Practical aspects of STELFONTA® (tigilanol tiglate injection)

GUIDE FOR VETERINARIANS ADMINISTERING STELFONTA

STELFONTA®

Shaping the future of animal health

Virbac

STELFONTA® (tigilanol tiglate injection) PRACTICAL ASPECTS OF ADMINISTRATION

Geography: US

CONTENTS

STELFONTA®

Shaping the future of animal health

Virbac

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.

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.

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

- Reduce the risk of mast cell degranulation (including death) with mandatory concomitant medications:
  - Corticosteroids, commencing 2 days prior to the injection.
  - H1 and H2 Blockers, commencing on injection day, continuing for 8 days.
- Discretionary pre-emptive pain relief to minimize discomfort during and post injection.

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 is recommended.
- Tumor surface should be intact; the drug can leak from ulcerated surfaces or biopsy sites.
- Re-measure the tumor on the day of treatment (LxWxHx1/2) and confirm the volume does not exceed 10cm^3.
- Calculate the dose: tumor volume x 1/2; ensuring total dose is not more than 5mL or 0.25mL/kg.
- Administer STELFONTA in a fanning motion through a single injection point with a Luer-Lock syringe and 23 gauge needle.
- Leave the site unbandaged when possible If covered, apply only a loose gauze bandage..
- Plan for and provide pain relief when necessary and adjust as needed.
- If degranulation occurs, signs are typically seen in the first five days of treatment.

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.
- Treated sites are usually left uncovered.
- Necrotic tumor mass will slough away leaving a "pocket" or deficit (wound) which may be extensive.

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

- 3 to 14 days: Wound formation is an intended and expected sign of STELFONTA® (tigilanol tiglate injection) efficacy. Wound may be extensive, requiring additional management and time to heal.
- Determinants of wound size are tumor location and volume, and enlargement of the local lymph node.

- **Non-responsive tumors may be retreated after day 28.** 75% of MCTs achieve a Complete Response after one treatment, 88% after one or two treatments. If a second treatment with STELFONTA is necessary, concomitant medications should be started with the same mandatory dosing schedule.
- **STELFONTA's Mechanism of Action:** Three inter-related effects, specifically, oncolysis, stimulation of acute inflammatory response and increased permeability of tumor vasculature.

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.

DOG SAFETY

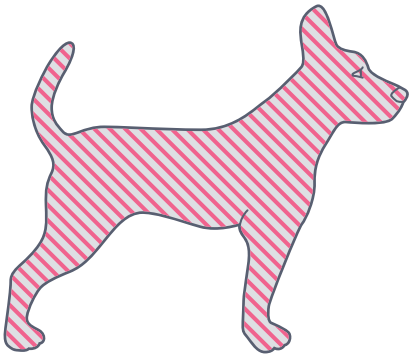
- Always administer a corticosteroid (e.g., prednisone or prednisolone), an H1 receptor blocking agent (e.g., diphenhydramine), and an H2 receptor blocking agent (e.g., famotidine) when treating with STELFONTA to decrease the potential for severe systemic adverse reactions, including death, from mast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

Please see full prescribing information, including BOXED WARNING and medication guide.

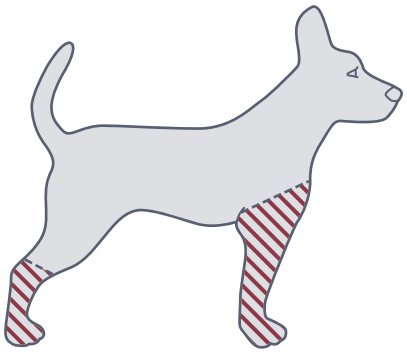
For medical technical assistance, to obtain a product insert, or to report adverse events, contact our Veterinary Technical Support staff at 1.800.338.3659.
Product information is also available at vet-us.virbac.com/Stelfonta

2. INDICATION

STELFONTA® (tigilanol tiglate injection) 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	**= 10cm³**
Maximum STELFONTA dose	**= 0.25mg/kg body weight**
Maximum total dose of STELFONTA per dog	**= 5mL**

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.

3. CASE SELECTION CONSIDERATIONS

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

Tumor considerations for case selection

- **Location:**
  - **Functional structures and mucocutaneous junctions:** destruction of a tumor located within functional structures (e.g., eyelid, muzzle or vulva) may lead to loss of these structures, potentially leading to functional or cosmetic changes. Consider the level of gross and microscopic extensions of the tumor.
  - **Distal location:** tumors located distally 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 feet.
  - **Sensitivity:** highly sensitive locations such as toes, face, and vulva may require sedation to ensure safe administration.
  - **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 =10cm^3 [1] and maximum dose = 0.25mg/kg body weight.
- **Stage:** STELFONTA is an intratumoral injection and is not indicated for 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.[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.

