Practical aspects of STELFONTA® (tigilanol tiglate injection)

GUIDE FOR VETERINARIANS ADMINISTERING STELFONTA

STELFONTA
(tigilanol tiglate injection)

Virbac

STELFONTA® (tigilanol tiglate injection) PRACTICAL ASPECTS OF ADMINISTRATION

Geography: USA

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STELFONTA (tigilanol tiglate injection)

Virbac

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OVERVIEW

Considerations for case selection: Tumor location, volume and ulceration along with patient stage of disease; patient concurrent medications, concurrent disease and temperament; owner ability to administer concomitant medications and comfort with wound management. See pages 10-16.

Pet Owner Education

Ensure pet owners are prepared for the stages of STELFONTA® (tigilanol tiglate injection) treatment including anticipating the wound, potential reactions and that they know when, with whom and how to communicate any concerns. A helpful resource specifically for pet owners is www.stelfonta.com.

STELFONTA is often administered earlier in the week, so the pet owner has access to the primary treating clinician during regular working hours, to address any concerns post treatment.

Treatment protocol consists of 4 stages:

1 Concomitant medications

- Essential medications to reduce the risk of mast cell degranulation (including death):
  - Corticosteroids (oral prednisone or prednisolone at anti-inflammatory doses), commencing 2 days prior to injection day for a total of 10 days (2 days prior, treatment day and 7 days after treatment).
  - H1 (oral diphenhydramine) and H2 (oral famotidine) blocking agents, commencing on injection day, continuing for 8 days.

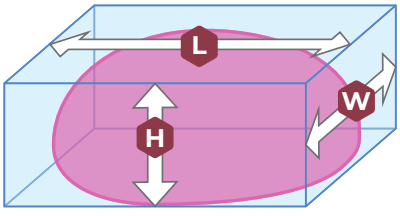
Pre-emptive analgesia to minimize discomfort is recommended prior to, during and after treatment with STELFONTA.

Drug	Day -2		Day -1		Treatment Day 0		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
Corticosteroid (prednisone/prednisolone 0.5 mg/kg PO)	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔		✔	
H1 blocker (diphenhydramine 2 mg/kg PO q12hr)					✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
H2 blocker (famotidine 0.5 mg/kg PO q12hr)					✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Pre-emptive pain relief					Recommended: pre-emptive pain management															

2 STELFONTA injection

- Sedation of patient may be required to ensure accurate and safe injection of tumor site while minimizing risk of self-injection.
- Shaving the hair surrounding the tumor will help visualize the tumor and aid accurate calculation of the tumor volume.

Modified ellipsoid calculation



L x W x H x ½

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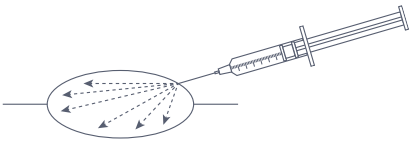
- Tumor surface should be intact; the drug can leak from ulcerated surfaces or biopsy sites.
- **Tumor volume:** Re-measure the tumor on treatment day (LxWxHx**½**) and confirm the volume does not exceed 10cm^3.
- **Dose:** Tumor volume x **0.5** = mL of STELFONTA® (tigilanol tiglate injection) to be injected. Use the Dose calculator.

Dose Calculator

- Ensure the total dose does not exceed 5 mL or 0.25 mL/kg and is not less than 0.1 mL. If the calculated dose is <0.1 mL, administer 0.1 mL. DO NOT treat if the required dose exceeds 5 mL or 0.25 mL/kg.
- Administer STELFONTA in a fanning motion through a single injection point with a Luer-Lock syringe and 23 gauge needle.

Cross section view

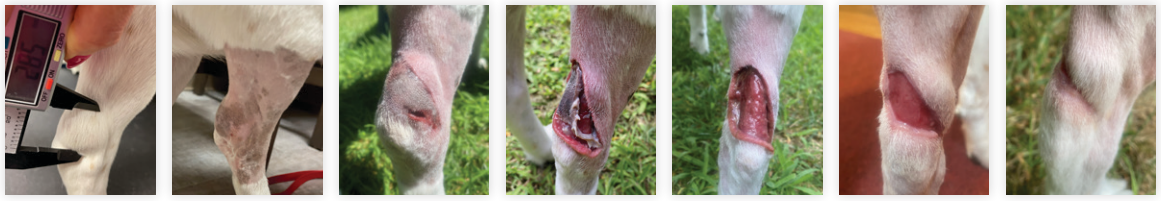


- The treated tumor site is usually left uncovered unless there's a risk of self-trauma, in which case an Elizabethan collar or a loose, dry gauze bandage may be used.
- Pre-emptive, proactive analgesia is recommended. Monitor and adjust pain management plan as needed.
- If degranulation occurs, signs are typically seen in the first 5-7 days of treatment. Early detection and treatment is critical to reduce the serious effects of degranulation.

3 Tumor destruction

- Within minutes STELFONTA starts to work; within hours acute inflammatory response is evident.
- 4 to 7 days: tumor destruction, via hemorrhagic necrosis and oncolysis, is typically seen.
- Discuss with owners that they should not allow the dog to lick the site for the first few days after treatment and they should discourage excessive licking for the remainder of the healing period. Tongue lesions have been reported.
- Necrotic tumor mass will slough away leaving a 'pocket' or wound which may be extensive.

Tumor destruction and healing typically occurs between 4-6 weeks*.



Pre STELFONTA | 2 hours after STELFONTA | Day 4 | Day 6 | Day 11 | Day 15 | Day 24

**Some cases have more extensive wounds and take longer to heal*

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4 **Tumor site healing**, via second intention

- Most wounds fully heal within 4-6 weeks. However, some wounds may be extensive, requiring additional management and time to heal.
- Tumor size determines the size of the wound, which influences the healing time, along with tumor location; typically, tumors on limbs take longer to heal. While a wound forms at the majority of tumor sites, complete responses have been achieved without the formation of a wound.

- **Non-responsive tumors may be retreated after day 28.** 75% of MCTs achieve a complete response after one treatment, 87% after one or two treatments. If a second treatment with STELFONTA® (tigilanol tiglate injection) is necessary, concomitant medications should be started with the same mandatory dosing schedule. The protocol for a second treatment is identical to the initial treatment protocol.
- **STELFONTA's Mechanism of Action:** three inter-related effects, specifically, oncolysis, stimulation of acute inflammatory response and increased permeability of tumor vasculature.

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1. SAFETY AND WARNINGS

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® (tigilanol tiglate injection) 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.

For case consultations, to obtain a product insert or to report adverse events, contact our Virbac Product Safety and Consulting team at 1-800-338-3659.

Visit https://vet-us.virbac.com/stelfonta for full prescribing information and additional case reviews.

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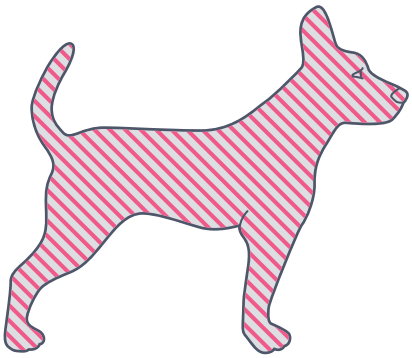
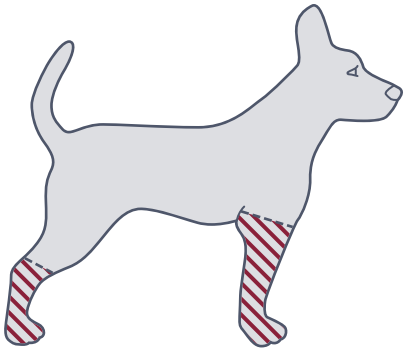
2. INDICATION

STELFONTA® (tigilanol tiglate injection) treatment achieves a complete response (CR) in 75% of mast cell tumors after a single injection; 87% CR after one or two treatments.

STELFONTA is a novel epoxytigilane that has been approved by the US Food and Drug Administration (FDA) for the intratumoral treatment of all grades of non-metastatic mast cell tumors, specifically:



Cutaneous MCTs located anywhere on the body



Subcutaneous MCTs located at or below the elbow and hock

Maximum treatable tumor volume	**= 10 cm^3**
Maximum total dose of STELFONTA per dog	**= either 0.25 mL/kg of body weight or 5 mL, whichever is lower. DO NOT treat if the required dose exceeds 5 mL or 0.25 mL/kg.**

STELFONTA should not be injected into *subcutaneous* mast cell tumors located above the elbow or hock (e.g., on the body, head, or neck) as necrotic debris from the injected tumor may accumulate in the subcutaneous space, increasing the risk of systemic adverse reactions, including death, from mast cell degranulation.

