersion has not been evaluated.

US-BRV-190600033

BRAVECTO® PLUS

(fluralaner and moxidectin topical solution) for Cats

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

Description:
Each tube is formulated to provide a minimum dose of 18.2 mg/lb (40 mg/kg) fluralaner and 0.9 mg/lb (2 mg/kg) moxidectin. Each milliliter contains 280 mg of fluralaner and 14 mg of moxidectin.

The chemical name of fluralaner is (+)-4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)- 4,5-dihydroisoxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2- trifluoroethylamino)ethyl]benzamide. The chemical name of moxidection is (2aE,4E,5'R, 6R,6'S,8E,11R,13S,15S,17aR, 20R,20aR,20bS)-6'-[(E)-1,3-Dimethyl-1-butenyl]-5',6,6',7,10,11, 14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5',6,8,19-tetramethylspiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6] benzodioxacyclooctadecin-13,2'-[2H]pyran]-4',17(3'H)-dione 4'-(E)-(O-methyloxime). Inactive ingredients: dimethylacetamide, glycofurol, diethyltoluamide, acetone, butylhydroxytoluene

Indications:
Bravecto Plus is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment of infections with intestinal roundworm (*Toxocara cati*; 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme*; 4th stage larvae, immature adults and adults). Bravecto Plus kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick) and *Dermacentor variabilis* (American dog tick)] for 2 months in cats and kittens 6 months of age and older and weighing 2.6 lb or greater.

Dosage and Administration:
Bravecto Plus should be administered topically as a single dose every 2 months according to the **Dosage Schedule** below to provide a minimum dose of 18.2 mg/lb (40 mg/kg) fluralaner and 0.9 mg/lb (2 mg/kg) moxidectin.

For prevention of heartworm disease, Bravecto Plus should be administered at 2-month intervals. Bravecto Plus may be administered year-round without interruption or at a minimum should be administered at 2-month intervals beginning at the cat's first seasonal exposure to mosquitoes and continuing until the cat's last seasonal exposure to mosquitoes. If a dose is missed and a 2-month interval between doses is exceeded, administer Bravecto Plus immediately and resume the dosing every 2 months.

When replacing a monthly heartworm preventative product, the first dose of Bravecto Plus should be given within one month of the last dose of the former medication.

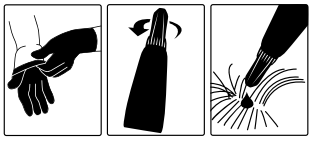
Dosing Schedule:

Body Weight Ranges (lb)	Fluralaner content (mg/tube)	Moxidectin content (mg/tube)	Tubes Administered
2.6 – 6.2	112.5	5.6	One
>6.2 – 13.8	250	12.5	One
>13.8 – 27.5*	500	25	One

* Cats over 27.5 lb should be administered the appropriate combination of tubes.

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

Step 1: Immediately before use, open the pouch and remove the tube. Put on gloves. Hold the tube at the crimped end with the cap in an upright position (tip up). The cap should be rotated clockwise or counter clockwise one full turn. The cap is designed to stay on the tube for dosing and should not be removed. The tube is open and ready for application when a breaking of the seal is felt.



Step 2: The cat should be standing or lying with its back horizontal during application. Part the fur at the administration site. Place the tube tip vertically against the skin at the base of the skull of the cat.

Step 3: Squeeze the tube and gently apply the entire contents of Bravecto Plus directly to the skin at the base of the skull of the cat. Avoid applying an excessive amount of solution that could cause some of the solution to run and drip off of the cat. If a second spot is needed to avoid run off, then apply the second spot slightly behind the first spot.

Greasy, oily, or wet appearance may occur at the application site in some cats.

Contraindications:
There are no known contraindications for the use of the product.

WARNINGS:

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

Do not contact or allow children to contact the application site until 2 hours post application.

Keep the product in the original packaging until use in order to prevent children from getting direct access to the product. Do not eat, drink or smoke while handling the product. Avoid contact with skin and eyes. If contact with eyes occurs, then flush eyes slowly and gently with water. **If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing, then seek medical advice immediately. Wash hands and contacted skin thoroughly with soap and water immediately after use of the product. If the product accidentally contacts skin and a sticky residue persists after washing, rubbing alcohol (70% isopropyl alcohol) can be applied to the area to remove the residue.**

The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

Precautions:
For topical use only. Avoid oral ingestion (see **Animal Safety**).

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

Use with caution in cats that are heartworm positive (see **Animal Safety**).

Bravecto Plus has not been shown to be effective in kittens less than 6 months of age.

The safety of Bravecto Plus has not been established in breeding, pregnant, and lactating cats.

The effectiveness of Bravecto Plus to prevent heartworm disease after bathing or water immersion has not been evaluated.

Adverse Reactions:
In a well-controlled U.S. field study, which included a total of 176 treated cats (135 with Bravecto Plus and 41 with a monthly topical active control), there were no serious adverse reactions.

Percentage of Cats with Adverse Reactions (AR) in the Field Study

Adverse Reaction	Bravecto Plus Group: Percent of Cats with the AR During the 120-Day Study (n=135 cats)	Active Control Group: Percent of Cats with the AR During the 120-Day Study (n=41 cats)
Vomiting	5.9%	12.2%
Alopecia (not at application site)	5.2%	2.4%
Pruritus	4.4%	12.2%
Application site pruritus	4.4%	4.9%
Diarrhea	3.7%	7.3%
Lethargy	3.7%	9.8%
Dry Skin	3.0%	0.0%
Elevated alanine aminotransferase (ALT)*	3.0%	0.0%
Hypersalivation	1.5%	1.5%
Application site alopecia	0.7%	0.0%

*ALT was greater than twice the upper reference range of 100 IU/L. These cats also had mild elevations of aspartate aminotransferase (AST) (less than twice the upper reference range of 100 IU/L). No clinical signs associated with liver disease were noted in these cats.

In well-controlled laboratory effectiveness studies, the following adverse reactions were seen after application of Bravecto Plus: pyrexia, tachypnea, mydriasis, pruritus, scabbing, and bloody stool.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in cats in foreign markets: polydipsia, swelling of chin and lips, periorbital swelling, blepharospasm, pruritus, erythema, aggression, agitation, pyrexia, mydriasis, hypersalivation, hyperactivity, alopecia, and excessive grooming. These adverse events occurred within 48 hours of administration.

In a European field study for fluralaner topical solution for cats, there were three reports of facial dermatitis in humans after close contact with the application site which occurred within 4 days of application. In foreign market experience reports for Bravecto Plus, one veterinarian experienced tingling and numbness of the fingers, hand, and arm, and swelling of the hand and arm after getting Bravecto Plus on her fingers. Additional signs, including blurred vision and disorientation, occurred after taking an antihistamine.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Merck Animal Health at 1-800-224-5318. Additional information can be found at www.bravecto.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

Clinical Pharmacology:
Peak fluralaner concentrations are achieved between 3 and 21 days following topical administration and the elimination half-life ranges between 11 and 18 days. Peak moxidectin concentrations are achieved between 1 and 5 days following topical administration and the elimination half-life ranges between 20 and 30 days.

Mode of Action:
Fluralaner is for systemic use and belongs to the class of isoxazoline-substituted benzamide derivatives. Fluralaner is an inhibitor of the arthropod nervous system. The mode of action of fluralaner is the antagonism of the ligand-gated chloride channels (gamma-aminobutyric acid (GABA)-receptor and glutamate-receptor).

Moxidectin is for systemic use and is a semisynthetic derivative of nemadectin, belonging to the milbemycin group of macrocyclic lactones. It binds to gamma-aminobutyric acid (GABA) and glutamate-gated chloride channels of the nerves and muscles of the parasite resulting in hyperpolarization, paralysis and death.

Effectiveness:
In two well-controlled laboratory studies, Bravecto Plus was 100% effective against induced heartworm infections when effective when administered more than 2 months prior to infection. Bravecto Plus was not effective when administered more than 2 months prior to infection.