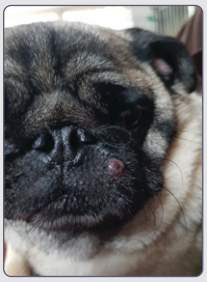
Patient considerations for case selection

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

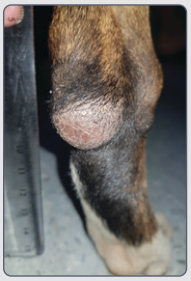
The safe use of STELFONTA has not been evaluated in dogs with concurrent diseases, or those that are pregnant, lactating, or intended for breeding.

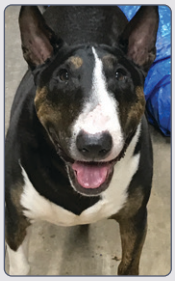
Owner considerations for case selection

- **Ability to administer** the full course of concurrent medications that are essential to reducing the risk of potentially severe adverse events, including death, from mast cell degranulation (see section 6).
- **Comfort with the process.** Explaining the potential responses to the pet owners can help prepare them for the tumor necrosis and healing of the tissue deficit.
- **Treatment Preference** due to familiarity with surgery.



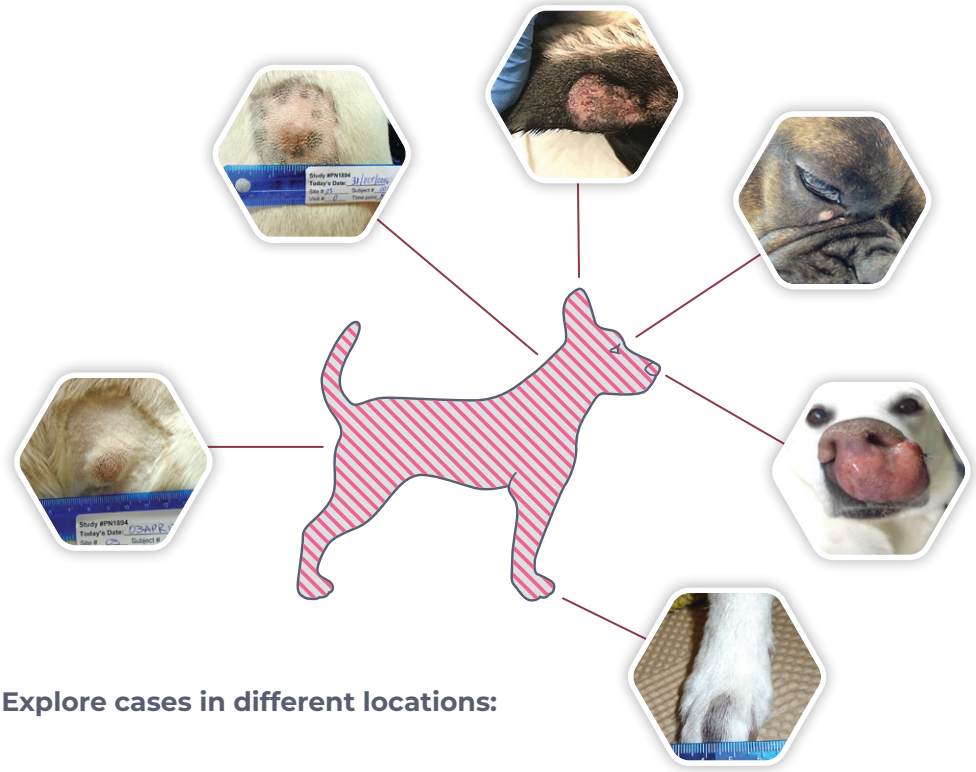
This **8-year-old Pug** was diagnosed with a 0.1cm^3 cutaneous mast cell tumor on his muzzle. Due to the inherent risk anesthesia poses for brachycephalic breeds, and his concurrent severe upper airway disease, his owner wanted to avoid anesthesia. Additionally, they expressed concern about the cosmetic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





This **6-year-old Bull Terrier** was diagnosed with a 3.6cm^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.

4. EXAMPLES OF PROGRESSION OF CLINICAL COURSE OF RESPONSE TO TREATMENT



Explore cases in different locations:

Case ID: Biggie
6 years
French Bulldog

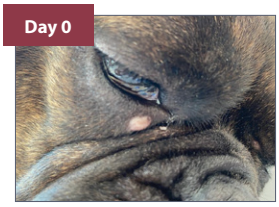
Case Summary: Dog with small, low grade MCT under lower eyelid; previous veterinarian treated with corticosteroids but no response, increased in size

Treatment:

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

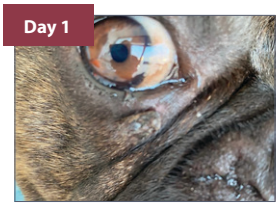
Complete response achieved

Day 0



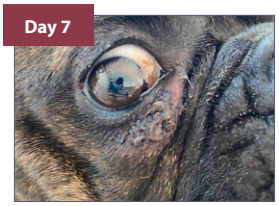
- Cutaneous MCT near medial canthus of the right eye