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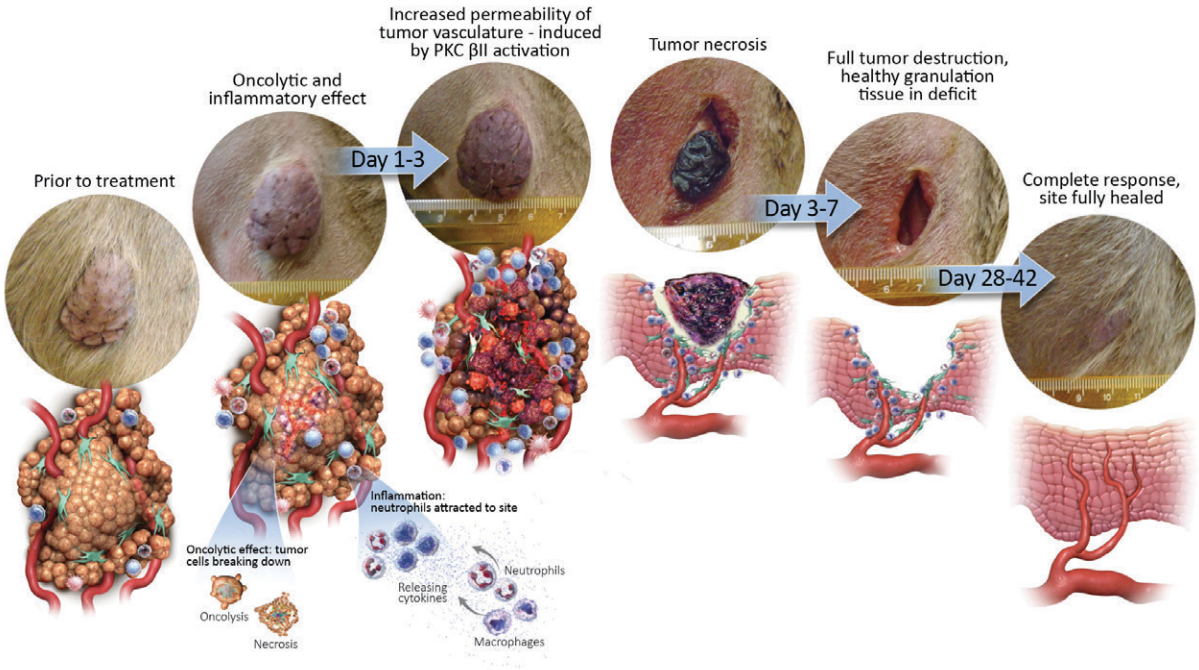
3. MECHANISM OF ACTION

STELFONTA® (tigilanol tiglate injection) destroys tumors via three inter-related effects:[1]

1. **Oncolysis of tumor cells** that are in direct contact with STELFONTA. This occurs within the first hours following treatment and results from disruption of mitochondrial functioning and tumor cell membranes.
2. **Stimulation of an acute inflammatory response** with swelling and erythema extending to the tumor margins and immediate surroundings:
    - » Restricting blood and oxygen supply to the tumor (causing localized hypoxia).
    - » Recruiting and activating innate immune cells (principally neutrophils and macrophages), which then target the tumor mass 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.
3. **Increased permeability of tumor vasculature** leading to tumor vascular destruction due to activation of the protein kinase C β-II isoform.

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 4-6 weeks, via second intention.[1,3]

Cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds requiring additional treatment and prolonged recovery times is possible.



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This targeted mode of action is clinically displayed in the following case. An 11-year-old Jack Russell Terrier was treated for a 0.5 cm^3 subcutaneous MCT located on the medial aspect of the elbow. Within the first 24 hours there was early signs of bruising, swelling, and heat. Tumor necrosis was evident by Day 7, with a healthy granulation tissue bed. A complete tumor response and wound healing by Day 28 following treatment.

Case ID: Paupette
11 years, 8 months
Jack Russell Terrier

Case Summary: Spayed female Jack Russell Terrier. Previously had a MCT from a different location removed surgically.

Treatment:

Weight	6.4kg
Tumor vol.	0.5cm^3
Location	Elbow
Doses received	1

Complete response achieved

Day 0

- Subcutaneous MCT on medial left elbow

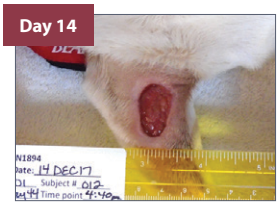
Day 1

- Bruising, swelling, pain and heat

Day 7

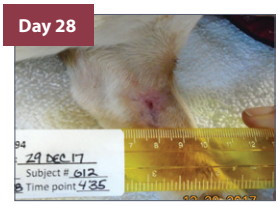
- Starting to granulate
- Necrotic tissue present
- Serous discharge

Day 14



- Wound granulation tissue and wound contracture

Day 28



- Small scab at the treatment site

Day 42

- Scar at treated site

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4. CASE SELECTION CONSIDERATIONS

STELFONTA® (tigilanol tiglate injection) may not be suitable for every patient or every mast cell tumor. When determining whether STELFONTA is a suitable treatment option, the following factors should be considered relating to the tumor, patient and pet owner.

Tumor considerations for case selection

- **Location:**
  - **Functional structures and mucocutaneous junctions:** destruction of a tumor located in or near, functional structures (e.g., eyelid, muzzle or vulva) may lead to compromise of these structures, potentially leading to functional or cosmetic changes. Consider the level of gross and microscopic extensions of the tumor, particularly for subcutaneous tumors.
  - **Distal location:** tumors located on extremities e.g., lower limb or tail can have increased edema due to gravity, reduced circulation, and lymphatic drainage.
  - **Limited subcutaneous tissue:** exposure of bones and tendons may occur where subcutaneous tissue is limited, such as the head and distal limbs.
  - **Sensitivity:** highly sensitive locations such as phalanges, face, and vulva/prepuce may require sedation to ensure safe administration, and ensure the full dose is administered.
  - **Subcutaneous depth:** as the tumor requires an exit point close to the skin's surface to allow the expulsion of necrotic matter, subcutaneous tumors above the hock or elbow are not suitable for treatment.[1]
- **Ulceration:** leakage of the drug from the surface could occur, decreasing the dose retained within the tumor and potentially reducing efficacy and increasing the risk of drug exposure to skin.
- **Tumor volume:** the treated tumor needs to be within approved guidelines for both safety and efficacy; the maximum treatable tumor volume is =10 cm^3. Ensure the dose does not exceed 5 mL or 0.25 mL/kg and is not less than 0.1 mL.
- **Stage:** STELFONTA is an intratumoral injection and is not indicated for patients with metastatic disease.

Note: As STELFONTA treatment leads to hemorrhagic necrosis of the tumor, grading the tumor *after* treatment is not possible. Cytological grading, using samples from a fine needle aspirate (FNA), is recommended prior to treatment to assist with staging decisions and treatment expectations.[4]

The surface of the tumor must be intact to reduce the risk of drug leakage; consider delaying treatment to allow for any puncture wounds to heal as in the case of a biopsy.

Patient considerations for case selection

- **Concurrent medications:** potential interactions with mandatory concomitant medications, or interference with immune function (e.g., immunosuppressants).
- **Concurrent disease:** potential contraindications with required concomitant medications (e.g. corticosteroid use may be contraindicated in patients with diabetes or pancreatitis).

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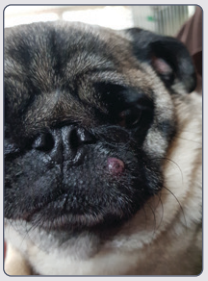
- **Patient temperament:** aggressive or highly anxious or active dogs may require sedation to administer safely.

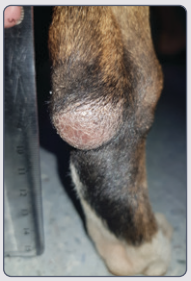
The safe use of STELFONTA® (tigilanol tiglate injection) has not been evaluated in dogs with concurrent diseases, or those that are pregnant, lactating, or intended for breeding.

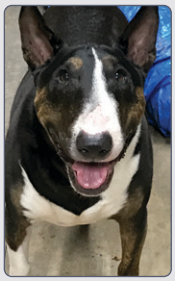
Owner considerations for case selection

- **Ability to administer** the full course of concomitant medications that are essential to reducing the risk of potentially severe adverse events, including death, from mast cell degranulation (see section 7).
- **Comfort with the process:** Explaining the potential responses to the pet owners can help prepare them for tumor necrosis and healing of the tissue deficit.



This **8-year-old Pug** was diagnosed with a 0.1 cm^3 cutaneous mast cell tumor on his muzzle. Due to the inherent risk anesthesia poses for brachycephalic breeds, and his concurrent severe upper airway disease, his owner wanted to avoid anesthesia. Additionally, they expressed concern about the cosmetic impact from surgery. The treating clinician administered STELFONTA and the tumor achieved complete response by Day 28.





This **6-year-old Bull Terrier** was diagnosed with a 3.6 cm^3 cutaneous MCT on the hock. He had a history of seizures and the owners were very concerned about him undergoing general anesthesia. Additionally, surgical removal of the tumor with adequate margins would have been challenging. The treating veterinarian administered STELFONTA and the tumor achieved a complete response at Day 28.