In well-controlled laboratory studies, Bravecto Plus was effective against naturally and experimentally induced adult and experimentally induced 4th stage larval and immature adult *Toxocara cati* and *Ancylostoma tubaeforme* infections in cats.

In a well-controlled laboratory study, Bravecto Plus killed 100% of fleas within 12 hours after treatment and reduced the numbers of live fleas on cats by >99% within 12 hours after treatment or infestation for 2 months. In well-controlled laboratory studies, Bravecto Plus demonstrated >90% effectiveness against *Dermacentor variabilis* 48 hours after treatment or infestation for 2 months but failed to demonstrate $\geq$ 90% effectiveness beyond 2 months. In well-controlled laboratory studies, Bravecto Plus demonstrated $\geq$ 98.1% effectiveness against *Ixodes scapularis* 48 hours after treatment or infestation for 2 months.

Animal Safety:
Margin of Safety Study: In a margin of safety study, Bravecto Plus was administered topically to 9- to 13-week-old (mean age 12 weeks) kittens at 1X, 3X, and 5X the maximum labeled dose of 93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg at three, 8-week intervals (10 kittens per group). The kittens in the control group (0X) were treated with mineral oil. There were no clinically-relevant, treatment-related effects on physical examination, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, serum amyloid A, and urinalysis), gross pathology, histopathology, or organ weights. Single incidences of self-limiting hypersalivation in three kittens (one kitten in the 1X group and two kittens in the 3X group) and pruritus at the administration site in one kitten in the 3X group were observed on the day of dose administration. Cosmetic changes at the application site included matting/clumping/spiking of hair, wetness, or a greasy appearance.

Oral Safety Studies: In an oral safety study, one dose of Bravecto Plus was administered orally to 4- to 9-month-old kittens at the maximum labeled dose of 93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg. The kittens in the control group were administered saline orally. There were no clinically-relevant, treatment-related effects on physical examination, body weights, food consumption, or clinical pathology (hematology, clinical chemistries, coagulation tests, serum amyloid A, and urinalysis). Five of six treated kittens experienced hypersalivation. One treated kitten experienced vomiting 2 hours after administration and another 8 hours after treatment. Treated kittens had reduced food consumption on the day of treatment.

In an oral safety study for fluralaner topical solution for cats, four out of six cats experienced coughing immediately after oral administration of the maximum labeled dose of 93.0 mg fluralaner/kg.

In a pilot oral safety study, adult cats orally administered 0.5X or 1X the maximum labeled dose of Bravecto Plus had foaming hypersalivation for up to five minutes and reduced food consumption on the day of dosing. One cat exhibited transient lacrimation from one eye during the first 15 minutes after dosing.

Safety in cats infected with adult heartworm (Dirofilaria immitis): Bravecto Plus was administered topically to cats infected with adult heartworm at 1X or 3X the maximum labeled dose of 93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg (8 cats per group). The cats in the control group (0X) received mineral oil topically. Two untreated cats were found dead prior to dosing. There were no clinically-relevant, treatment-related effects on body weights, clinical pathology (hematology, clinical chemistry, and coagulation profile), gross pathology or histopathology. Self-limiting hypersalivation due to grooming was observed on the day of treatment in both treatment groups (6/8 cats in the 1X group and 7/8 cats in the 3X group). In addition, three treated cats (2/8 cats in the 1X group and 1/8 cats in the 3X group) developed adverse neurologic signs during the study and were euthanized due to quality-of-life concerns. Clinical signs in one cat in the 1X group included vomiting, depression, vocalization, and ataxia 38 days that included ataxia, paresis, and muscle tremors 25 days after dosing. A cat in the 3X group exhibited depression, dehydration, a hunched position, and inability to stand 22 days after dosing. Heartworms were found in the epidural space in the second cat of the 1X group and the cat in the 3X group.

Field Safety Study: In a well-controlled field study, Bravecto Plus was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics and steroids. No adverse reactions were observed from the concurrent use of Bravecto Plus with other medications.

Storage Conditions:
Do not store above 77°F (25°C). Store in the original package in order to protect from moisture. The pouch should only be opened immediately prior to use.

How Supplied:
Bravecto Plus is available in three tube sizes to treat cats ranging in weight from 2.6 lb – 27.5 lb (1.2 kg to 12.5 kg). Each tube is packaged individually in a pouch. Product may be supplied in 1 or 2 tubes per carton.

Approved by FDA under NADA # 141-518

Rev: 08/2019

MERCK Animal Health

Vendor News

Vetsource updates platform with text notifications

Did you know your clients can sign up for text message updates about their shipped order? When purchasing from your shopping site, clients can opt in by entering their phone number in the space provided on the order thank-you page. Once opted in, a text message will be sent for each shipment associated with the order letting them know it's on the way. They'll also receive a link to track the order on the carrier's site! Learn more about TVC's partnership with Vetsource here.

Hill's Pet Nutrition launches pet weight management campaign

Join Hill's Pet Nutrition in ending pet obesity. Through March 31, Hill's will run a national campaign to educate pet parents on how to recognize if their pet is overweight, and encourage them to "Ask your vet" about a healthy weight program. This is coupled with a special offer for clinics on select weight management foods. See the promotion here or learn about other fun aspects of the initiative including an incentive for VIP Market users to earn free food and document your pet's weight loss journey.

Promotions

GeniusVets:

Download your free Social Media Toolkit from GeniusVets. Click here for details.

Hill's Pet Nutrition:

- Save 10% on select weight management diets. Click here for details.
- Earn PurrrchasePoints™ when you send Hill's direct to the pet with any vet sponsored home delivery platform. ***TVC Exclusive Promotion***

Securos:

Receive a 20% discount when you purchase the Tri-Denta Complete Kit with a new 3-in-1 sterilization tray. Click here for details.

Vetoquinol:

Buy 10 get 2 free on Flexadin® Advanced with UC-11® 60 Count Chews. Click here for details.
TVC Exclusive Promotion

Vetsource:

Autoship promotions for pet parents on your favorite TVC brands. Click here for details.

Breakthrough Cancer Treatment

Virbac's soon-to-be-released cancer fighting drug could be a paradigm shift for veterinarians and the pets they treat

Pamela Jones, DVM, knows the sense of dread that pet owners go through when they discover a mass on their beloved dog or cat.

"I have a dog that has probably 12 different masses," said Jones, who is board-certified by the American College of Veterinary Internal Medicine in medical oncology and by the American College of Veterinary Radiology in radiation oncology. "I think I've looked at eight of them, and I'm a little bit behind on the fact that I should be looking at the other four."

Mast cell tumors are the most common type of skin tumor found in dogs and the second most common skin tumor in cats, according to the American College of Veterinary Surgeons. These represent 14 – 21% of all skin tumors diagnosed in dogs. They are usually noticed in middle aged patients but can occur in patients of any age.

Having a procedure that can be performed in any practice within the United States alone brings more relief and reassurance to owners that something can be done for their pet.

The most common method of treatment for mast cell tumors has been surgical removal. But that's where things can get complicated. Surgery can be difficult for elderly patients, or patients with other diseases such as heart disease. Where the tumors are located could also pose risks and problems.

"If the tumor is located on a limb, or in a difficult spot, such as the face or somewhere there are other structures, it could pose difficulties," Jones said. "A large enough surgery to completely remove the tumors and cure the pet of them without worrying about it coming back can be difficult in some of those locations."

Quick road to recovery

Virbac, through a collaboration with QBiotics, has found another safe, effective way to treat mast cell tumors in dogs with the release of STELFONTA® (tigilanol tiglate injection). STELFONTA® is a an innovative intratumoral injection treatment that removes 75% of canine Mast Cell Tumors with a single treatment* and in most cases does so in a non-invasive way.

After injecting the tumor with STELFONTA, "within two hours you will start to see a response," said Jones. For instance, the pet owner and veterinarian would see on the outside that the tumor becomes swollen. Its color may turn red, with a bruise-like appearance. This is the rapid and local inflammatory response at the tumor site. After a couple of days, the tumor necroses and dies. Usually in most cases, by seven days the dead tissue falls away.