Day 1



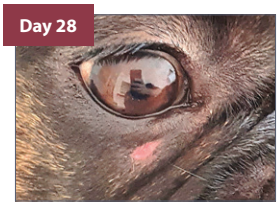
- Swelling at site

Day 7



- Necrotic material present

Day 28



- Complete wound healing
- Complete tumor response

Day 42

- No tumor recurrence
- Minimal scarring present at site

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

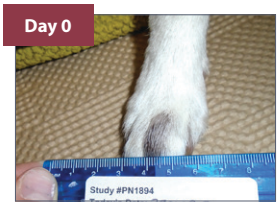
Case Summary: Senior female dog with a moderate sized initial wound (2.2 x 1.7cm) on Day 7

Treatment:

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

Complete response achieved

Day 0

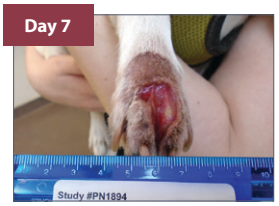


- Round cutaneous mass on right front foot between toes

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:

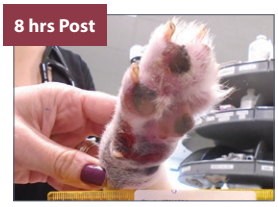
Weight	9.8kg
Tumor vol.	3.1cm³
Location	Metacarpus
Doses received (initially control group)	1

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

Case ID: Zuma
7 years
Labrador

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

Treatment:

Weight	28.7kg
Tumor vol.	3-4cm³
Location	Nasal planum
Doses received	1

Complete response achieved

Day 0

- Cutaneous MCT on nasal planum

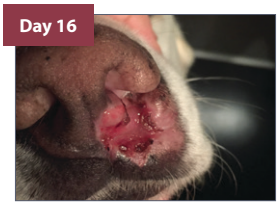
Day 5

- Necrotic material present

Day 9

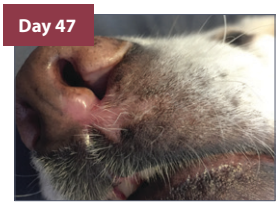
- Healthy granulation tissue

Day 16



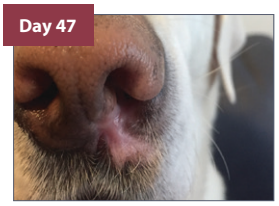
- Wound contraction

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

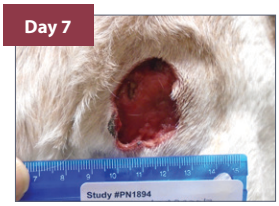
Day 1

- 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

Case ID: Benji
12 years, 5 months
Boxer

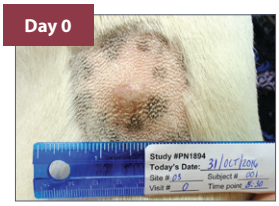
Case Summary: Senior female dog, overweight with a large initial wound (6.0 x 4.3 cm) on Day 7

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

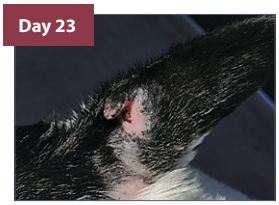
Day 4

- tumor necrosis

Day 7

- Granulating wound

Day 23



- Complete tumor response

Day 30

- Complete wound healing

5. 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.	○ Concomitant medications (corticosteroid, H1 and H2 blocking agents) are essential to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation. ○ Consider pain control.
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 0.5** (modified ellipsoid). ○ Dose (mL) = Tumor volume **X 0.5**. **Treatment administration** ○ Use a 23G needle with a Luer-lock syringe. ○ Deliver as evenly as possible throughout the tumor using a fanning technique. ○ Most wounds are left unbandaged, to heal via second intention.	○ Maximum treatable tumor volume = 10 cm^3. ○ Maximum total dose/dog = 5 mL. ○ Maximum dose per kg BW = 0.25 mL/kg. ○ Minimum dose 0.1mL. ○ Wear appropriate PPE. ○ Take care to avoid accidental self-injection.
3 TUMOR DESTRUCTION	**Inflammatory response** ○ Within 2 hours after treatment an acute inflammatory response is observed with swelling and erythema to the tumor margins and immediate surrounding tissues.[1-3] **Tumor necrosis** ○ Tumor necrosis begins within 4 hours of treatment and complete necrosis is typically evident within 4-6 days. ○ A wound or “pocket” 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, lameness in the treated limb, vomiting, diarrhea, and hypoalbuminemia.

4 TUMOR SITE HEALING	○ Tumor sites heal via second intention, 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 excessive wounds and prolonged recovery time.
OUTCOME ASSESSMENT	**Suggested re-check schedule** ○ Ideally the treating clinician will be available for the re-checks - a consideration when selecting the treatment day. ○ Days 1-4, monitor for degranulation clinical signs; ensure continued concomitant medications and assess pain management. ○ Day 7, assess wound size and reinforce wound management. ○ At Day 28, assess tumor response and determine if further treatment is necessary. **Non-responsive tumors** ○ STELFONTA treatment has been shown to deliver a complete response in 75% of MCTs after a single injection. ○ 88% of dogs achieved complete response after one or two treatments.[1,3] ○ Potential for false diagnosis of non-response if FNA cytology evaluation is performed prior to 28 days post treatment.	