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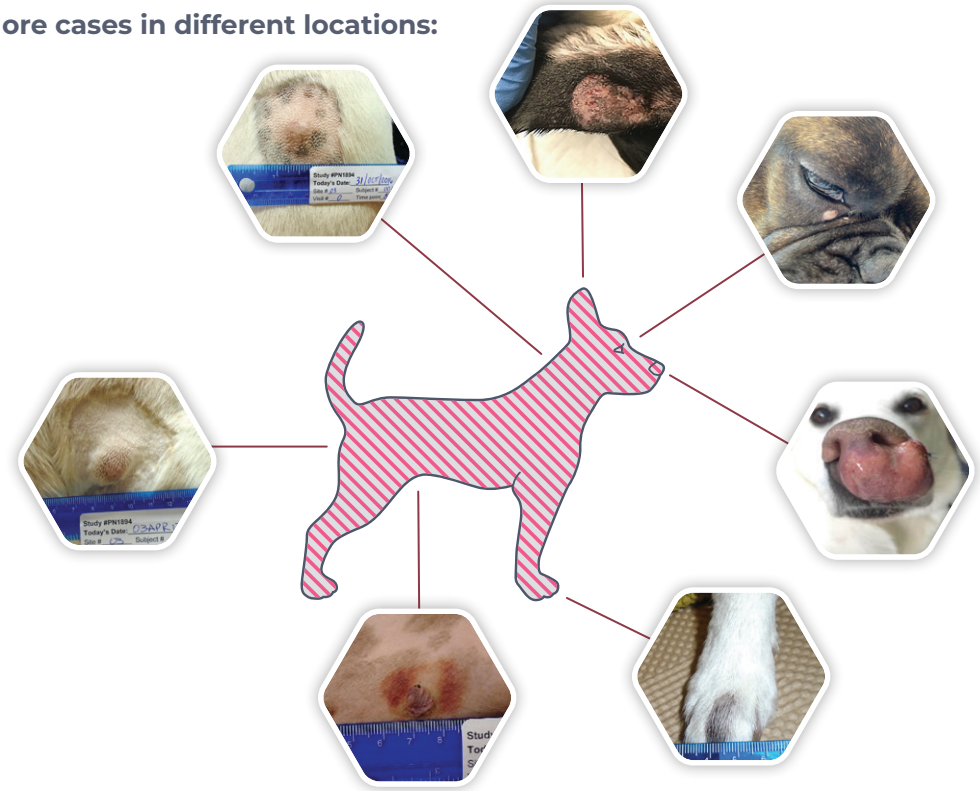
5. CASE EXAMPLES

Explore cases in different locations:



Case ID: Biggie
6 years
French Bulldog

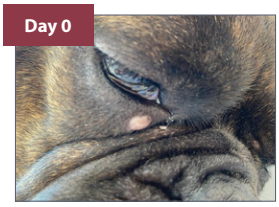
Case Summary: Dog with small, low grade MCT under lower eyelid; previous veterinarian treated with corticosteroids but no response, increased in size.

Treatment:

Weight	8.6kg
Tumor vol.	1cm³
Location	Face
Doses received	1

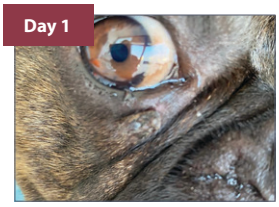
Complete response achieved

Day 0



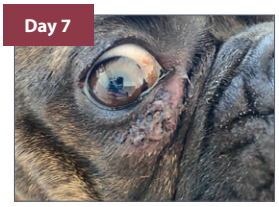
- Cutaneous MCT near medial canthus of the right eye

Day 1



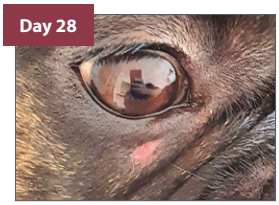
- Swelling at site

Day 7



- Necrotic material present

Day 28



- Complete wound healing
- Complete tumor response

Day 42

- No tumor recurrence
- Minimal scarring present at site

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Case ID: Ava
11 years, 8 months
Parson Russell Terrier

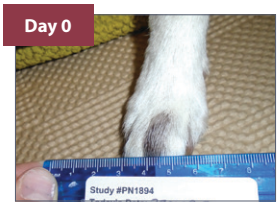
Case Summary: Senior female dog with a moderate sized initial wound (2.2 x 1.7cm) on Day 7.

Treatment:

Weight	10.7kg
Tumor vol.	1.1cm³
Location	Metacarpus
Doses received	1

Complete response achieved

Day 0

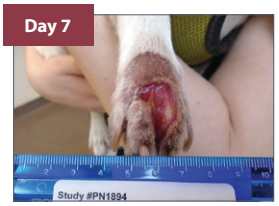


- Round cutaneous mass on right front foot between toes

Day 1

- Marked swelling on right front foot

Day 7



- Granulating wound present
- Maximum wound size 3.1cm²

Day 14

- Wound present (2.9 X 1.5cm) contracture

Day 28

- Small, nearly healed wound (0.7 X 0.1cm)
- Complete tumor response

Day 42

- Wound resolution
- Complete tumor response

Case ID: Puddles
10 years
Small mixed breed

Case Summary: High grade MCT with enlarged lymph node and hypothyroidism diagnosed at screening.

Treatment:

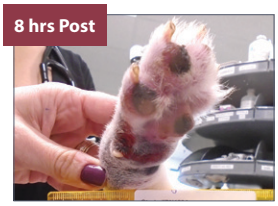
Weight	9.8kg
Tumor vol.	3.1cm³
Location	Metacarpus
Doses received (initially control group)	1

Complete response achieved

Day 0

- Cutaneous MCT on left metacarpus

8 hrs Post



- Forelimb is swollen and painful

Day 7

- Wound size is 186.4cm²

Day 14

- Wound size 122.6cm²

Day 28

- Wound size is 10.9cm²

Day 84

- Wound size 3.7cm²

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Case ID: Zuma
7 years
Labrador

Case Summary: Adult female dog with cutaneous MCT on nasal planum.

Treatment:

Weight	28.7kg
Tumor vol.	3.5cm³
Location	Nasal planum
Doses received	1

Complete response achieved

Day 0

- Cutaneous MCT on nasal planum

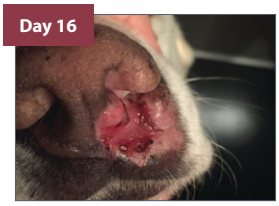
Day 5

- Necrotic material present

Day 9

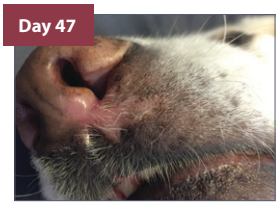
- Healthy granulation tissue

Day 16



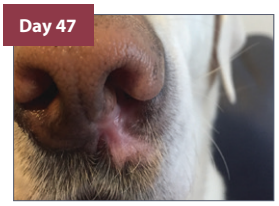
- Wound contraction

Day 47



- Full wound healing

Day 47



- Full wound healing

Case ID: Bart
8 years, 3 months
Beagle

Case Summary: Senior male dog with hypertriglyceridemia and a large initial wound (4.1 x 3.2 cm) on Day 7.

Treatment:

Weight	17.2kg
Tumor vol.	3.8cm³
Location	Hip
Doses received	1

Complete response achieved

Day 0

- Cutaneous MCT on the right caudal high, thigh region

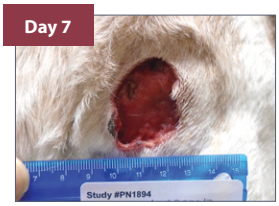
Day 1

- Bruising, swelling, pain and heat

Day 4

- Bruising, swelling, pain and heat
- Necrotic material present
- Serous discharge

Day 7



- Granulating wound
- Maximum wound size 10.3cm²
- Serous exudate

Day 28

- Complete tumor response
- Complete wound healing

Day 42

- No tumor recurrence minimum 24 months post treatment

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Case ID: Benji
12 years, 5 months
Boxer

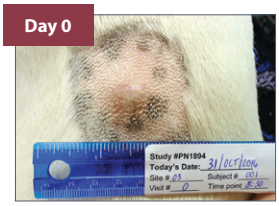
Case Summary: Senior female dog, overweight, fleas, gingival hyperplasia, dental disease.

Treatment:

Weight	27.5kg
Tumor vol.	5.3cm³
Location	Cranial Dorsum
Doses received	1

Complete response achieved

Day 0



- Cutaneous MCT in the dorsal intrascapular space

Day 1

- tumor site has a bruised surface

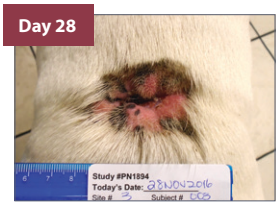
Day 7

- Non-pitting edema
- Hemoserous exudate

Day 14

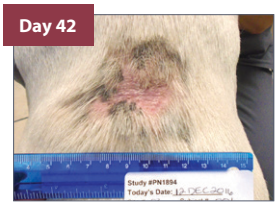
- Wound present
- Seropurulent discharge

Day 28



- Complete tumor response
- Scab with thickened skin surrounding area
- FNA negative

Day 42



- Flat, smooth scar tissue remains
- No tumor recurrence minimum 24 months

Case ID: Babou
13 years
French Bulldog

Case Summary: Senior dog with a large cutaneous MCT at the base of the ear.

Treatment:

Weight	10.8kg
Tumor vol.	3.12cm³
Location	Ear
Doses received	1

Complete response achieved

Day 0

- Cutaneous MCT at the base of the ear

Day 1

- Bruising and swelling present at the site

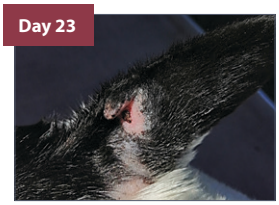
Day 4

- tumor necrosis

Day 7

- Granulating wound

Day 23



- Complete tumor response

Day 30

- Complete wound healing

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Case ID: Pattie
7 years, 9 months
Basset Hound

Case Summary: Senior dog with cutaneous MCT on ventral abdomen.