The patient is left with an open wound, but it's a very healthy, open wound. Another unique aspect of STELFONTA is that it stimulates wound healing.

"As an oncologist, the necrosis of the tumor is amazing, but the other aspect of it – the wound healing – is just phenomenal," said Jones. Within six weeks, the majority of patients already have a healed wound.

That's such a paradigm shift in thinking that it will take some educating on the part of veterinarians and clients to get used to, but the implications are tremendous. "It provides pet owners with another option," Jones said. "So often with cancer and pets, we are left with very few options, or often only a single option of surgery."

Having a procedure that can be performed in any practice within the United States alone brings more relief and reassurance to owners that something can be done for their pet. And for veterinarians, it frees up valuable clinic time that would have been consumed with pre-op, anesthesia, surgery, recovery, etc.

As of press time, Virbac planned to send trial samples out to veterinary oncologists in the coming weeks, with the next phase of the rollout targeting general practitioners sometime in March. ■

Among dogs treated with STELFONTA®:

- 75% of mast cell tumors achieved resolution of the target tumor with just one treatment
- 87% of dogs achieve resolution of the target tumor 28 days after either the first or 28 days after a second treatment.
- The treatment is generally well-tolerated and does not adversely affect quality of life
- 12 weeks after a single injection, 96% of dogs remained disease free at the site of the treated tumor
- In 96.5% of cases, full healing was observed within 3 months (bandaging, use of Elizabethan collars and topical or systemic antibiotics were only needed in rare circumstances)
- Most wounds were completely re-epithelialized within 28 to 42 days of treatment, with good cosmetic outcomes

Many dogs are not good candidates for surgery because of multiple factors. Factors that can make surgery less suitable:

Location	› Cosmetic and/or functional compromise › Ability to close the wound
Pathology	› Edema, reactive stromal cells and inflammatory cells make determination of the surgical margins difficult
Size of the tumor	› 1.4% increase in incomplete excision per cm
Body weight	› Decreased body weight is a risk factor for incomplete excision
General anesthesia	› Older dogs with comorbidities have higher anesthetic risk › Some breeds (brachycephalic) have higher anesthetic risk
Client choice and preference	› Preference to avoid surgery and surgical aftercare

STELFONTA®
(tigilanol tiglate injection)
1 mg/mL

SEEING IS BELIEVING

"Mast cell tumor removal in a single treatment?

Sounded crazy to me, then I tried it."

Dr Samuel Geller,
Veterinarian

To place an order, contact your Virbac representative, or call 1-844-4-VIRBAC (1-844-484-7222).

To learn more, visit https://vet-us.virbac.com/stelfonta.

STELFONTA® (tigilanol tiglate injection)

4 HOURS

7 DAYS

6 WEEKS

Hours: visible changes

Days: tumor destruction

Weeks: tumor site typically healed

IMPORTANT SAFETY INFORMATION

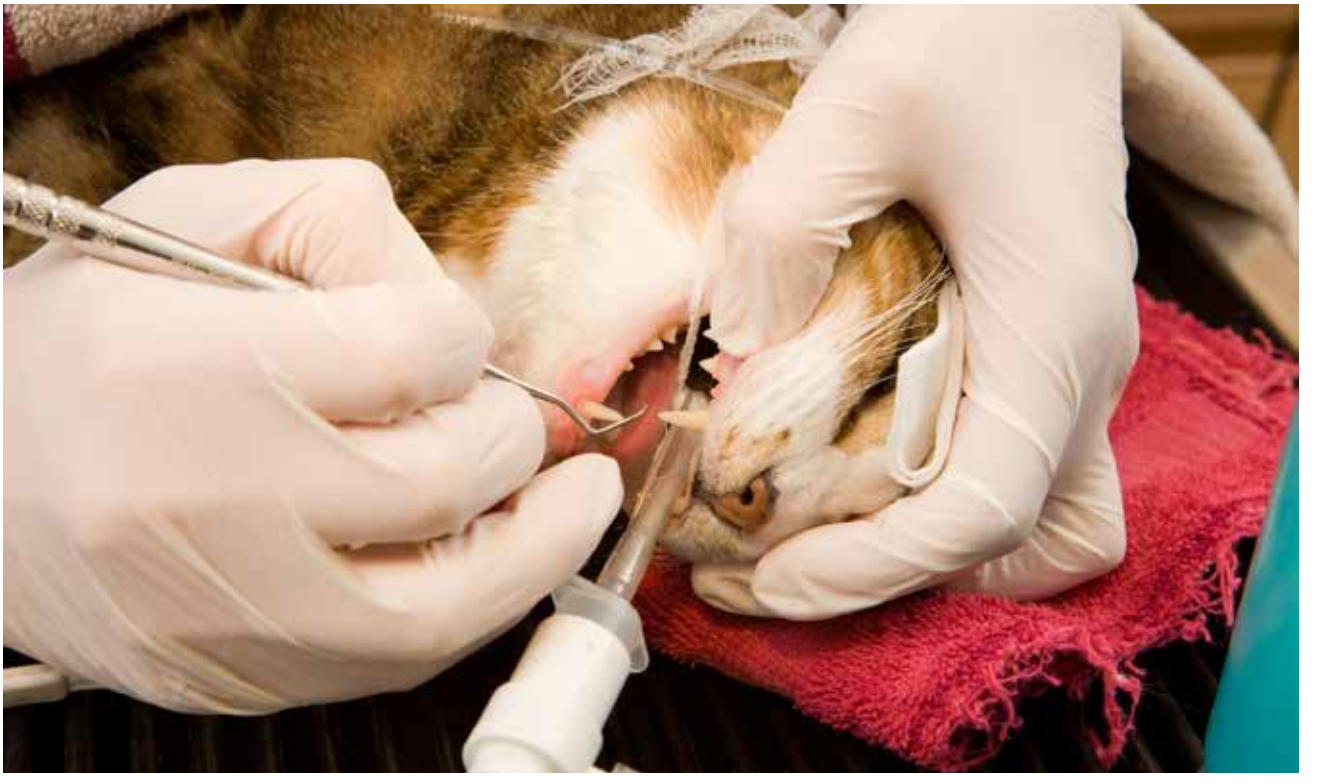
Accidental self-injection of STELFONTA® (tigilanol tiglate injection) may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary. In dogs, do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock. Formation of wounds, possibly extensive, is an intended and likely response to treatment with STELFONTA along with associated swelling, bruising and pain; these wounds are expected to heal. Appropriate pre- and post-treatment medications must be given, including a corticosteroid plus blocking agents for both H1 and H2 receptors, in order to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation. For full prescribing information, contact VIRBAC at 1-800-338-3659 or visit https://vet-us.virbac.com/stelfonta.

Virbac Shaping the future of animal health

Dentistry on the Cusp

New equipment, new training, new graduates point to a growing focus on veterinary dentistry

By Mark Thill



General veterinarians are doing more routine dental cases than ever. More important, they are doing them better, said Brook Niemiec, DVM, FAVD, DAVDC, Veterinary Dental Specialties and Oral Surgery, San Diego, California. Now, thanks to a decision in September by the American Veterinary Medical Association's Council on Education (COE), recent graduates may do better still.

"Dentistry is an integral part of veterinary medical practice and is a crucial component for the health and welfare of multiple animal species," wrote the COE in its revisions to minimum standards in veterinary medical education. "It is essential that students are trained in dentistry."

Specifically, the COE – which accredits DVM or equivalent educational programs – added just two words – "and dentistry" – to Standard 9 on curriculum. The Standard now says that curriculum must include exposure to "principles and hands-on experiences in physical and laboratory diagnostic methods and interpretation … disease prevention, biosecurity, therapeutic intervention (including surgery and dentistry), and patient management and care … involving clinical diseases of individual animals and populations."