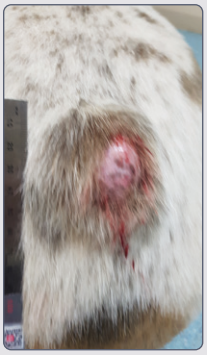
6. TREATMENT PROTOCOL – DETAIL

There are four stages to treating MCTs with STELFONTA® (tigilanol tiglate injection), however the clinician's time is weighted towards stages one and two. STELFONTA's mechanism of action initiates healing via second intention (often referred to as "hands off healing") 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

Concomitant medications are an essential component of the STELFONTA treatment protocol to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation. Always administer the following mandatory medications[1]:

- **Corticosteroids** (e.g., oral prednisone or prednisolone at anti-inflammatory dose), starting medication 2 days prior to STELFONTA treatment and continuing for 8 days post-treatment (10 days total). In the pivotal trial, prednisolone/prednisone was dosed at 0.5mg/kg q12hrs for 7 days, then 0.5mg/kg q 24hrs for 3 days.
- **H1 receptor blocking agent** (e.g., oral diphenhydramine), starting medication on the day of STELFONTA treatment and continuing for a total of 8 days. In the pivotal trial, diphenhydramine was dosed at 2mg/kg q 12hrs for 8 days.
- **H2 receptor blocking agent** (e.g., oral famotidine), start medication on the day of STELFONTA treatment and continuing for a total of 8 days. In the pivotal trial, famotidine was dosed at 0.5mg/kg q 12hrs for 8 days.



This 12-year-old cross-breed had a large cutaneous mast cell tumor on the dorsal back. He received the full concomitant medications prior to treatment, however when he returned home his owner was unable to administer the medication when the dog failed to eat the food that the medication was hidden in. 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 these clinical signs and provide appropriate treatment can lead to serious sequelae including death.

Minimizing discomfort *during* the injection

Clinicians have reported a correlation between discomfort at time of injection and:

- Location of the injection site (head, vulva, feet, and toes may be highly sensitive).
- Temperature of the drug STELFONTA injected (ambient temperature has been reported by clinicians to reduce the level of discomfort).
- Individual pain sensitivities/temperament.
- Size of tumor relative to the patient.
- Increased intratumoral pressure and skin tension following 50% vol/volume dosing.

Note: Store STELFONTA vials refrigerated at 2°C to 8°C (35°F to 46°F) and protect from light.

Pre-emptive plan to minimize discomfort *following* the injection

The injection of STELFONTA® (tigilanol tiglate injection) results in an acute local inflammatory response with swelling, bruising, and erythema, followed by tumor necrosis. The patient may experience discomfort during the first few days to a week, with reduced level of discomfort as the inflammatory response subsides and the tumor separates from the surrounding tissue.

Pain management considerations to minimize discomfort following the STELFONTA injection:

- Concomitant medications (prednisolone/prednisone, H1 and H2 antagonists) can reduce the level of bruising and swelling due to localized degranulation reactions and reduce the level of pain or discomfort experienced.
- Pain medication is at the discretion of the treating clinician, with multimodal therapy sometimes required. During the pivotal study, the following were observed regarding pain therapy:
  - 69% of patients received a pain medication within the first 7 days after treatment[3],
  - Median course duration of 6 days and an average of 9 days[3], and
  - The most commonly administered pain medications included tramadol, gabapentin, and buprenorphine[3].

STAGE 2: STELFONTA injection

Checklist for treatment day

- Ensure the patient has received the essential concomitant medications, commencing with prednisone 2 days prior to the injection, adding H1 and H2 blocking agents on the morning of treatment day.
- Ensure the tumor surface is intact and any previous biopsy site has healed (minimum 14 days).
- Confirm the pet owner understands 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 protective clothing: gloves, eyewear, gown/lab coat.
- 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, so the pet owner can more easily contact them to address any concerns post treatment during regular working hours.

Calculate the dose

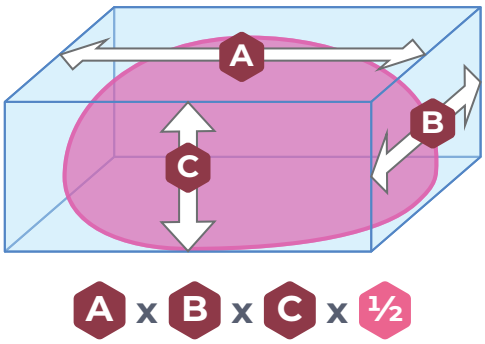
STELFONTA® (tigilanoltiglate injection) is administered as an intratumoral injection at a dose of 0.5mL per cm^3 of tumor volume.