Treatment:

Weight 28.8kg
Tumor vol. 0.3cm³
Location Abdomen
Doses received 1
(initially Control Group)

Complete response achieved

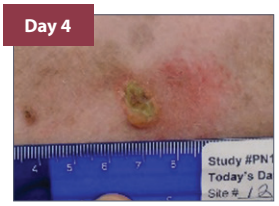
Day 0

- Bruising around the MCT before treatment

Day 1

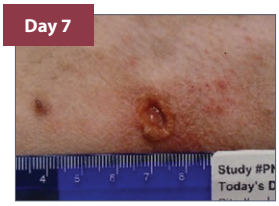
- Bruising and swelling.
- Enlargement of left inguinal lymph node

Day 4



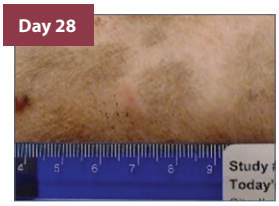
- Necrosis of tumor.
- Erythema in surrounding skin

Day 7



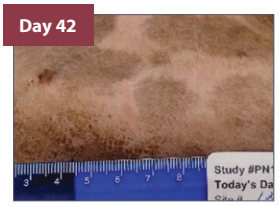
- Wound formed (1.5 X 1.0cm)

Day 28



- Complete wound resolution
- Complete tumor response

Day 42



- Tumor free at site minimum 12 months post-treatment

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6. TREATMENT PROTOCOL – OVERVIEW

	Key points	Warnings & safety considerations
1 CONCOMITANT MEDICATIONS	▪ Reduction of risk & severity of possible degranulation reactions. ▪ Pre-emptive management of localized inflammation and pain. ▪ Provide the Medication Tracker	▪ Concomitant medications (corticosteroid, H1 and H2 blockers) are essential to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation. ▪ Pre-emptive pain management.
2 STELFONTA INJECTION	**Calculating the dose** ▪ Dosing is based on tumor volume. ▪ **Volume** is calculated by multiplying tumor length, width and height (in cms), **X 1/2** (modified ellipsoid). ▪ **Dose** (mL) = Tumor volume **X 0.5**. **Treatment administration** ▪ Enter via single injection point. ▪ Deliver as evenly as possible throughout the tumor using a fanning technique.	▪ Maximum treatable tumor volume = 10 cm^3. ▪ Maximum total dose/dog = 5 mL or 0.25 mL/kg, whichever is lower. ▪ If the calculated dose is <0.1 mL, administer 0.1 mL. ▪ Wear gloves, eye protection and lab coat/gown. ▪ Take care to avoid accidental self-injection.
3 TUMOR DESTRUCTION	**Inflammatory response** ▪ Within 2 hours post-treatment, acute inflammation with swelling and redness appears around the tumor and nearby tissues.[1-3] **Tumor necrosis** ▪ Tumor necrosis begins within 4 hours of treatment and complete necrosis is typically evident within 4-7 days. ▪ A wound is created where the tumor once was.	▪ The most common adverse reactions from STELFONTA® (tigilanol tiglate injection) treatment (reported in the field effectiveness study) included wound formation, injection site pain and lameness in the treated limb. See product insert on page 30 for further information on adverse events and frequency.

4 TUMOR SITE HEALING	▪ Most wounds are left unbandaged, to heal via second intention. ▪ Tumor sites heal with minimal intervention, typically within 4-6 weeks of tumor destruction.	▪ Treatment with STELFONTA® (tigilanol tiglate injection) has been associated with cellulitis and severe tissue sloughing, resulting in extensive wounds and prolonged recovery time.
OUTCOME ASSESSMENT	**Post treatment care** ▪ Consider availability of treating clinician for rechecks when selecting treatment day. ▪ Days 1-7, owner to monitor for signs of degranulation and ensure concomitant medications and analgesics are administered. ▪ Day 7, assess wound: minimal intervention where possible. ▪ At Days 28-42, assess tumor response and determine if further treatment is necessary. **Non-responsive tumors** ▪ STELFONTA treatment achieves complete response in 75% of MCTs after a single injection. ▪ 87% of dogs achieved complete response after one or two treatments.[1,3] ▪ Wait until at least 28 days after treatment to assess response as residual mast cells may be present at the site for up to 4-6 weeks.	

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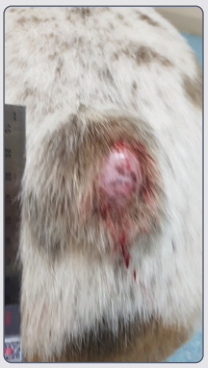
7. TREATMENT PROTOCOL – DETAIL

There are four stages to treating MCTs with STELFONTA® (tigilanol tiglate injection). STELFONTA's mechanism of action initiates healing via second intention requiring little, if any, intervention in most cases. Some wounds, however, may be more extensive requiring additional management and healing time.

STAGE 1: Concomitant medications

Essential medications are a critical aspect of the protocol to reduce the potential for severe systemic adverse reactions, including death, from mast cell degranulation. Always administer the following mandatory medications[1]:

- **Corticosteroids** (oral prednisone or prednisolone) starting 2 days prior to STELFONTA treatment at 0.5 mg/kg every 12 hours for 7 days, then 0.5 mg/kg every 24 hours for 3 days (10 days total).
- **H1 receptor blocking agent** (oral diphenhydramine) starting on STELFONTA treatment day at 2 mg/kg every 12 hours for at total of 8 days.
- **H2 receptor blocking agent** (oral famotidine) starting on STELFONTA treatment day at 0.5 mg/kg every 12 hours for a total of 8 days.



This 12-year-old mixed-breed had a cutaneous mast cell tumor on the lumbar spine. He received the pre-treatment concomitant medications as instructed. After receiving his injection, upon returning home, he wasn't interested in his food and the owner was unable to administer his medication. The following day, the dog was very lethargic and inappetent, and was subsequently hospitalized and provided with supportive care to treat a degranulation reaction. This patient had a successful outcome due to the vigilance of the owner. Failure to recognize clinical signs consistent with degranulation and provide appropriate treatment can lead to serious sequelae including death.

Minimizing Discomfort Associated with STELFONTA® Injection

To reduce patient discomfort during and after STELFONTA administration, clinicians should consider both pre-emptive and post-injection strategies.

Pre-emptive Measures:

Administer pain relief and, if appropriate, sedation for injection.

Factors influencing injection-site discomfort include:

- Injection site sensitivity (e.g., head, vulva, distal limb and phalanges).
- STELFONTA temperature – ambient temperature may reduce discomfort. Consider letting the vial reach room temperature just prior to injection.
- Patient-specific factors such as pain sensitivity and temperament.

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- Tumor size relative to patient size.
- Increased intratumoral pressure and skin tension from 50% vol/volume dosing.

Post-Injection Pain Management:

STELFONTA induces an acute local inflammatory response (swelling, bruising, erythema), followed by tumor necrosis. Discomfort typically peaks within the first few days and subsides as inflammation resolves. Discomfort typically diminishes as the inflammatory reaction subsides and the tumor separates from the surrounding tissue.

- Consider multimodal analgesia. During pivotal studies:
- 69% of patients received pain medication within 7 days post-treatment.
- Median duration was 6 days, with an average of 9 days.
- Common analgesics included tramadol, gabapentin, and buprenorphine.
- Concomitant use of prednisolone/prednisone and H1/H2 antagonists may reduce degranulation-related swelling and pain.
- Encourage gentle movement to reduce swelling and discomfort.

STAGE 2: STELFONTA injection

Checklist for treatment day

- ☐ Confirm with pet owner the patient has received the pre-treatment concomitant medications, commencing with corticosteroids at least 2 days before STELFONTA injection, and H1 and H2 blocking agents?
- ☐ Is the tumor surface intact and any previous biopsy site has healed (minimum 14 days)?
- ☐ Does the pet owner understand what to expect, how to administer the concomitant medications and how/when to follow up?
- ☐ Clip hair from around the tumor particularly in thick haired locations to enable accurate tumor measurement. This will also minimize the accumulation of necrotic material that can lead to persistence of odor. Take care to avoid excessive manipulation of the tumor.
- ☐ Wear personal protective equipment.
- ☐ Consider whether sedation of the dog may be necessary to ease administration as well as avoid accidental self-injection of STELFONTA that may cause severe wound formation.

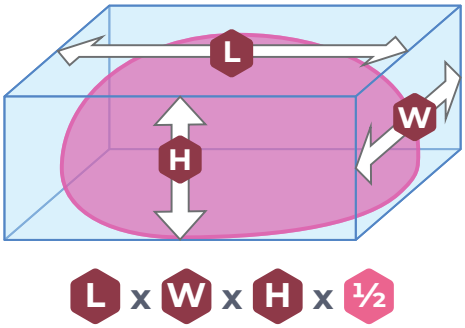
Many veterinarians chose to administer STELFONTA earlier in the week, allowing the pet owner to more easily contact them to address any concerns post treatment during regular working hours.

Calculate the dose – on treatment day

STELFONTA® (tigilanol tiglate injection) is administered as an intratumoral injection at a dose of 0.5 mL per cm^3 of tumor volume.

1. **Calculate tumor volume using modified ellipsoid formula:** Use calipers to measure the length, width, and height of the tumor to determine the tumor volume in cm^3:
   - [length (cm) x width (cm) x height (cm)] **x 1/2**
   - Confirm the tumor volume does not exceed 10 cm^3
2. **Weigh dog** to confirm body weight in kilograms.
3. **Calculate the dose** (mL) of STELFONTA to inject: Tumor volume x **0.5 mL**
   - Ensure the maximum total dose is not more than 5 mL.
   - Ensure the required dose is within the mL/kg guidelines of 0.25 mL/kg. Do not underdose the tumor (caution treating big tumors in small dogs).