"Honestly, it should have occurred years ago," Brenda L. Mulherin, DVM, DAVDC, and clinical professor of dentistry

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and oral surgery at Iowa State University, told *Today's Veterinary Practice*, an NAVC publication. "Veterinary dentistry is something that almost all general practitioners will need to have some knowledge of. While most practitioners will need to perform some type of oral procedure at least once in their career, the knowledge that is bestowed upon most graduates is minimal."

dentistry, said Niemiec. And they are responding accordingly.

"We did a study from 2008-12 where we looked at the number of retained roots from extractions. It was over 90%. Imagine if 90% of your patients died under anesthesia; I think you would change something. But currently, more vets are taking dental radiographs, and this has decreased

"The biggest pushback to dental care is fear of anesthesia, with finances a close second. Working patients up increases anesthetic safety. We know we are going to decrease the function of the vital organs slightly during anesthesia."

– Brook Niemiec, DVM, FAVD, DAVDC, Veterinary Dental Specialties and Oral Surgery

"Students have always wanted more dentistry," said Dr. Amy Stone at the University of Florida College of Veterinary Medicine. "They fight over spots and rotations." Accordingly, UF has grown its dental program steadily since the late 1990s. Interest in dentistry has heightened among the entire profession as well, "partly because spays and neuters are now done in rescues before they have gotten out into the general practice," she said. "Dentistry has now become more of a focus."

Dentistry is an investment

Most veterinarians understand the medical and financial benefits of performing

– though not completely alleviated – retained roots."

Still, there exist some disconnects regarding proper dental care, he added. To achieve a significant medical benefit, dental care requires a significant investment in equipment and training.

"Dentistry is done well or not at all," he said. "One thing we are seeing much more of is iatrogenic pathologic jaw fractures. This is because vets know that these teeth need to be extracted but don't have the equipment or training to extract them safely. The increasing popularity of small and toy breed dogs is also to blame."

Investment comes with a cost to the client, he added. But most clients are willing to bear that cost if they are properly educated. "The main issue is that veterinarians and staff say, 'Fluffy needs a cleaning' instead of 'Fluffy needs a cleaning or all these bad things can/will happen; these are all the steps that are required, and [this is what we do] to ensure safety and effectiveness.' It's this training and effort that is critical."

Anesthesia safety is paramount, and thorough pre-operative testing protocols are essential to successful dentistry, said Niemiec. "The biggest pushback to dental care is fear of anesthesia, with finances a close second. Working patients up increases anesthetic safety. We know we are going to decrease the function of the vital organs slightly during anesthesia. A healthy pet deals with it fine, a sick one can't. A pet lost under anesthesia likely means many who don't get the care they need. Further, by explaining the value of the pre-op protocol, we ease the client's concern. Finally, it is a direct source of income for the clinic."

Assessment in a year

AVMA's Council on Education "does not prescribe the number of classes, laboratories, etc. that a college has in any area of the curriculum," Dr. Karen Brandt, head of AVMA's Education Division, told *Veterinary Advantage*. "The standard states the curriculum in veterinary medicine is the purview of the faculty of each college, but must be managed centrally based on the mission and resources of the college."

In order for colleges to adjust to a revised standard, the Council on Education will not initiate assessment of a revised standard until after one year.

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Veterinarians in Connecticut invited to administer COVID-19 vaccines

Connecticut and the Canadian province of Manitoba have taken steps to enlist licensed veterinary professionals along with other health care workers to administer COVID-19 vaccines, the VIN News Service reports. Connecticut appeared to be the only state to include veterinarians in the list of professionals who can administer the vaccine, said Michael San Filippo, a spokesperson for the AVMA. "Typically, professional liability policies cover the veterinarian in their delivery of veterinary services; human vaccination would seem to fall outside the scope of those services," he said. "Veterinarians should contact their professional liability carrier to see whether they are covered. They should also see what coverage might be provided by the state/local authority and reach out to their personal insurer to see if this would be covered under any umbrella policy."

Studies will look at human-animal bond impacts on human health

The Human Animal Bond Research Institute announced five new research projects focusing on the impact of the human-animal bond on human health. Studies will look at canine-assisted anxiety reduction in pediatric emergency care; the influence of pet ownership on gut microbiota and cardiovascular disease risk; the effects of animal-assisted interventions on development for adolescents in residential treatment; pet ownership and aging; and equine-assisted therapy's effects on older adults with Parkinson's disease.

Veterinarians try to protect teams, maintain services during pandemic

Veterinarians and veterinary association leaders have described difficulties protecting their teams from the coronavirus while continuing to treat patients amid rising case levels this fall, the AVMA reports. By early December, the country was recording 200,000 cases daily. "Sometimes, we have limited staff because there are people out with exposure or with COVID, and so we have to adjust as each day comes," said Derine Winning, a North Dakota practice owner. "And we're still trying to treat illness. We're still trying to prevent pain and suffering in our patients. We're still practicing preventive health care, especially in light of public health concerns." Little information is available so far on how the virus has spread in veterinary settings, especially as public health departments struggle to keep up with contact tracing.

First year of pet ownership is hardest, survey finds

Eight in 10 respondents in a recent survey said the first year of pet ownership is the most important, and 64% believe the first year is also the most difficult. The survey was commissioned by pet food manufacturer Royal Canin "to investigate the highs and lows of pet ownership in the first year," according to the announcement. Seventy-three percent of the 2,000 dog and cat owners surveyed said they bonded more with their pet in the first year than in any other. Tough decisions owners faced included how to train their new pet (46%), what kind of food to feed their pet (40%) and what kind of feeding schedule would be best for their pet (39%).

Virbac

STELFONTA®

(tigilanol tiglate injection)

1 mg/mL

For intratumoral injection in dogs only
Antineoplastic
Single use vial

WARNING: SEVERE WOUND FORMATION IN HUMANS; EXTENSIVE WOUND FORMATION, MAST CELL DEGRANULATION, AND DEATH IN DOGS DUE TO MAST CELL DEGRANULATION

Human Safety

- **Accidental self-injection of STELFONTA® may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary (see Dosage and Administration, Human Warnings and Adverse Reactions).**

Dog Safety

- **Always administer a corticosteroid (e.g. prednisone or prednisolone), an H1 receptor blocking agent (e.g. diphenhydramine), and an H2 receptor blocking agent (e.g. famotidine) when treating with STELFONTA to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation (see Contraindications and Dosage and Administration).**
- **Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see Contraindications, Warnings and Adverse Events).**
- **Treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds that require additional treatment and prolonged recovery times (see Warnings, Precautions and Adverse Events).**

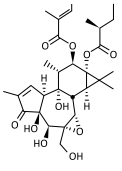
CAUTION

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

DESCRIPTION

The active ingredient for tigilanol tiglate injection is a phorbol ester that activates alpha, beta I, beta II, and gamma isoforms of protein kinase C. The chemical name is (4S,5S,6R,7S,8R,9R,10S,11R,12R,13S,14R)-12-(2E)-2-methylbut-2-enoatyl-13-[(2S)-2-methylbutyroyl]-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one. The molecular formula is C30H42O10 and its molecular weight is 562.65 g mol[-1]. Each mL of STELFONTA contains 1 mg tigilanol tiglate and sterile water for injection (60% v/v), propylene glycol (40% v/v), sodium acetate (<0.1% w/v), and glacial acetic acid (<0.1% w/v).

The chemical structure for tigilanol tiglate is:



INDICATION

STELFONTA injection is indicated for use in dogs for the treatment of:

- non-metastatic cutaneous mast cell tumors
- non-metastatic subcutaneous mast cell tumors located at or distal to the elbow or the hock

DOSAGE AND ADMINISTRATION

ALWAYS PROVIDE THE CLIENT INFORMATION SHEET TO THE DOG OWNER BEFORE DOSE ADMINISTRATION.

Concomitant medications

Administer the following medications to decrease the potential for severe systemic adverse reactions from mast cell degranulation:

- **Corticosteroid (e.g. oral prednisone or prednisolone at anti-inflammatory dose):** Start medication 2 days prior to STELFONTA treatment and continue for 8 days post-treatment (10 days total).
- **H1 receptor blocking agent (e.g. oral diphenhydramine):** Start medication on the day of STELFONTA treatment and continue for a total of 8 days.
- **H2 receptor blocking agent (e.g. oral famotidine):** Start medication on the day of STELFONTA treatment and continue for a total of 8 days.