Note the following restrictions:

- Maximum treatable tumor volume is $10cm^3$;
- Maximum total dose per dog is 5mL of STELFONTA per dog;
- Maximum dose of STELFONTA 0.25 mL/kg body weight;
- Minimum tumor dose is 0.1mL.

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 0.5**
   - Confirm the tumor volume does not exceed $10cm^3$.
2. **Weigh dog** to confirm body weight in kilograms.
3. **Calculate the dose** (mL) of STELFONTA to inject: Tumor volume x **0.5mL**
   - Ensure the maximum total dose is no more than 5mL.
   - Ensure dose is within the mL/kg guidelines of 0.25mL/kg.

Modified ellipsoid calculation

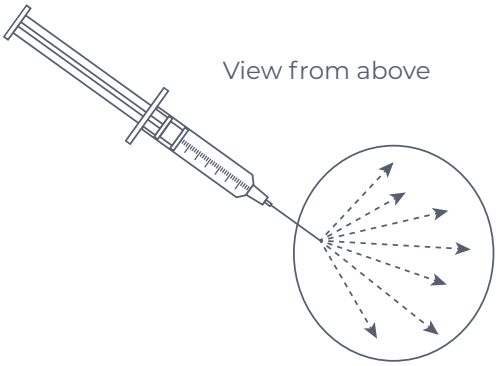


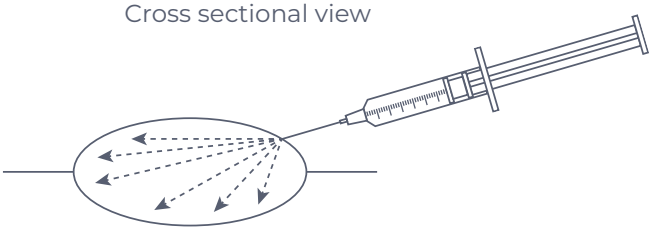
A x B x C x ½

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 of an appropriate length for the tumor.
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. Applying light pressure for 30 seconds over the needle exit hole using a gloved finger. If leakage does occur, rinse the injection site with saline to wash STELFONTA from the skin surface. Do not re-administer. To minimize risk of accidental self-injection, dispose of the uncapped needle and syringe as appropriate for routine medical waste.
4. **Leave the site unbandaged** where possible 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.
5. **Determine whether pain relief is required** depending on the level of discomfort experienced by individual patient.
6. **Reiterate expectations to the pet owner** regarding the wound, signs of degranulation and importance of compliance for all 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 usually seen. While localized bruising and swelling is an expected response, more extensive wounds or more severe systemic reactions should receive immediate veterinary attention. Reassure 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 sometimes takes longer and is characterized by blackening, shrinkage and softening of the tumor. There may be noticeable leakage of fluid, normally in small amounts, from the wound.
- **Site care:** The treated tumor site is typically left uncovered to allow the patient to remove necrotic material. 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.
- **Sloughing:** The necrotic tumor mass will fall away forming a wound with a pocket or crater-like defect. Surgical debridement is not required, and it may interfere with wound healing benefits of STELFONTA, potentially compromising wound healing and/or response. Only remove necrotic tissue that is loosely attached and can be easily removed without resistance.

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.

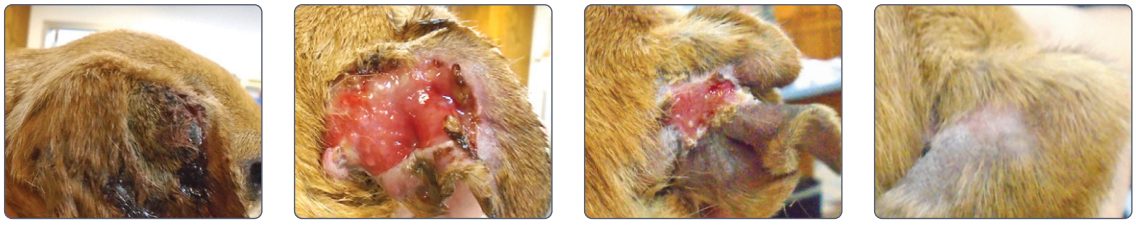
Occasionally, due to tumor location, the underlying tissues including bones and tendons may be exposed but in most cases granulation tissue covers these tissues quickly without deleterious effect of these structures.

STAGE 4: Tumor site healing

- 3-14 days after treatment, wound formation is an intended and expected event and a sign of STELFONTA®'s (tigilanol tiglate injection) efficacy. Tumor destruction is by hemorrhagic necrosis and oncolysis of the mass resulting in a tissue deficit, or wound.[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 and by Day 14 in the remainder of cases. This process can be related to tumors located on parts of the body that the dog cannot access to clean, such as the head and neck. The following case is an example of the treatment site being inaccessible to the patient.