Modified ellipsoid calculation



L x W x H x ½

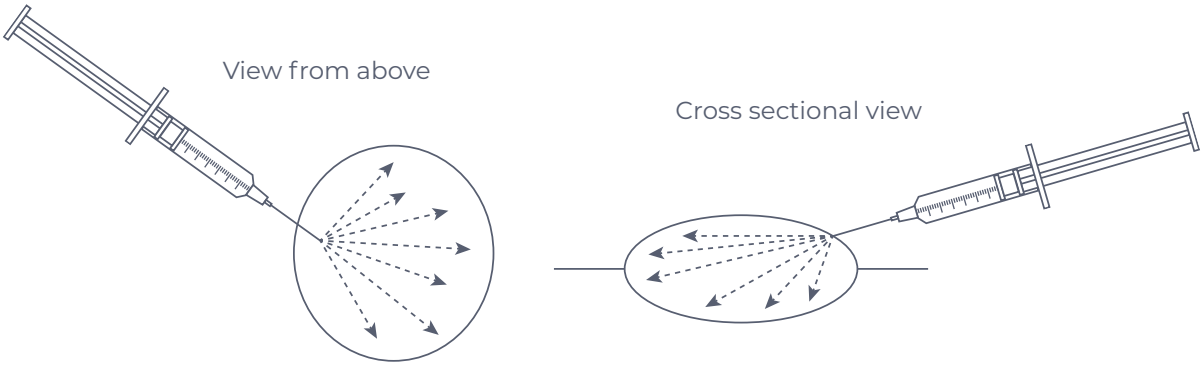
Note the following restrictions:

- Maximum treatable tumor volume is 10cm^3;
- Maximum total dose per dog is 5 mls or 0.25 mL/kg bodyweight of Stelfonta, whichever is lower;
- DO NOT TREAT if the required dose exceeds 5 mL or 0.25 mL/kg;
- Minimum tumor dose is 0.1 mL. If the dose is <0.1 mL, administer 0.1 mL.

Access the dose calculator: How to calculate STELFONTA dose (tigilanol tiglate)

Injecting STELFONTA

1. **Draw the required dose** into a Luer-lock syringe with a 23-gauge needle.
2. **Entering the tumor from a single injection point,** draw the syringe plunger back slightly to ensure STELFONTA is not injected into a blood vessel. Use a fanning motion to disperse STELFONTA evenly throughout the tumor. If the tumor protrudes above the surface of the skin, insert the needle at approximately 45°. Avoid injecting into the margins, beyond the periphery, or deep to the tumor.



3. **Remove the needle** after pausing to allow tissue dispersion once the total dose of STELFONTA® (tigilanol tiglate injection) has been administered. **Apply light pressure** for 30 seconds over the needle exit hole using a gloved finger. If leakage occurs, **rinse the injection site** with saline to wash STELFONTA from the skin surface. Do not re-administer if leakage occurs. To minimize the risk of accidental self-injection, **dispose of the uncapped needle and syringe** as appropriate for routine medical waste.
4. **Reiterate expectations to the pet owner** regarding the wound, signs of degranulation and importance of compliance for essential concomitant medications.

STAGE 3: Tumor destruction

- **Minutes:** STELFONTA starts to work within minutes following the injection, evidenced by early signs of erythema, blanching, and swelling.
- **Hours:** Acute inflammatory response, and associated bruising, swelling, heat, and pain is typically observed. While localized bruising and swelling is an expected response, extensive wounds or severe systemic reactions should receive immediate veterinary attention. Remind pet owners when and how to contact their veterinarian with concerns.
- **Days:** Necrotic destruction of the tumor is typically seen within 4-7 days, but may take longer and is characterized by blackening, shrinkage and softening of the tumor. Serosanguinous discharge may be observed, normally in small amounts from the wound.
- **Site care:** The treated tumor site is typically left uncovered. If there is concern that there is excessive licking or rubbing of the site causing trauma, an Elizabethan collar or dry loose gauze bandage may be necessary. In the pivotal trial, two (2%) patients wore an Elizabethan collar, and one (1%) patient was bandaged following treatment.

  Do not allow the dog to lick the tumor for the first few days after treatment and discourage excessive licking for the remainder of the healing period.

  Where possible leave the site unbandaged to allow:

  - Drainage and resolution of edema from the treatment site;
  - Ambient oxygen to aid site healing;
  - Wound exudate and necrotic debris to slough away;

  Bandaging is seldom required, but if bandaging is deemed necessary, the bandage should be kept light and non-restrictive to allow for the expected local edema to occur.
- **Sloughing:** The necrotic tumor mass will fall away forming a wound with a pocket or crater-like defect. Surgical debridement is not usually necessary; it was not required in the clinical trials and may interfere with the wound healing benefits of STELFONTA. Only remove necrotic tissue that is loosely attached and can be easily removed without resistance.[5]

Reassure pet owners the wound is part of the treatment process and reiterate that while not necessary, the wound can be gently flushed with water when there is excessive discharge, or it is malodorous.

Occasionally, due to tumor location, the underlying tissues including bones and tendons may be exposed but in most cases granulation tissue covers these tissues quickly without deleterious effect of these structures. It is suggested the owner review photos of what to expect at https://stelfonta.com/mast-cell-tumor-pictures.

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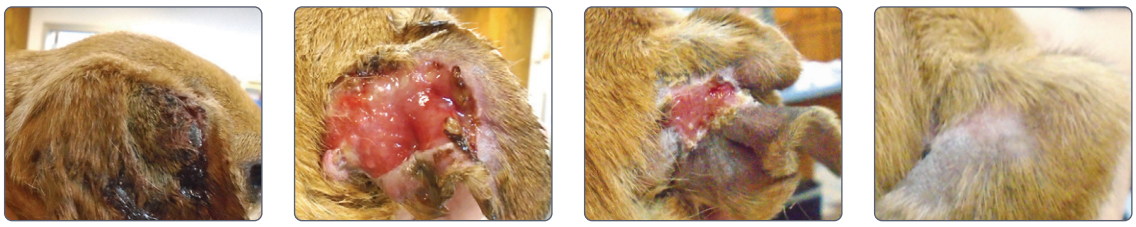
STAGE 4: Tumor site healing

- Tumor necrosis and subsequent wound formation are a sign of efficacy and typically occur 3-7 days post injection.[1,3,5,6,7,8]
- At Day 7, in the field study, maximal wound size was observed in 89% of cases receiving a single treatment; the majority of tumor sites are fully healed within 4-6 weeks.
- After the first few days, dogs can access the site to clean the wound. The following case shows an atypical progression, due to an inaccessible location on the dog's ear.

Case: This 6-year-old Chihuahua mix dog was treated for a 1.1 cm^3 cutaneous mast cell tumor at the dorsal base of the pinna. Following initial bruising, swelling, and necrosis in the first 1-7 days, the necrotic material remained attached to the wound surface, but by Day 14 could be easily detached so was removed at this point. Do not debride a STELFONTA® (tigilanol tiglate injection) wound unless loosely attached.

Full case available here.



Day 7 | Day 14 | Day 28 | Day 43, fully healed

Larger wounds may form in some cases. Analysis from patients treated with STELFONTA in the pivotal trial, shows that tumor size determines the size of the wound, which influences the healing time, along with tumor location; typically, tumors on limbs take longer to heal.[3,5] There is a positive correlation between tumor volume and wound surface area.

- The extent of microscopic disease can be difficult to determine, which may lead to larger than expected wounds that can, in turn, require additional management and extended healing time.
- Local lymph node enlargement and associated secondary lymphatic obstruction (inflammation or metastasis) may impede drainage of edema fluid from the treatment site and surrounding tissue leading to larger wound formation.
- Patients compromised with concurrent disease may form larger wounds and experience slower healing (e.g., hypothyroidism and other neoplastic conditions).[5] The two dogs in the pivotal trial that formed the largest wounds had concurrent disease (hypothyroidism and bone neoplasia).
- Wounds on the lower limbs may heal more slowly than those on the body/trunk and upper limbs as wound closure on the limbs relies predominantly on re-epithelialization instead of contraction for wound closure. Amputation has been reported in some cases.

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Case: This 7-year-old Boxer presented with a 1.25 cm^3 subcutaneous MCT located at the right hock. There was a granulating wound bed with tendon exposure at Day 7, but the dog was comfortable and not interfering with the site. Full wound closure was noted at a visit on Day 49.

Subcutaneous Mast Cell Tumor
7 years, 4 months
Boxer

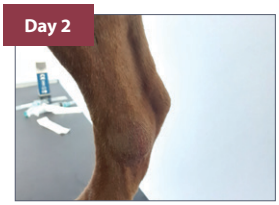
Case Summary: Boxer with subcutaneous MCT just distal to the medial hock on the right hind limb.

Treatment:

Weight	28kg
Tumor vol.	1.25cm^3
Calculated dose	0.7mL

Complete response achieved

Day 2



- Subcutaneous mass distal hock

Day 3

- Erythema and bruising extended proximal and distal to hock
- Moderate maloderous exudate
- Mild discomfort

Day 7

- Granulating deficit after tumor separation
- Tendon visible
- Dog comfortable and not interfering with site

Day 28

- Wound contracture
- Small nodule of tissue present in cranio-dorsal aspect - no FNA or re-treatment at this time

Day 49

- Full wound closure
- Tissue nodule self-resolved with no treatment

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8. POST TREATMENT MONITORING

Recheck appointments are recommended to monitor treatment progression following STELFONTA® (tigilanol tiglate injection).

Scheduling follow-ups at the suggested intervals below can assist the treating clinician in evaluating the response and guiding ongoing patient care.

- **Days 1-7**, ensure the pet owner monitors for signs of degranulation and potential pain and remind them of the importance of concomitant medications. Encourage movement at home to minimize swelling and pain. Some clinicians have owners send pictures during this phase.
- **Day 7**, assess the size of the wound, reinforce with the owner the importance of minimal intervention, and address any concerns.
- **Days 28-42**, assess the tumor response and determine if further treatments are necessary.