Dosing Instructions

Administer STELFONTA as an intratumoral injection at a dose of 0.5 mL per cm^3 of tumor volume, as determined by the following calculations:

- **Determine the Tumor Volume in cm^3:**
  0.5 x [length (cm) x width (cm) x height (cm)]
- Confirm the Tumor Volume does not exceed 10 cm^3. Do not use STELFONTA if tumor volume is >10 cm^3.
- **Calculate the Dose Volume (mL) of STELFONTA to inject:**
  Tumor Volume x 0.5 mL
- Confirm the dose of STELFONTA does not exceed 0.25 mL/kg body weight.
- Do not exceed 5 mL per dog, regardless of tumor volume or body weight.
- The minimum dose of STELFONTA is 0.1 mL, regardless of tumor volume or body weight. If the calculated dose is <0.1 mL, administer 0.1 mL.

Administration of STELFONTA:

Sedation may be necessary to safely and accurately administer STELFONTA to decrease the chance of accidental self-injection. Wear gloves, eye protection, and lab coat or gown in the preparation and administration of STELFONTA. Care should be taken to restrict injections to the tumor only. STELFONTA should not be injected into the margins, beyond the periphery, or deep to the tumor.

- Shave the tumor site. Avoid manipulation of the tumor.
- Draw the calculated volume of STELFONTA into a sterile Luer-lock syringe with a 23 gauge needle.
- Identify an appropriate injection point on the edge of the tumor. See Figure 1. Insertion of the needle depends on the tumor's location, form, and appearance. If a tumor protrudes above the surface of the skin, insert the needle at an oblique angle of approximately 45°.
- Insert and embed the needle in the tumor through a single injection site and draw the syringe plunger back slightly to ensure STELFONTA is not injected into a blood vessel. While applying even pressure on the syringe plunger, move the needle back and forth in a fanning manner to inject STELFONTA into the tumor. See Figure 1. The drug should fully perfuse the entire tumor.
- When the total dose of STELFONTA has been administered, pause to allow tissue dispersion before removing the needle from the tumor. Pull back on the syringe plunger to create a small negative pressure before removing the needle to minimize leakage from the injection site.
- After the needle is withdrawn, apply light pressure for 30 seconds over the needle exit hole using a gloved finger. If leakage does occur, rinse injection site with saline to wash STELFONTA from the skin surface. Do not re-administer.
- To minimize risk of accidental self-injection, do not recap the needle. Dispose of the needle and syringe.

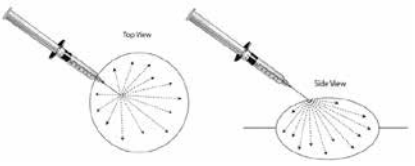


Figure 1: Dispersion of STELFONTA throughout the tumor.

CONTRAINDICATIONS

Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see **Adverse Reactions**).

WARNINGS

Human Safety

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

Caution is required during treatment to avoid accidental self-injection. Dogs undergoing treatment with STELFONTA should be adequately restrained and sedation used if necessary. Use a Luer-lock syringe to administer STELFONTA. Do not recap the needle. Accidental self-injection may result in local inflammatory reactions, including swelling, redness and severe wound formation. In case of accidental self-injection, immediately rinse the area with water, seek medical advice immediately, and show the package insert to the physician.

Wear personal protective equipment consisting of disposable gloves, protective eye wear, and a lab coat or gown when handling STELFONTA. STELFONTA is an irritant and accidental exposure to skin, eye, or by ingestion should be avoided. In case of dermal or ocular exposure, repeatedly wash the exposed skin or eye with water. If wearing contacts, rinse the eyes first then remove contacts and continue to rinse with water. If symptoms such as local signs of redness and swelling occur, or if there has been ingestion, seek the advice of a physician and show them the package insert.

Limited data is available on the potential teratogenic effects of STELFONTA. Therefore, STELFONTA should not be administered by women who are pregnant or planning to become pregnant.

People with known hypersensitivity to tigilanol tiglate or to any of the excipients should avoid contact with STELFONTA.

Animal Safety

Dogs should be monitored during and for 5-7 days after intratumoral treatment with STELFONTA for signs of systemic mast cell degranulation such as vomiting, diarrhea, lethargy, anorexia/hyporexia, altered breathing, hypotension, urticaria, edema at or away from the treated site, or bruising at or away from the treated site. If signs are observed, appropriate treatment should be started immediately.

Always administer the recommended concomitant medications (corticosteroids, H1, and H2 receptor blocking agents) with STELFONTA. Death has occurred following mast cell degranulation when these concomitant medications were not administered according to this Package Insert (see **Dosage and Administration** and **Adverse Reactions**).

STELFONTA can induce a substantial local inflammatory reaction which may result in pain, bruising, and swelling. During this time, an analgesic may be needed in addition to the use of corticosteroids and both H1 and H2 receptor blocking agents.

Treatment with STELFONTA causes tumor necrosis which is part of the mechanism of action of the drug. Bruising, heat, pain, and swelling may begin at the site within 2 hours of treatment. By day 7 after treatment, wound formation including full thickness dermal necrosis with exudate, peripheral tissue edema, erythema, skin discoloration, tissue sloughing, and necrotic eschar may occur.

In addition to tumor necrosis, treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds (see **Adverse Reactions**).

Do not inject STELFONTA into normal subcutaneous tissue or adjacent tissues (e.g. beyond tumor margins) because severe edema, erythema and necrosis of the injected tissue may occur.

PRECAUTIONS

STELFONTA has not been evaluated in dogs with signs of systemic disease due to the mast cell tumor(s).

STELFONTA is not intended for the treatment of metastatic mast cell tumors.

The safe and effective use of STELFONTA has not been evaluated for simultaneous treatment of more than one mast cell tumor.

The safe and effective use of STELFONTA has not been evaluated in dogs with a mast cell tumor volume >10 cm^3.

Use STELFONTA with caution in tumors located within mucocutaneous regions (e.g., eyelids, vulva, prepuce, and anus) as tumor necrosis could cause a change in morphology of the mucocutaneous region resulting in loss of functional integrity.

Use STELFONTA with caution in mast cell tumors with significant ulceration as leakage of the drug from the ulcerated area may occur following treatment potentially reducing effectiveness.

The safe use of STELFONTA has not been evaluated in dogs with concurrent diseases that may result in delayed wound healing.

After treatment with STELFONTA, dogs may require additional care of the treated site to aid in the healing process. An Elizabethan collar or a non-constricting dry gauze bandage may be needed to prevent the dog from self-traumatizing the treated site.

After treatment with STELFONTA, separation from other household animals may be necessary to prevent grooming and trauma to the treated site.

The safe use of STELFONTA under conditions of use has not been evaluated in dogs younger than 3.5 years old.

The safe use of STELFONTA has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS

Human Exposure

There was one human exposure during the field study where the veterinarian had a needle stick injury to the thumb at completion of tumor treatment and was injected with an unknown amount of STELFONTA. The incident resulted in pain and necrosis of the center of the thumb at the point of needle stick. The wound healed over a period of three months. See Pictures 1 and 2 below. A separate needle stick injury was reported with a maximum potential dose of 0.1 mL tigilanol tiglate into the distal extremity of the left index finger, resulting in a localized burning sensation, local inflammation, bruising, muscular pain up the left arm, and localized tissue necrosis. Muscular pain resolved in the first 12-24 hours and the wound healed in 8 weeks. There have been other needle stick injuries reported, with at least one injection into a thumb, with minimal (stinging, pain, and swelling) to no adverse events associated with these accidental self-injections.