Case: This 6-year-old Chihuahua cross dog was treated for a 1.1cm^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. This hard tissue was easily detached without resistance on the Day 14 recheck. The inability for a patient to access the site can delay removal of the necrotic material which may slow the healing process in some cases. It is recommended to leave the necrotic material in place until it is only 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 volume, enlargement of the local lymph node, and tumor location were determinants of wound size.[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 a longer time to resolve.
- 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.

Case: This 7-year-old Boxer presented with a 1.25cm^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

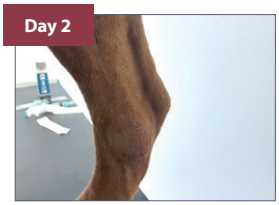
Case Summary: Boxer with subcutaneous MCT just distal to the medial hock on the right hind limb

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

7. RECHECK SCHEDULE

There are no mandatory rechecks following STELFONTA® (tigilanol tiglate injection) treatment; possible rechecks may include the days below. Consider treating on a day that will enable re-checks to be undertaken by the treating clinician:

- **Days 1-4**, monitor for signs of degranulation; remind owner of the importance of concomitant medications and assess pain management.
- **Day 7**, to assess the size of wound, reinforcing wound management and addressing any owner concerns.
- **Day 28**, to assess the tumor response and determination if further treatments are necessary.
- Further assessments for wound healing and/or recurrence should be at the discretion of the attending veterinarian.

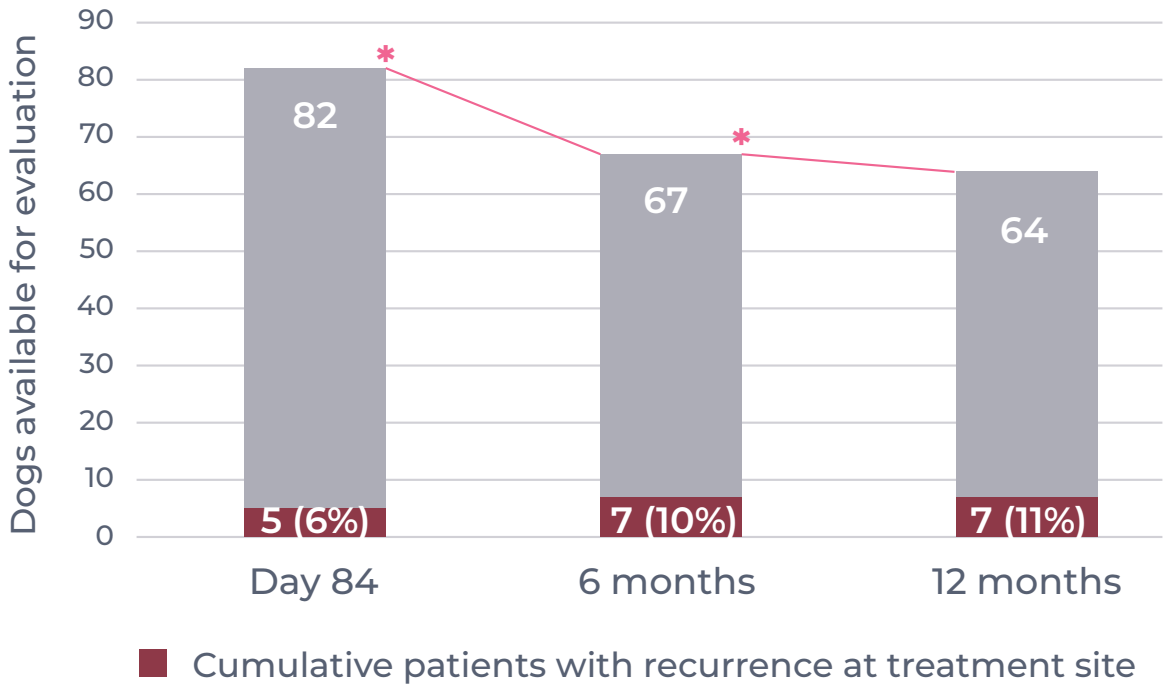
Some patients may need additional rechecks within or outside of these times. If the following signs are seen it is recommended to evaluate the patient as soon as possible:

- Excessive pain or lameness (limping)
- Excessive bruising or swelling
- Lethargy or inappetence
- Repeated vomiting or diarrhea
- Difficulty breathing
- Changes such as increased or excessive swelling and bruising, extensive wound formation, or increased irritation.

8. DISEASE FREE INTERVAL

- Local recurrence of MCTs at the treatment site occurred in (only) 7 dogs, all within the first 6 months of treatment with the majority (5/7, 71%) in the first 3 months.
- Within 12 weeks, in this study, tumor recurrence happened in the majority of cases (5/7, 71%) with the remainder of recurrences before 6 months (2/7, 29%)[9]

RECURRENCE FREE INTERVAL, TIGILANOL TIGLATE



* Dogs available for evaluation decline due to losing contact with their owner or died due to unrelated causes.

9. 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, 88% 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 to confirm this prior to the administration of a second STELFONTA treatment. It is important to note, that small numbers of mast cells may be present as part of the normal wound healing process.