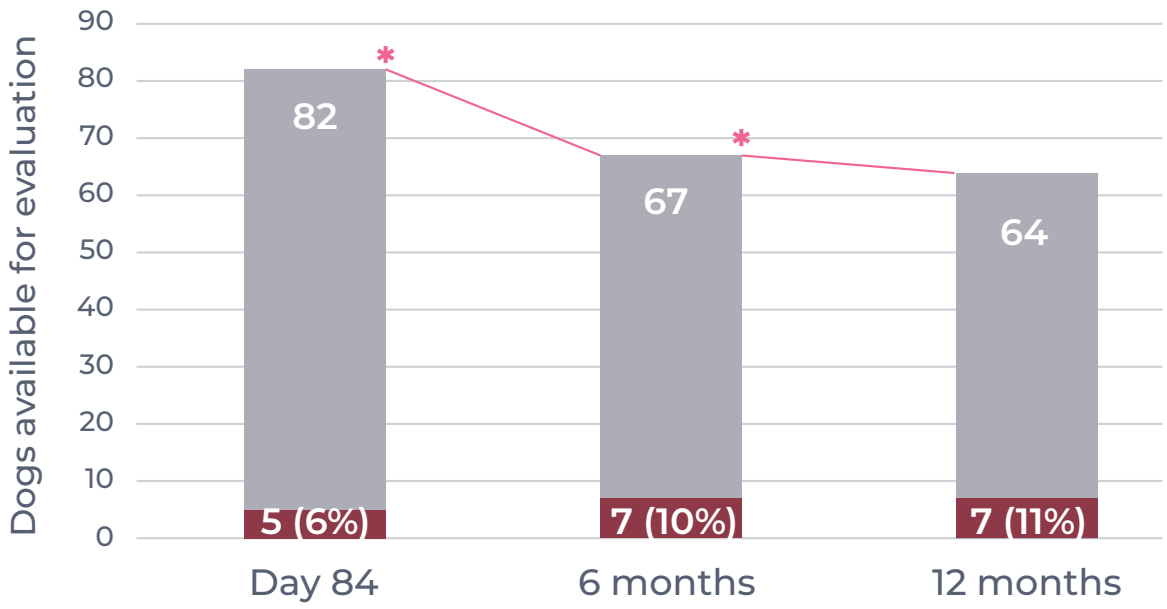
Some patients may need additional rechecks within or outside of these times. If the following signs are seen it is recommended to evaluate the patient as soon as possible:

- Excessive pain or lameness
- Excessive bruising or swelling
- Lethargy or inappetence
- Vomiting or diarrhea
- Difficulty breathing
- Extensive wound formation
- Recumbency.

9. DISEASE FREE INTERVAL

- Local recurrence of MCTs at the treatment site occurred in 7 dogs, all within the first 6 months of treatment with the majority (5/7, 71%) in the first 3 months.[9]

RECURRENCE-FREE INTERVAL, TIGILANOL TIGLATE



* Dogs available for evaluation declined due to loss of owner contact or death due to unrelated causes.

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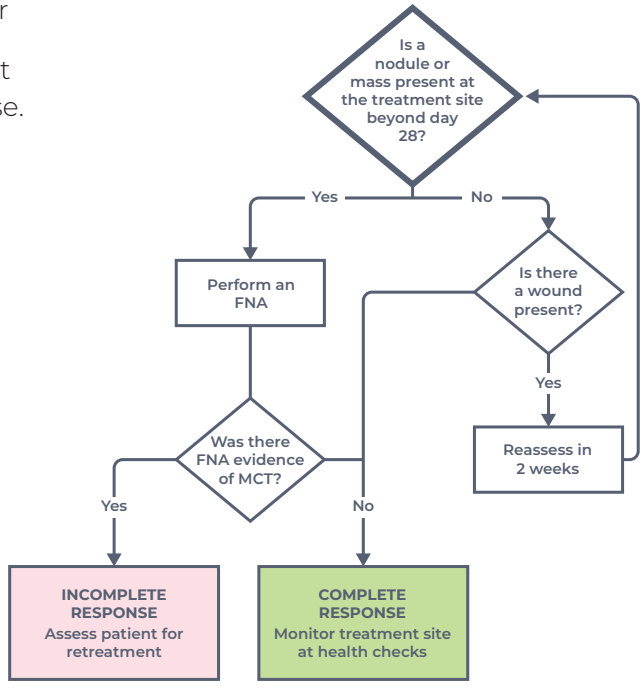
10. NON-RESPONSIVE TUMORS (MCTS WITH AN INCOMPLETE RESPONSE)

STELFONTA® (tigilanol tiglate injection) treatment resulted in a complete response in 75% of mast cell tumors after a single injection. Furthermore, 87% of dogs achieved complete response after one or two treatments.[3]

If a residual tumor at the treated site is suspected, a fine needle aspirate should be performed at a minimum of 28 days post treatment. It is important to note, that small numbers of mast cells may be present as part of the normal wound healing process. Wait a minimum of 28 days before repeating the STELFONTA treatment to allow for individual differences in treatment response and wound healing and the identification of residual mass for accurate tumor dosing. Prior to any decision to re-treat any tumor that did not achieve complete response, consider and address the possible reasons for lack of initial treatment response:

- Underdosing due to:
  - Inaccurate tumor volume or dose calculation
  - Difficulty fanning the drug throughout the tumor due to tumor density, or patient movement during the injection
  - Leakage of the drug caused by:
    - Ulceration or multiple injection sites within the tumor
    - Previous, unhealed biopsy sites
    - Pressure from within the tumor
- Concurrent medications or diseases that may interfere with the immune response.



Click to read the guidelines for the recheck schedule:
https://stelfonta.com/Stelfonta-Wait-until-28-guide.pdf

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For tumors that did not achieve a complete response following STELFONTA® (tigilanol tiglate injection) additional treatments may be given using the same protocol as the initial treatment.

This 4-year-old Boston Terrier was treated for a 3.8 cm^3 cutaneous mast cell tumor on the right rear paw. At 28 days following the STELFONTA injection, a partial response was recorded. The concurrent medication regime was reinitiated, and the tumor dosed according to the new tumor volume of 0.2 cm^3. There was a complete response recorded at Day 28 following the second STELFONTA injection.

Case ID: Macey
4 years, 11 months
Boston Terrier Cross

Treatment:

Weight	8.6kg
Tumor vol.	3.8cm^3
Location	Metatarsus
Doses received	2

Complete response achieved

Case Summary: Complete response following 2 injections.

Day 0

- Cutaneous MCT on right rear paw

Day 4

- Bruising, swelling, pain and necrosis

Day 7

- Tumor sloughing from dorsal aspect of digit 4
- Rear leg swollen and pitting edema from stifle to paw

Day 28

- Residual tumor at distal aspect of the wound
- Second treatment given (0.1mL tigilanol tiglate)

Day 37

- Tissue on medial aspect is still mildly thickened

Day 58

- Tissue remains slightly thickened
- FNA negative for MCT
- Tumor free at day 84

11. SUMMARY

Factors to consider for a successful STELFONTA® (tigilanol tiglate injection) treatment:

- Use STELFONTA for the treatment of non-metastatic cutaneous MCTs anywhere on the body *and* subcutaneous MCTs only located at or distal to the elbow or hock.
- Educate pet owners about the treatment process (including wound formation) and ensure they are committed to administer *the full course of concomitant medications* to minimize the potentially fatal risk of degranulation.
- Before the injection, confirm with the dog owner that they have administered the prednisolone on the morning of treatment and the previous two days.
- Use the dose calculator located here, to calculate the correct dose for the size of tumor and weight of dog.
- Ensure the full dose reaches the tumor cells by injecting STELFONTA into a single injection point and distributing the drug in a fanning motion throughout the tumor.

Dose Calculator

- Use caution and consider sedation to avoid accidental self-injection and wear appropriate personal protective equipment.
- Only treat tumors with an intact surface – free of ulceration and unhealed biopsy sites – to minimize STELFONTA leakage.
- Wait at least 28 days before assessing whether a repeat injection is needed. If possible, avoid intervention of the STELFONTA treatment site, allowing for healing via second intention.
- Discourage licking for the first few days and avoid trauma from excessive licking until the site heals; typically the treatment site is left uncovered but a loose gauze bandage can be used if necessary.

FURTHER INFORMATION:

Pet Owners

- Photos of treated tumors to show pet owners – https://stelfonta.com/mast-cell-tumor-pictures/
- Email series to guide owners through treatment – https://stelfonta.com/email-support-program/
- Medication tracker – https://stelfonta.com/Stelfonta-medication-tracker-v1.pdf

Clinicians

- Dose calculator – https://stelfonta.com/how-to-calculate-correct-stelfonta-dose
- Website for veterinarians – www.vet-us.virbac.com/stelfonta
- Clinical case images – https://stelfonta.com/clinical-case-images
- Recheck schedule, Wait until 28 days – https://stelfonta.com/Stelfonta-Wait-until-28-guide.pdf

12. REFERENCES

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CONTACT INFORMATION

For case consultations, to obtain a product insert or to report adverse events, contact our Virbac Product Safety and Consulting team at 1 800 338 3659.

Visit https://vet-us.virbac.com/stelfonta for full prescribing information and additional case reviews.