Picture 1. Thirteen days after self-injection

Picture 2. Seventy-four days after self-injection

Field Study

In a well-controlled, multi-center, randomized, double-masked field study evaluating the effectiveness and safety of STELFONTA for the treatment of cutaneous and subcutaneous mast cell tumors in dogs, 117 dogs treated with STELFONTA and 42 dogs receiving sham treatment (untreated control) were evaluated for safety. Eighty-one dogs were treated with STELFONTA on Day 0. Thirty-six previously untreated control dogs were treated with STELFONTA on Day 30. In addition, 18 dogs treated with STELFONTA on Day 0 had the same tumor re-treated with STELFONTA on Day 30 due to incomplete response. The most common adverse reactions included wound formation, injection site pain, lameness in the treated limb, vomiting, diarrhea, and hypoalbuminemia. Wound formation, vomiting, and diarrhea were mainly observed within the first 7 to 10 days after treatment. Injection site pain and lameness in the treated leg were mainly observed within the first 2 days after treatment. Hypoalbuminemia was mainly observed within the first 28 days after treatment. All dogs received concomitant medications as noted in the Effectiveness section. The adverse reactions during the study are summarized in Table 2 below.

Table 2: Adverse Reactions During the Field Study

Adverse Reaction	STELFONTA 1st Treatment (n = 117)	STELFONTA 2nd Treatment (n = 18)	UNTREATED CONTROL (n = 42)
Wound formation	110 (94.0%)	12 (66.7%)	3 (7.1%)
Injection site pain	61 (52.1%)	7 (38.9%)	1 (2.4%)
Lameness in treated limb	29 (24.8%)	2 (11.1%)	1 (2.4%)
Vomiting	24 (20.5%)	3 (16.7%)	4 (9.5%)
Diarrhea	24 (20.5%)	3 (16.7%)	2 (4.8%)
Hypoalbuminemia[a]	21 (18.0%)	2 (11.1%)	1 (2.4%)
Injection site bruising/ erythema/edema/ irritation	20 (17.1%)	3 (16.7%)	1 (2.4%)
Anorexia	14 (12.0%)	2 (11.1%)	3 (7.1%)
Regional lymph node swelling/enlargement	13 (11.1%)	1 (5.6%)	1 (2.4%)
Tachycardia	12 (10.3%)	0 (0.0%)	1 (2.4%)
Weight loss	12 (10.3%)	3 (16.7%)	5 (11.9%)
Cystitis	10 (8.6%)	1 (5.6%)	2 (4.8%)
Dermatitis	9 (7.7%)	1 (5.6%)	1 (2.4%)
Personality/behavior change	8 (6.8%)	0 (0.0%)	2 (4.8%)
Infection at injection site	8 (6.8%)	0 (0.0%)	0 (0.0%)
Tachypnea	7 (6.0%)	2 (11.1%)	1 (2.4%)
Pruritus	6 (5.1%)	3 (16.7%)	2 (4.8%)
Lethargy/Depression	6 (5.1%)	1 (5.6%)	1 (2.4%)
Pyrexia	3 (2.6%)	2 (11.1%)	0 (0.0%)

[a] There was a statistically significant decrease in albumin and albumin/globulin ratios at Day 7 in the STELFONTA group compared to the control group. The hypoalbuminemia ranged from 2.0 to 2.6 g/dL (reference range 2.7-3.9 g/dL).

Note: If an animal experienced the same adverse reaction more than once, only the highest grade was tabulated.

Adverse reactions were graded using the Veterinary Co-operative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE).[1] Most adverse reactions were Grade 1 (mild) or 2 (moderate). Grade 3 (severe) and 4 (life-threatening) adverse reactions in dogs treated with STELFONTA included: lameness in the treated limb (6 dogs), injection site pain (4 dogs), wound formation (3 dogs), lethargy/depression (3 dogs), anorexia (2 dogs), infection at injection site (1 dog), pruritis (1 dog), and tachycardia (1 dog).

Adverse reactions associated with use of the required concomitant corticosteroids were similarly reported in STELFONTA and untreated control dogs and included elevated alkaline phosphatase, polyuria, and polydipsia.

Wound Formation

Tumor observations were conducted at 2, 4, 8, and 24 hours and 4 days after treatment. The 81 dogs treated with STELFONTA on Day 0 were reported most frequently with swelling, bruising, pain and heat at all tumor observation timepoints. The following were reported at 24 hours post treatment:

- Swelling: 97.5% (79/81 dogs)
- Bruising: 91.4% (74/81 dogs)
- Pain: 69.1% (56/81 dogs)
- Heat: 53.1% (43/81 dogs)

At 24 hours post treatment, intact skin was reported in 71.6% (58/81 dogs) of STELFONTA® (tigilanol tiglate injection) treated dogs. On Day 4 intact skin was reported in 17.3% (14/81 dogs) of STELFONTA treated dogs. On Day 4, the following observations were reported with the highest frequency:

- Necrosis: 55.6% (45/81 dogs)
- Crater pockets: 37.0% (30/81 dogs)
- Exudate: 37.0% (30/81 dogs)
- Eschar: 28.4% (23/81 dogs)
- Ulceration: 11.1% (9/81 dogs)

A wound healing assessment was performed on the effectiveness dataset which included 80 dogs in the STELFONTA group and 38 dogs in the untreated control group. Wounds developed in 92.5% (74/80) of STELFONTA treated dogs and 2.6% (1/38) of untreated control dogs by Day 7. On Day 28, the presence of wounds was 40% (32/80) in the STELFONTA group and 2.6% (1/38) in the

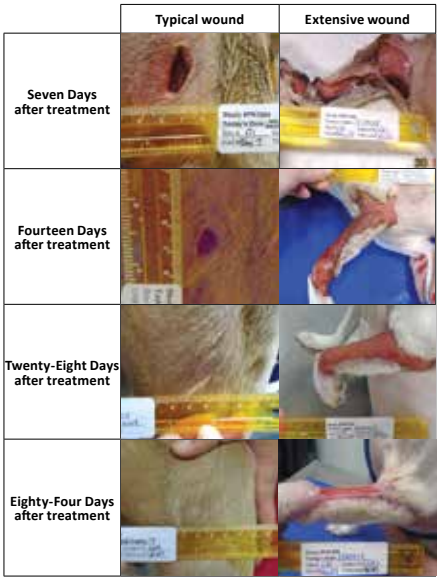
untreated control group. On Day 42 and Day 84, the presence of wounds was 27.1% (16/59) and 1.8% (1/57), respectively, in the STELFONTA group.

Exudate from the treated site including serous, serosanguinous, sanguineous, seropurulent, and purulent discharges were seen mainly on Day 7 and to a lesser extent on Day 14. Sloughing of the treated site was observed from Day 7 to Day 42, with decreasing frequency after Day 7. Peripheral pitting or non-pitting edema and erythema of the surrounding area were observed from Day 7 to Day 28, with decreasing intensity and frequency after Day 7. Necrotic eschar and epithelialization of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14. Granulation or hyper-granulation of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14.

The average wound size at Day 7 for a STELFONTA treated dog was 3.3 cm x 2.4 cm (original average tumor size 1.9 x 1.6 x 0.9 cm). On Day 28, the average wound size was 2.0 x 1.4 cm.

The largest total wound for a STELFONTA treated dog was reported seven days after treatment. The treated tumor was located on the left caudal stifle and the original tumor size measured 2.4 x 2.1 x 1.4 cm. The wound area initially consisted of three individual wounds recorded on the treated limb (both medial and lateral sides): 7.5 x 4.5 cm, 7.0 x 3.5 cm, and 11.5 x 7.0 cm. The wounds had reduced to 3.5 x 1.4 cm, 3.9 x 1.5 cm, and 9.7 x 4.3 cm 28 days after treatment, and 0.5 x 0.7 cm and 2.5 x 2.9 cm 42 days after treatment and were no longer present at 84 days after treatment.