It is recommended to wait a minimum of 28 days before repeating the STELFONTA treatment to allow for individual differences in treatment response and wound healing. It is important to wait until the exact location and extent of the residual tumor can be identified to improve efficacy of future treatments. 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.

For tumors that did not achieve a complete response following STELFONTA® (tigilanol tiglate injection) treatment, additional treatments are based on the volume of the tumor on the day of the additional treatment. This 4-year-old Boston Terrier was treated for a 3.8cm^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 0.2cm^3. There was a complete response recorded at Day 28 following the second STELFONTA injection.

Case ID: 01-008
4 years, 11 months
Boston Terrier Cross

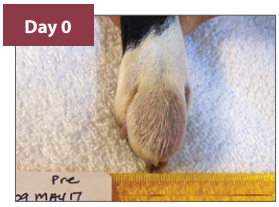
Case Summary: Complete response following 2 injections

Treatment:

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

Complete response achieved

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

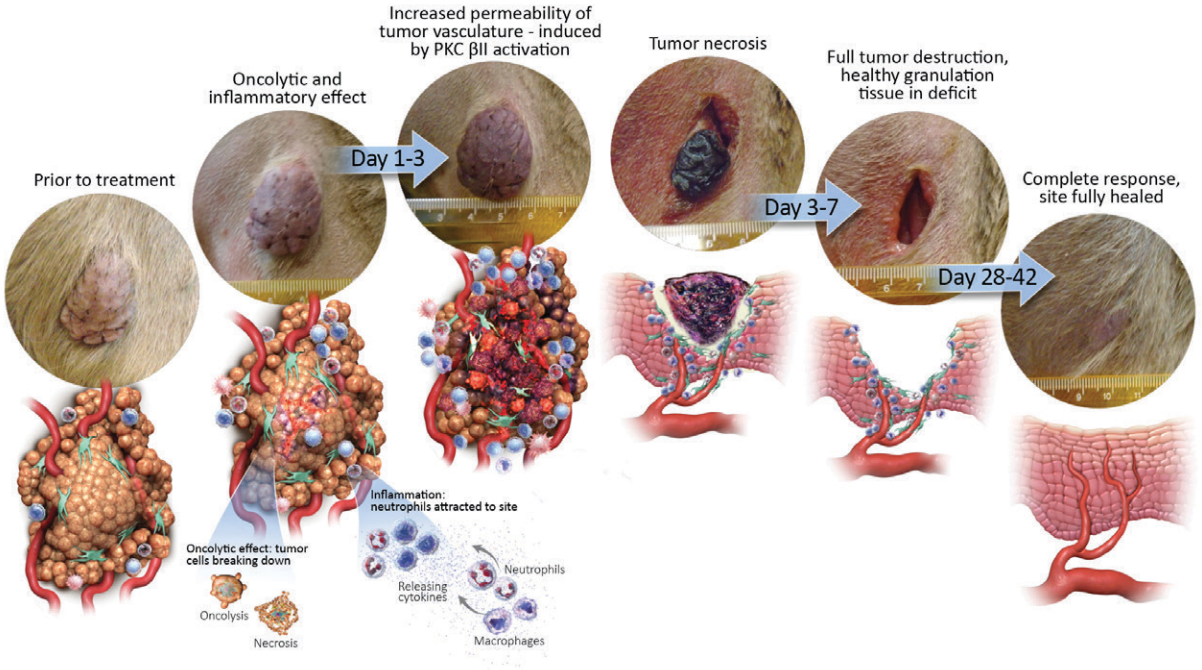
10. MECHANISM OF ACTION

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 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 time is possible.



This targeted mode of action is clinically displayed in the following case. An 11-year-old Jack Russell Terrier was treated for a 0.5cm^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: 01-012
11 years, 8 months
Jack Russell Terrier

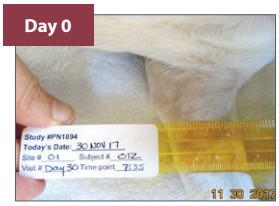
Case Summary: Desexed female Jack Russell Terrier. Previously had a MCT from a different location removed surgically. Part of control; received tigilanol tiglate treatment Day 30.

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

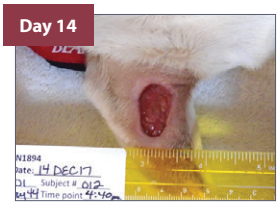
Day 1

- Bruising, swelling, pain and heat

Day 7

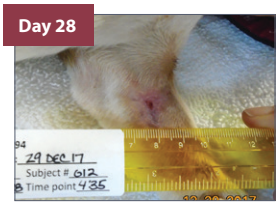
- Starting to granulate
- Necrotic tissue present
- Serous discharge

Day 14



- Wound granulation tissue and wound contracture

Day 28



- Small scab at the treatment site

Day 42

- Scar at treated site

11. SUMMARY

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

- Use STELFONTA for the treatment of nonmetastatic cutaneous MCTs anywhere on the body and subcutaneous MCTs ***only*** located below 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.
- Prior to the injection, confirm with the pet owner that the concomitant medications have been provided, commencing 2 days prior.
- 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.
- Use caution to avoid accidental self-injection and wear appropriate PPE.
- Only treat tumors with an intact surface – free of ulceration and unhealed biopsy sites – to minimize STELFONTA leakage.
- Wait 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.
- Treatment site is to remain uncovered; if covering is deemed essential, only cover the site with a loose gauze bandage.