STELFONTA®
(tigilanol tiglate injection)
1 mg/mL

Virbac

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

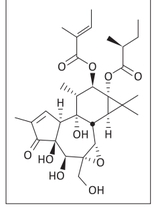
- **Always administer a corticosteroid (e.g. prednisone or prednisolone), an H1 receptor blocking agent (e.g. diphenhydramine), and an H2 receptor blocking agent (e.g. famotidine) when treating with STELFONTA to decrease the potential for severe systemic adverse reactions, including death, from mast 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

Tigilanol tiglate chemical structure



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).

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. Carefully consider the potential benefits and risks of STELFONTA before deciding to use STELFONTA.

It is crucial to follow the dosing and administration instructions to use the product safely and effectively (see **Boxed Warning, Animal Warnings, Precautions, Clinical Pharmacology**).

Concomitant medications

Administer the following medications to decrease the potential for severe systemic adverse reactions from mast cell degranulation (see **Effectiveness**). Do not underdose concomitant medications and confirm that the dog owner administered the medications as prescribed prior to the day of STELFONTA treatment.

- **Corticosteroid (oral prednisone or prednisolone at anti-inflammatory dose):** Start medication 2 days prior to STELFONTA treatment at a dose of 0.5 mg/kg orally every 12 hours for 7 days (2 days prior, the day of treatment, and 4 days after treatment), then 0.5 mg/kg orally every 24 hours for an additional 3 days (10 days total).
- **H1 receptor blocking agent (oral diphenhydramine):** Start medication on the day of STELFONTA treatment at a dose of 2 mg/kg orally every 12 hours and continue for a total of 8 days (the day of treatment and 7 days after treatment).
- **H2 receptor blocking agent (oral famotidine):** Start medication on the day of STELFONTA treatment at a dose of 0.5 mg/kg orally every 12 hours and continue for a total of 8 days (the day of treatment and 7 days after treatment).
- Fill out the medication schedule (drug name, dose, route of administration, date) on the Client Information Sheet to help the dog owner administer these medications correctly.

Consider administering analgesic medications prior to, during, and after treatment with STELFONTA.

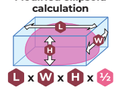
Dosing Instructions

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:

STEP 1. Calculate Tumor Volume:

- Measure the tumor dimensions (Length, Width and Height) with calipers on the day of STELFONTA injection.
- Determine the Tumor Volume using the modified ellipsoid formula to account for the tumor shape (cube volume x ½) as below:

Modified ellipsoid calculation



_____ X _____ X _____ X **½** = _____ cm^3
Length (cm) **W**idth (cm) **H**eight (cm) Tumor Volume

- Confirm the Tumor Volume does not exceed 10 cm^3.
- Do not use STELFONTA if Tumor Volume is >10 cm^3.

STEP 2. Calculate the mL of STELFONTA to inject:

_____ X **0.5** = _____ mL of STELFONTA
Tumor Volume (cm^3) Dose (0.5 mL/cm^3) mLs to be injected

- Confirm the dose of STELFONTA does not exceed 0.25 mL/kg body weight and do not use if the calculated dose exceeds this.
- 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.
- **Confirm the calculated dose of STELFONTA** using the online dosing calculator at www.stelfonta.com/calculator (or scan the QR code to the right).

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.

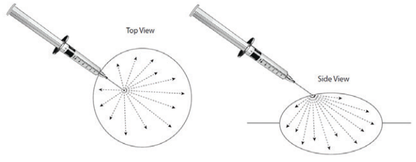


Figure 1: Dispersion of STELFONTA throughout the tumor.

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 Warnings

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 they 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 Warnings

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 concomitant medications (prednisone or prednisolone, diphenhydramine, and famotidine), as directed in the Dosage and Administration section, with STELFONTA in order to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation (see **Adverse Reactions**).

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.

STELFONTA can induce a substantial local inflammatory reaction which may result in severe pain and swelling, bruising, cellulitis, extensive wound formation, and severe tissue sloughing extending away from the treated site. Consider administering analgesic medications prior to, during, and after treatment with STELFONTA in addition to the use of corticosteroids and both H1 and H2 receptor blocking agents.

Amputation of an extremity has been reported in some cases (see **Post-Approval Experience**).

Some dogs require wound care and pain management for an extended period.

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

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.

Some discharge from the site following treatment is expected. Wear disposable gloves to clean the site with warm water as necessary.

After treatment with STELFONTA, dogs may require additional care of the treated site to aid in the healing process, especially if there is extensive wound formation (see **Animal Safety Warnings** and **Post-Approval Experience**).

Tongue lesions have been reported (see **Post-Approval Experience**). Do not allow the dog to lick the site for the first few days after treatment. Discourage excessive licking for the remainder of the healing period.

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.

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

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

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

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

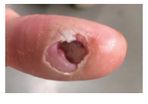
The safe use of STELFONTA has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS

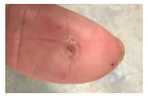
Human Exposure

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 1 below.

Table 1: 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)
- Pain: 69.1% (56/81 dogs)
- Bruising: 91.4% (74/81 dogs)
- Heat: 53.1% (43/81 dogs)

At 24 hours post treatment, intact skin was reported in 71.6% (58/81 dogs) of STELFONTA 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)
- Exudate: 37.0% (30/81 dogs)
- Crater pockets: 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.

CLIENT INFORMATION SHEET

STELFONTA®
(tigilanol tiglate injection)
1 mg/mL

This Client Information Sheet contains important information about STELFONTA®. Before your dog is treated, you should carefully read this information and discuss the following with your veterinarian:

- How STELFONTA works.
- All parts of your dog's treatment plan. **It is very important to follow the treatment plan exactly as directed.**
- The risks and benefits of STELFONTA, including the potential for serious side effects.

This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk with your veterinarian if you do not understand any of this information or if you want to know more about STELFONTA.

What is STELFONTA?

- STELFONTA is a drug used to treat mast cell tumors, a common form of cancer that affects dogs.
- The active ingredient in STELFONTA is tigilanol tiglate, a substance that works by:
  - » Breaking down the tumor cell walls
  - » Disrupting blood vessels in the tumor
  - » Destroying the tumor and forming a 'pocket' or wound where the tumor was.

What should I tell my veterinarian before my dog is treated with STELFONTA?

- Tell your veterinarian about all other medications your dog is taking, including prescription drugs, over the counter drugs, flea and tick medications, heartworm and deworming medications, and vitamins and supplements (including herbal or homeopathic products).
- Tell your veterinarian about your dog's previous or current medical conditions, including any infection.
- Tell your veterinarian if your dog is pregnant, is nursing puppies, or is intended for breeding purposes.

How is STELFONTA given to my dog?

- Your veterinarian will inject your dog's tumor with STELFONTA. The injection will be given at the veterinary clinic. Your dog may need to be sedated during the procedure.

What additional medications need to be given to my dog before, on, and after the day of treatment with STELFONTA?

- To help prevent the potential for severe side effects that can occur, your veterinarian will prescribe three medications:
  - » You must start to give your dog the corticosteroid two days before the STELFONTA treatment day and continue for a total of 10 days.
  - » You will start giving your dog the H1 and H2 blockers on the STELFONTA treatment day and continue for a total of 8 days.
- Your veterinarian will fill out the medication schedule included in this Client Information Sheet for you to follow, so that you can give your dog the medications correctly.
- If you are unable to give your dog the medications as directed, talk to your veterinarian about other options. **Do not skip these medications.**

How will STELFONTA affect my dog?

- STELFONTA is used to treat a mast cell tumor on your dog.
- It can be difficult to predict how your dog's tumor will respond to STELFONTA.
- A wound will form where STELFONTA was administered. It is difficult to predict the size and severity of the wound formed. In some cases, an extensive wound that is deeper and/or larger than the original treatment site may develop, which may lead to unexpected complications.
- Tumors treated with STELFONTA typically go through a 4- to 6-week tumor breakdown and healing process.
- The healing process may take longer in some dogs.
- During the tumor breakdown and healing process, your dog may require additional care of the treated tumor site to aid in the healing process.

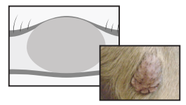
See the diagrams for more information.

LESS THAN 4 HOURS AFTER STELFONTA TREATMENT:

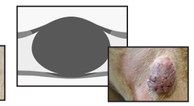
Start of Tumor Breakdown

Within the first few hours following treatment with STELFONTA, the cells in the tumor and tumor blood vessels will begin to break down. You will be able to see a change in the color of the tumor. At the same time there is usually swelling at the treated tumor site.

DAY 1: BEFORE STELFONTA TREATMENT



2-4 HRS AFTER STELFONTA TREATMENT

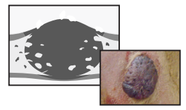


1-7 DAYS AFTER STELFONTA TREATMENT:

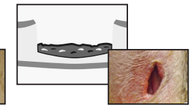
Continued Tumor Breakdown

The treated tumor site will become blackened. The skin over the surface of the tumor may breakdown and fluid may leak from the tumor. Swelling of the treated tumor site may continue causing some discomfort to your dog through this stage. Your veterinarian can prescribe pain medication to help your dog through this period if needed. As the tumor breaks down there will be a 'pocket' or wound where the tumor once was. A healthy wound bed will be seen, reddish in color, which will allow healthy new skin to grow.

24 HRS POST-TREATMENT: TUMOR BREAKDOWN EVIDENT



DAY 7: TUMOR BREAKDOWN WITH FORMATION OF HEALTHY WOUND BED

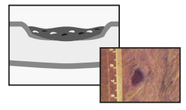


7 - 42 DAYS AFTER STELFONTA TREATMENT:

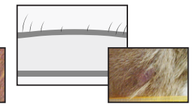
Wound Resolution

Healthy new skin will grow and close over the pocket or wound where the tumor once was. In many dogs, the hair will regrow, and skin will return to its original color.