One dog treated with STELFONTA was reported with an extensive wound formation (wound size 25.0 x 9.5 cm) with severe tissue slough (Grade 3) nine days after treatment of a mast cell tumor on the left metacarpal area (original tumor size 2.5 x 1.9 x 1.3 cm). The wound extended proximally up the leg to the shoulder and required bandaging of the leg and antibiotics. Scar contracture formed, requiring treatment under sedation to release the scar tissue. Clinical pathology abnormalities included elevated band neutrophils, anemia, and hypoalbuminemia. The wound had not fully healed by the end of the study 89 days after treatment. See pictures below comparing progression of this extensive wound formation versus commonly observed wound progression.



One dog treated with STELFONTA was reported with a bacterial infection and cellulitis in the right rear leg 9 days after treatment of a mast cell tumor on the right rear paw. There was bruising of the upper thigh and necrotic skin on the caudal right thigh and cranial aspect of the hock. Bloody discharge under the necrotic tissue revealed rod bacteria and toxic neutrophils. The dog was treated with intravenous fluids and antibiotics.

Systemic Mast Cell Degranulation and Death

Two dogs from two separate pilot studies died from a suspected mast cell degranulation reaction. Both dogs were treated with STELFONTA for a subcutaneous mast cell tumor located above the hock and did not receive the concomitant medications as prescribed.

In a pilot field study, one dog with a large (10 cm^3) subcutaneous mast cell tumor on the right hip was treated with STELFONTA. The dog had a partial Response Evaluation Criteria in Solid Tumors Guideline (RECIST)[2] response to the initial STELFONTA injection and was re-treated with STELFONTA, 30 days following the initial injection. The patient did not receive any of the recommended concomitant medications of prednisolone, chlorpheniramine and famotidine from 24 hours after the second STELFONTA injection. On Day 2 following the second STELFONTA injection, the dog became anorexic, painful, and lethargic and had marked swelling of the right hind limb extending to the chest with hemorrhagic, ruptured blisters near the hock joint. Blood work showed anemia, hypoproteinemia, liver enzyme elevations, and white blood cell changes (leukocytosis, neutrophilia, monocytosis, and thrombocytopenia). The dog was hospitalized, received a blood transfusion, and was administered intravenous fluids, prednisolone, chlorpheniramine and tramadol. Pitting edema progressed to the neck by four days following treatment. Despite supportive care, the dog died five days following treatment likely due to degranulation of the mast cell tumor and internal necrotic discharge of the tumor.

In a separate pilot field study, one dog with a moderate (2.53 cm^3) subcutaneous mast cell tumor on the left caudal hindlimb was treated with STELFONTA. The dog was treated with chlorpheniramine and meloxicam on treatment day (Day 0) and Day 1 only. The dog did not receive further concomitant medication. On Day 3 the dog was lethargic and there was significant edema at the injection site. While intravenous fluid and antibiotic therapy was initiated on Day 3, the dog rapidly deteriorated and died on the following day likely due to degranulation of the mast cell tumor. Pathology findings included widespread cellulitis, panniculitis (likely of bacterial origin), and septic peritonitis.

To report suspected adverse reactions, to obtain a Safety Data Sheet (SDS), or for technical assistance, call 800-338-3659. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

INFORMATION FOR DOG OWNERS

Owners should be given the Client Information Sheet to read before STELFONTA is administered and should be advised to observe their dog for potential side effects, including signs of degranulation and excessive wound formation, as described in the sheet. Advise dog owners about possible adverse reactions, when to contact a veterinarian, and how to care for the treated tumor site.

Some discharge from the site following treatment is expected. The site can be cleaned with warm water as necessary. Advise owners to wear disposable gloves when cleaning the area.

CLINICAL PHARMACOLOGY

Mechanism of Action

In non-clinical pharmacology studies, tigilanol tiglate has been shown to have three inter-related effects that are responsible for its anti-tumor effectiveness. The first effect is to cause oncolysis of tumor cells that are in direct contact with tigilanol tiglate. The oncolysis occurs within the first hours following treatment and results from the disruption of mitochondrial functioning. Secondly, at the same time, tigilanol tiglate activates a protein kinase C (PKC) signaling cascade which propagates throughout the tumor, resulting in an acute inflammatory response with swelling and erythema extending to the tumor margins and immediate surroundings. This inflammatory response is normal and necessarily contributes to the activity of tigilanol tiglate by (a) restricting blood and oxygen supply to the tumor (causing localized hypoxia) and (b) recruiting and activating innate immune cells (principally neutrophils and macrophages), which then target the tumor and release reactive oxygen species, proteases, and cytokines that function in an antimicrobial role. This acute inflammatory response generally resolves within 48 to 96 hours. The third component of the antitumor activity of tigilanol tiglate is associated with direct effects of the drug in increased permeability of the tumor vasculature (via activation of the Beta-II isoform of PKC) leading to tumor vascular destruction. The resulting outcome is tumor destruction with a deficit or wound remaining where the tumor was located. Complete healing of the resulting wound following tumor destruction by STELFONTA is typically within 6 weeks.

Pharmacokinetics

Pharmacokinetic properties of STELFONTA were evaluated in a pilot study monitoring systemic levels following intratumoral injection, with a dose delivered according to the size of the mast cell tumor. A dose of 0.5 mg/cm^3 (0.5 mL/cm^3) was used in dogs with tumor volumes ranging from 0.1 to 6.8 cm^3 resulting in doses ranging from 0.002 mg/kg to 0.145 mg/kg and total doses ranging from 0.05 mg to 3.4 mg per dog. A total of 6 cutaneous and 5 subcutaneous mast cell tumors were treated in 10 dogs (one dog had two tumors treated consecutively). The following range of pharmacokinetic parameters were determined for STELFONTA in plasma: 1) elimination half-life ($t_{½}$): 2.85 to 36.87 hours; 2) maximum plasma concentration (C_{max}): 0.356 ng/mL to 13.8 ng/mL; and 3) area under the plasma concentration time-curve to the last quantifiable plasma concentration (AUC_{last}): 2.25 h*ng/mL to 31.24 h*ng/mL. There was no relationship between drug exposure (C_{max} and AUC_{last}) with tumor location (cutaneous or subcutaneous) or with total dose. In an evaluation of the pharmacokinetic data from the 5 dogs with cutaneous tumors, dose levels ranged from 0.002 mg/kg to 0.145 mg/kg. The highest C_{max} was 11.1 ng/mL and the highest AUC_{last} was 31.24 h*ng/mL at a dose of 0.125 mg/kg. For the other 5 dogs with subcutaneous tumors, doses ranged from 0.049 mg/kg to 0.094 mg/kg. The highest Cmax was 13.8 ng/mL and the highest AUC_{last} was 30.81 h*ng/mL at a dose of 0.094 mg/kg.

EFFECTIVENESS

The effectiveness of STELFONTA was evaluated in a well-controlled, multi-center, randomized, double-masked, field study in client-owned dogs. Enrolled dogs had non-metastatic World Health Organization stages Ia (one tumor confined to the dermis, without regional lymph node involvement) and IIIa (multiple dermal tumors; large infiltrating tumors without regional lymph node involvement) mast cell tumors that were (i) cutaneous, or (ii) subcutaneous and located at or distal to the elbow or the hock). A total of 123 client-owned dogs with a mast cell tumor measuring less than or equal to 10 cm^3 were randomized to treatment with a single injection of STELFONTA (n=81) or untreated control (n=42). On the day of treatment, the average tumor volume was 1.7 cm^3 (range 0.1 to 9.8 cm^3).

A total of 118 dogs were included in the effectiveness analysis; 80 dogs were in the STELFONTA group and 38 dogs were in the untreated control group. Response to treatment was evaluated using the RECIST[2], where complete response (CR) is resolution of the target tumor, partial response (PR) is at least a 30% decrease in the longest diameter of target tumor, stable disease (SD) is a decrease of less than 30% or increase of less than 20% of the longest diameter of the target tumor, and progressive disease (PD) is greater than a 20% increase in the longest diameter of the target tumor.