12. REFERENCES

1. STELFONTA® (tigilanol tiglate injection) prescribing information, US. 2020
2. Cullen, J.K., Boyle, G.M., Yap, PY. *et al*. *Activation of PKC supports the anticancer activity of tigilanol tiglate and related epoxytiglianes.* Sci Rep 11, 207 (2021). https://doi.org/10.1038/s41598-020-80397-9
3. De Ridder TR, Campbell JE, Burke-Schwarz C, *et al*. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). J Vet Intern Med. 2020;1–15. https://doi.org/10.1111/jvim.15806
4. Camus M, et al. Cytologic criteria for mast cell tumor grading in dogs. Veterinary Pathology. 2016. Vol 53. 1117-1123. DOI: 10.1177/03009858166721
5. Reddell P, *et al.* Wound formation, size and healing after mast cell tumor injection of tigilanol tiglate treatment in dogs. Journal of Internal Veterinary Medicine. 2020. DOI: 10.1111/jvim.16009
6. Ladizinsky D, Roe D. New insights into oxygen therapy for wound healing. Wounds Res. 2010;22(12):294-300.17.
7. Yip WL. Influence of oxygen on wound healing. Int Wound J. 2015;12(6):620-624.18.
8. Sen CK. Wound healing essentials: let there be oxygen. Wound Repair Regen. 2009;17(1):1-18.
9. Jones PD, Campbell JE, Brown G, Johannes CM, Reddell P. Recurrence-free interval 12 months after local treatment of mast cell tumors in dogs using intratumoral injection of tigilanol tiglate. J Vet Intern Med.2020;1–5. https://doi.org/10.1111/jvim.16018

IMPORTANT SAFETY INFORMATION

Call Virbac Veterinary Technical Product Support for case consultation at 1.800.338.3659.

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

Brief Summary: Before using STELFONTA® (tigilanol tiglate injection) consult the product insert, a summary of which follows:

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

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 on the product insert).**

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 on the product insert).**
- **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 on the product insert).**
- **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 on the product insert).**

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

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

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

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

Dosing Instructions: STELFONTA is injected into the tumor at a dose of **0.5 mL per cm³** of tumor volume, as determined by measuring the tumor and calculating the dose based on **0.5 x length x width x height.**

The Tumor Volume is not to exceed 10 cm³. The dose of STELFONTA is not to exceed 0.25 mL/kg body weight. The dose is not to 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.

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 on the product insert).

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

Wear disposable gloves when cleaning the treated tumor site to avoid contact with any residual drug. Thoroughly wash your skin that comes in contact with the treated tumor site, wound, or wound discharge.

STELFONTA may cause side effects, even at the prescribed dose. Ensure the dog receives their prescribed medications to decrease the potential for severe, life-threatening side effects from mast cell degranulation. Counsel owners to monitor the dog during the healing process and contact their veterinarian if they notice excessive pain, lameness, tiredness, refusal to eat for more than one day, repeated vomiting or diarrhea, trouble breathing, changes to the treated tumor site (including increased or excessive swelling and bruising, extensive wound formation, increased irritation) or any other symptoms that concern them.

PRECAUTIONS: STELFONTA® (tigilanol tiglate injection) has not been evaluated in dogs with signs of systemic disease due to the mast cell tumor(s).

STELFONTA is not intended for the treatment of metastatic mast cell tumors. The safe and effective use of STELFONTA has not been evaluated for simultaneous treatment of more than one mast cell tumor. The safe and effective use of STELFONTA has not been evaluated in dogs with a mast cell tumor volume >10 cm³.

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

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

The safe use of STELFONTA has not been evaluated in dogs with concurrent diseases that may result in delayed wound healing. After treatment with STELFONTA, dogs may require additional care of the treated site to aid in the healing process. An Elizabethan collar or a non-constricting dry gauze bandage may be needed to prevent the dog from self-traumatizing the treated site.

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

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

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

Adverse Reactions: In a field study, the most common adverse reactions seen out of 117 dogs included wound formation (94%), injection site pain (52.1%), lameness in the treated limb (24.8%), vomiting (20.5%), diarrhea (20.5%), and hypoalbuminemia (18%). 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 of the product insert.

Wound Formation

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

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

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

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

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

Effectiveness: See full prescribing information for details on effectiveness.

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

Approved by FDA under NADA # 141-541

Distributed by Virbac AH, Inc.
P.O Box 162059,
Fort Worth, Texas 76161
Tel. 1-800-338-3659
Version date: August 2020