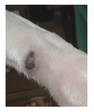
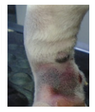
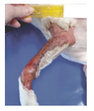
DAY 14 AFTER STELFONTA TREATMENT: TUMOR SITE

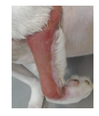
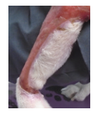
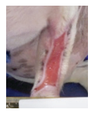


DAY 28 AFTER STELFONTA TREATMENT: TREATED TUMOR SITE HEALED



Some dogs experience extensive wounds after STELFONTA treatment that take longer to heal, as in the case below.

Treatment day	24 hours post-treatment	7 days post-treatment	14 days post-treatment
			
Mast cell tumor above left paw.	Forelimb is swollen and painful.	Extensive wound developed, requiring veterinary care and bandaging days 8-12.	Wound healing; swelling and lameness present.

28 days post-treatment	42 days post-treatment	84 days post-treatment
		
Surgery needed to improve movement of leg. Splint applied for one month. No tumor present.	Wound continues to heal; swelling and lameness present.	Healing and limb use continues to improve. No evidence of tumor detected.

What are some possible side effects of STELFONTA?

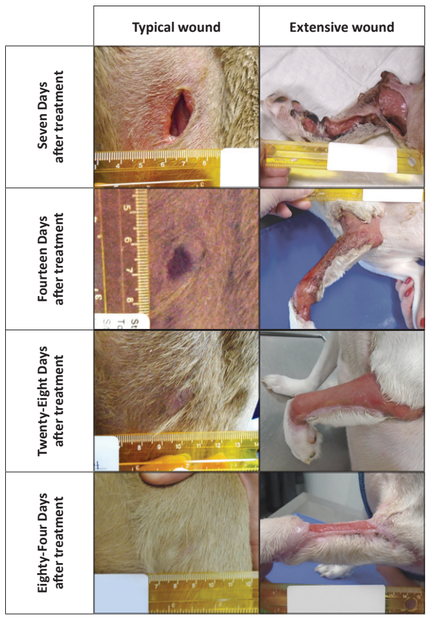
- STELFONTA may cause side effects, even at the prescribed dose. These side effects include, but are not limited to:
  - » During the first days after treatment, you may see bruising or swelling around the treated tumor site. The swelling may cause your dog some discomfort and pain for several days after treatment. Your dog may seem tired during this time and may eat less.
  - » In some cases, extensive swelling, severe pain, large amounts of discharge, odor, infection, or wound formation extending into the area surrounding the tumor site may develop, delaying wound healing and requiring additional management of the wound. If any of these occur, contact your veterinarian who will assess if your dog requires additional treatments during this time (e.g., pain medications, bandages, an Elizabethan collar, antibiotics). **(see reverse side)**

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 the 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.

Post-Approval Experience (2024)

The following adverse events are based on post-approval adverse drug experience reporting for STELFONTA. 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 these data.

The following adverse events reported in dogs are listed in decreasing order of reporting frequency:

Injection site reactions (wound formation, swelling, pain, necrosis, skin sloughing, bleeding, bruising and erythema). These injection site reactions varied in severity and ranged from localized to extending away from the injection site.

Other signs reported include anorexia, lameness, lethargy, diarrhea, vomiting, fever, tachypnea/dyspnea, and ulceration or necrosis of tongue.

In some cases, when STELFONTA was used to treat a mast cell tumor on an extremity, the entire extremity became swollen, painful, and developed tissue sloughing. Some of these cases resulted in amputation.

In some cases, death (including euthanasia) has been reported as an outcome of the adverse events reported above.

CONTACT INFORMATION

To report suspected adverse drug experiences, to obtain a Safety Data Sheet (SDS), or for technical assistance, contact Virbac at 1-800-338-3659 or us.virbac.com.

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 (CIS) to read before STELFONTA is administered.

Owners should be advised to observe their dog for potential side effects, including signs of systemic mast cell degranulation, excessive pain and swelling, and excessive wound formation. Advise dog owners about the possibility of severe side effects, including amputation and death, 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.

Discuss the importance of the concomitant medications and ensure that the owner is aware of the schedule of medications that should be administered. The owner should use the Medication Schedule on the CIS to keep track of the medications they have administered.

Discuss with owners that they should not allow the dog to lick the site for the first few days after treatment and they should discourage excessive licking for the remainder of the healing period.

An Elizabethan Collar may be utilized to prevent self-trauma of the treatment site. After treatment the owner may need to separate the dog from other household animals to prevent grooming and trauma to the treated site.

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 anti-tumor 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 (t½): 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 C_{max} 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

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2. Eisenhauer EA, Therase P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1), *Eur J Cancer.* 2009; 45(2):228-247.
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Approved by FDA under NADA # 141-541

Distributed by Virbac AH, Inc., P.O. Box 162059, Fort Worth, TX 76161
Tel. 1-800-338-3659 PC5111B
Version date: November 2024 A-IN-001.02

CLIENT INFORMATION SHEET

» Amputation has been reported as a result of extensive swelling and wound formation.
» Mast cell degranulation can occur, especially during the first 5-7 days after treatment. Mast cell degranulation is a type of allergic reaction that occurs when inflammatory substances are released from your dog's tumor when mast cells are destroyed.

Mast cell degranulation can cause severe side effects and potentially be fatal. Contact your veterinarian if you notice any of the following signs:
– trouble breathing or excessive panting
– excessive bruising and swelling
– vomiting
– diarrhea
– hives
– decreased appetite (refusal to eat for more than 1 day).

- Other side effects may occur. For more information about side effects ask your veterinarian.
- Side effects can occur with or without warning, and in some cases may result in death.

Contact your veterinarian if you notice any of the following changes in your dog. These changes may mean your dog is experiencing a serious side effect.

- Excessive pain or lameness (limping)
- Excessive licking of the treatment site
- Tiredness, weakness or refusal to eat for more than 1 day
- Repeated vomiting or diarrhea
- Trouble breathing or excessive panting
- A rash or hives anywhere on the body
- Changes to the treated tumor site, including increased or excessive swelling and bruising, large amounts of discharge, strong odor, or extensive wound formation
- Any other symptoms that your dog may show that concern you.

What do I need to know to safely care for my dog before and after treatment with STELFONTA® (tigilanol tiglate injection)?

- Your veterinarian will prescribe medications to decrease the potential for allergic reactions due to mast cell degranulation that can occur during the treatment process. **It is essential that you give the medications as prescribed** (use the Medication Schedule provided below to help you keep track of the dosing schedule).
- The treated tumor site is typically left uncovered. In some cases, your veterinarian may decide to cover the treated tumor site with a bandage.
- Notify your veterinarian if your dog seems uncomfortable. Your veterinarian may prescribe additional medications for pain.
- Some discharge from the treated tumor site following treatment is expected. The treated tumor site can be cleaned with warm water as necessary. Wear disposable gloves when cleaning the treated tumor site.
- Do not allow your dog to lick the tumor site for the first few days after treatment. Discourage excessive licking for the remainder of the healing period.
- If your dog is licking or rubbing the treated tumor site, contact your veterinarian. Your veterinarian may recommend an Elizabethan collar ("e-collar") or a bandage to cover the wound.
- If another animal in the household is licking or grooming the treated tumor site, the animals should be separated to prevent trauma to the area.

What precautions do I need to take when caring for my dog before and after treatment with STELFONTA?

- Thoroughly wash any skin that comes in contact with the treated tumor site, wound, wound discharge, or material contaminated with wound discharge (e.g. bedding).
- Do not wash any items soiled with wound discharge with other laundry.

Is there more information?

- This client information sheet gives the most important information about STELFONTA. For more information about STELFONTA, please talk with your veterinarian.
- To report a suspected adverse reaction (side effect) call 1-800-338-3659. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Use the Medication Schedule below to help you keep track of the medicine you need to give your dog.

Medication schedule

The following medications are to be given when your pet is treated with STELFONTA to help decrease and/or prevent side effects:

- Corticosteroid (prednisone or prednisolone): Start medication as directed **two days before STELFONTA treatment day**, continue on the treatment day, and for an additional 7 days after the treatment day, which will be a total of 10 days.
- H1 and H2 blockers (diphenhydramine and famotidine): Start medications as directed **on STELFONTA treatment day** and continue for an additional 7 days, which will be a total of 8 days.
- Use the following chart to help you keep track of the dosing schedule, make an "X" in the box when that dose of medication is given. Do not administer the medication if the box is grayed out.
- If you are unable to give your dog the medications orally (by mouth), or your dog is vomiting or not eating, talk to your veterinarian to determine what other options may be used for administration. **Do not skip these medications**.

	Before STELFONTA Treatment				STELFONTA Treatment Day		After STELFONTA Treatment													
	2 days before Date:		1 day before Date:		Date:		1 day after Date:		2 days after Date:		3 days after Date:		4 days after Date:		5 days after Date:		6 days after Date:		7 days after Date:	
Drug	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
Corticosteroids Name:																				
H1 blocker Name:																				
H2 blocker Name:																				

Note for veterinarian – the above chart is intended to be a visual aid for the client to administer the concomitant medications correctly. Fill in the chart with the specific dates of administration and the specific names of the medications prescribed.

Space reserved for veterinarian to provide full directions for administration of concomitant medications (name of drug, route of administration, amount, frequency, and duration)

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