The primary effectiveness variable compared CR rates of the target tumor between groups 28 days after treatment. At 28 days after treatment, a statistically significantly greater proportion of dogs in the STELFONTA treated group (60/80; 75%) achieved CR compared to dogs in the untreated control group (2/38; 5.3%) (p<0.0001). An objective tumor response (CR + PR) was observed in 64/80 (80%) of the STELFONTA treated dogs. Of the 60 dogs in the STELFONTA group that experienced CR at Day 28, response assessment was conducted for 59 dogs at Day 42 and for 57 dogs at Day 84. At Day 42, 59/59 (100%) were disease-free at the injection site, and at Day 84, 55/57 (96%) were disease-free at the injection site.

For all dogs, corticosteroids (prednisone or prednisolone) were initiated 2 days prior to treatment at a dose of 0.5 mg/kg orally twice daily and continued for 7 days total (2 days before, on the day of treatment and 4 days after treatment), then 0.5 mg/kg once daily for an additional 3 days. An H1 receptor blocking agent (diphenhydramine [2 mg/kg orally twice daily]) and H2 receptor blocking agent (famotidine [0.5 mg/kg orally twice daily]) were initiated on the day of treatment and continued for 7 days.

Other medications prescribed based on veterinary discretion included antibiotics, analgesics, and sedatives. The majority of antibiotics were used to treat injection site infections. The majority of analgesics were used to treat tumor pain and were mainly initiated on the day of or day after treatment. Sedatives were used for treatment administration, conducting diagnostics, anxiety, and temperament issues.

Quality of Life (QoL)[3] was assessed by owners throughout the study and the mean scores for the QoL assessment was similar between the STELFONTA and untreated control groups at all time points.

Eighteen of the 20 STELFONTA treated dogs without CR received a second treatment. Twenty-eight days following the second treatment, CR was observed in 8/18 (44.4%) of these dogs. Forty-two days following the second treatment, CR was observed in 7/18 (38.9%) of treated dogs.

TARGET ANIMAL SAFETY

The margin of safety and toxicity of STELFONTA was evaluated in one laboratory safety study and one laboratory cardiovascular study utilizing final market formulation, and one pilot field study that used non-commercial formulation.

Laboratory Safety Study

In a 4-week laboratory safety study, 48 healthy Beagle dogs 6 to 8 months old were administered STELFONTA intravenously over a 15-minute infusion once a week for four weeks on Days 1, 8, 15, and 22, at doses of 0, 0.025, 0.05, or 0.075 mg/kg body weight (ranges between 0.02-0.036, 0.039-0.056, and 0.06-0.08 mg/kg, respectively due to dosing variability). Control dogs (0 mg/kg) received a vehicle control at a volume equal to the 0.075 mg/kg dose. The intravenous route was chosen for this study because subcutaneous injection was too toxic and intratumoral administration was not possible.

There were twelve dogs per group (6 male, 6 female). Four dogs/sex/group were necropsied two days following the last dose and two dogs/sex/group were necropsied following a 2-week recovery period.

All dogs survived the study, and there were no STELFONTA-related effects on body weight, body temperature, ophthalmic exam, electrocardiographic parameters, and organ weights.

The following were observed only in dogs in the groups administered STELFONTA: decreased food consumption from Days 22-29, vomiting/retching during infusion or immediately post-infusion, wound formation at the infusion site after the second or third dose, decrease in activity sporadically throughout the study, and elevations in alanine aminotransferase on Day 23.

The following were observed in all groups, including vehicle control and increased in a dose dependent manner: limited use of the leg that received the infusion occurred soon after dosing, weakness after the first dose, salivation and infusion site edema and erythema increased in frequency and severity throughout the study, and tremors occurred immediately post-infusion and increased in severity with dose.

Vomiting, retching, or tremors were typically transient and resolved within 1 hour of dosing while salivation also typically resolved within 4 hours.

Loose feces were observed in all groups in a non-dose dependent manner. Polydipsia occurred in the control, 0.05 and 0.075 mg/kg groups. Trending towards decreasing hematocrit (but still within reference intervals) was observed in all groups. One dog in the 0.05 mg/kg group was mildly anemic during recovery. Monocytosis and elevated fibrinogen were seen on Days 2 and 23 in a dose-dependent manner.

Gross pathology findings at the infusion site included inflammation, redness, and thickening of the skin. Correlative histopathology findings of the infusion site included hemorrhage, edema, inflammation, mixed cell infiltration, fibrosis, and chronic organizing thrombosis. Only one of the recovery dogs had changes at the infusion site consisting of proliferation of the intima. One dog in the 0.075 mg/kg group had a severe wound, confirmed on histopathology as ulcerative inflammation and severe necrosis with bacteria present. Gross pathology findings also included red, mottled, firm, and enlarged lymph nodes in all dose groups, including recovery dogs, confirmed on histopathology as inflammation, lymphoid hypercellularity, hemorrhage, and sinus histiocytosis. Pituitary cysts were observed in 7 dogs in all STELFONTA treated groups. One dog each from the 0.075 mg/kg group was observed to have kidney tubular vacuolation, dilation of the ventricles of the brain, and chronic inflammation of both the left thigh skeletal muscle and left sciatic nerve.

Laboratory Cardiovascular Study

In a 12-day laboratory cardiovascular study, 4 healthy male conscious telemeterized Beagle dogs approximately 2-4 years old were administered STELFONTA as a single intravenous infusion. Treatment consisted of four groups: vehicle control and STELFONTA at doses of 0.01, 0.025 and 0.075 mg/kg body weight. All four dogs received all treatments with at least a 3-day wash-out period.

All dogs survived the study and there were no STELFONTA-related effects on body temperatures, blood pressure, or electrocardiograms. The following were observed only after administration of STELFONTA in all dose groups: salivation, vocalization, incoordination, tremors, red feces, and decreased feces output. Retching, vomiting, incoordination, and changes in activity levels (increased and decreased) occurred in the 0.075 mg/kg group only. Tachycardia was seen for the first 2.5 hours after the 0.075 mg/kg dose only. The following were observed after administration of control or STELFONTA: excessive panting, decreased appetite, and limited usage/swelling of leg or paw. All dogs lost weight during the study. Clinical signs resolved around 4 hours post dosing.

Pilot Field Study

In a 28-day unmasked field study, 10 client-owned dogs, 6-14 years old were administered tigilanol tiglate (non-commercial formulation) once as an intratumoral injection at a dose of 0.5 mg tigilanol tiglate per cubic centimeter (cm^3) of tumor volume, not exceeding 0.25 mg/kg body weight (maximum dose of 5 mg). One dog was enrolled a second time to treat a second mast cell tumor after successful treatment of the first tumor. See pharmacokinetic results from this study under **Clinical Pharmacology**.

The most common observations after tigilanol tiglate administration were injection site reactions including necrosis, swelling (localized edema and edema extending well beyond the tumor injection site), pain, restlessness, inflammation, erythema, bleeding ulcerations, bruising/discoloration, sloughing of tissue, open wound, mild drainage, malodor, and presence of granulation tissue. Three dogs experienced dermatitis with or without skin necrosis in a region nearby but distinct from the tumor injection site. One dog experienced non-weight bearing lameness, muscle atrophy and enlarged popliteal lymph node. One dog vomited after administration. Three dogs required longer healing times beyond 28 days, with the longest requiring 5 months. Hypoalbuminemia was observed in 5 dogs with hypoproteinemia observed in 1 of these 5 dogs on Day 7 and was resolved by Day 28.

STORAGE INFORMATION

Store STELFONTA vials refrigerated at 2°C to 8°C (35°F to 46°F).

Do not freeze.

Keep the vial in the carton at all times to protect the vial from light.

For single use only.

Dispose of any unused product in accordance with disposal for routine medical waste.

HOW SUPPLIED

STELFONTA is supplied as a sterile, colorless liquid in a 5 mL clear, single-use glass vial containing 2 mL of STELFONTA at a concentration of 1 mg/mL tigilanol tiglate in sterile water for injection.

REFERENCES

1. Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.1. *Vet Compar Oncol.* 20 Jul 2011.
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3. Lynch S, Savary-Bataille K, Leeuw B, Argyle DJ. Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer. *Vet Compar Oncol.* 2011; 9 (3):172-82.

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