ANNEX I

SUMMARY PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

STELFONTA 1 mg/ml solution for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Tigilanol tiglate 1 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For the treatment of non-resectable, non-metastatic (WHO staging) subcutaneous mast cell tumours located at or distal to the elbow or the hock, and non-resectable, non-metastatic cutaneous mast cell tumours in dogs.
Tumours must be less than or equal to 8 cm^3 in volume, and must be accessible to intratumoral injection.

4.3 Contraindications

In order to minimise product leakage from the tumour surface upon injection, do not use in mast cell tumours with a broken surface.
Do not administer the product directly into the surgical margins following the surgical removal of a tumour.

4.4 Special warnings for each target species

The effect of STELFONTA on mast cell tumours is restricted to the location of injection, as it is not systemically active. STELFONTA should therefore not be used in case of metastatic disease.
Treatment does not prevent the development of *de novo* mast cell tumours.
Treatment causes a change in the tissue architecture. It is therefore unlikely that an accurate histological tumour grading can be obtained after treatment.

4.5 Special precautions for use

Special precautions for use in animals:

The product must strictly be administered intratumorally, as other routes of injections are associated with adverse reactions. Unintentional intravenous (IV) administration should be avoided at all times, since this is expected to cause severe systemic effects. After injection of tigilanol tiglate into the subcutaneous tissues, even at low concentrations/doses, treated dogs exhibited restlessness and vocalisation, as well as severe local reactions at the injection sites. Injection into non-neoplastic tissues can cause a transient, local response resulting in localised inflammation, oedema, redness and pain. Cases of wound formation have been observed following subcutaneous injection of tigilanol tiglate.

Treatment induces a substantial local inflammatory reaction, generally lasting up to approximately 7 days. More information on wounds is given in sections 4.6 and 5.1. Consideration should be given to providing additional analgesia if required, based on clinical assessment by the veterinarian. Any bandaging used must be loose to allow for anticipated local oedema.

Treating tumours in mucocutaneous locations (eyelids, vulva, preputial opening, anus, mouth) and at the extremities (e.g. paws, tail) could impair functionality due to the loss of tissue associated with the treatment.

The product is an irritant; therefore, use of the product in the proximity of sensitive tissues, in particular the eye, should be avoided.

In order to reduce the occurrence of local and systemic adverse events related to mast cell degranulation and histamine release, all treated dogs must be provided with concomitant supportive therapies, consisting of corticosteroids and H1 and H2 receptor blocking agents, both before and after treatment (see section 4.9).

Owners should be advised to check for signs of potential mast cell degranulation reactions. These include vomiting, anorexia, severe pain, lethargy, inappetence or extensive swelling. If signs of degranulation are observed, the treating veterinarian should be contacted straight away, so that appropriate treatment can be started immediately.

Following treatment, drinking water should always be available.

The safety of the product has not been established in dogs that are less than 12 months of age.

Tumours that lie completely in the subcutaneous tissue with no dermal involvement may have difficulty in creating an exit site for necrotic tissue removal. This may necessitate an incision to allow for drainage of necrotic tissue.

The product is to be administered only by a veterinarian.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Special precautions to be taken by the professional user (veterinarian):

Veterinarians should inform the pet owner about the special precautions to be taken at home.

People with known hypersensitivity to tigilanol tiglate or to propylene glycol should avoid contact with the product. The product is an irritant and potentially a skin sensitiser.

Accidental self-injection may result in severe local inflammatory reactions, including pain, swelling, redness and potential wound formation/necrosis, which may take several months to resolve. Caution is required during treatment to avoid self-injection. Dogs undergoing treatment with the product should be adequately restrained, including by sedation if necessary. Use a Luer lock syringe to administer the product. In case of accidental self-injection, seek medical advice immediately and show the package insert to the physician.

Accidental exposure to skin, eye, or by ingestion should be avoided. Leakage of the product from the site of injection may occur directly after administration. Personal protective equipment consisting of disposable impervious gloves and protective eye glasses should be worn when handling the product and/or touching the site of injection. In case of dermal or ocular exposure, repeatedly wash the exposed skin or eye 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 leaflet.

The safety of the veterinary medicinal product has not been established during pregnancy or lactation. Pregnant women and breastfeeding women should take care to avoid accidental self-injection, contact with the injection site, leaking product and tumour debris.

Special precautions to be taken by the animal owner:

Low levels of tigilanol tiglate residues might be present in the wound debris. In case of severe leakage of wound debris, which may occur in the first weeks following administration of the product, the wound should be covered. If however covering the wound is contraindicated due to its healing, the dog must be kept away from children. Wound debris should only be handled with protective equipment (disposable gloves).

In case of any contact with wound debris, the affected area(s) on the person should be thoroughly washed. Contaminated areas or bedding should be thoroughly cleaned/washed.

The safety of the veterinary medicinal product has not been established during pregnancy or lactation. Pregnant women and breastfeeding women should take care to avoid contact with the injection site, leaking product and tumour debris.

4.6 Adverse reactions (frequency and seriousness)

Manipulation of mast cell tumours may cause the tumour cells to degranulate. Degranulation can result in swelling and redness at and around the tumour site as well as systemic clinical signs, including stomach ulceration and bleeding and potentially life-threatening complications, including hypovolemic shock and/or a systemic inflammatory response. In order to reduce the occurrence of local and systemic adverse events related to mast cell degranulation and histamine release, all treated dogs must be provided with concomitant supportive therapies, consisting of corticosteroids and H1 and H2 receptor blocking agents, both before and after treatment.

Formation of wounds is an intended reaction to treatment and is expected following the use of this veterinary medicinal product in all cases. In the pivotal field study, a maximum wound surface area was observed at 7 days after treatment for most patients, although in a small number of cases wound size increased up to 14 days post treatment. Most wounds were completely re-epithelised within 28 to 42 days of treatment (with individual cases that healed by day 84. In most cases, the wound area will increase with increasing tumour size. However, this is not a reliable predictor for wound size or severity, and duration of healing. These wounds resolve by second intention healing with minimal intervention. Wound management measures may be required as deemed necessary by the responsible veterinarian. The speed of healing is related to the size of the wound.

Commonly reported local adverse events, such as pain, injection site bruising/erythema/oedema, lameness in a treated limb and wound formation, are related to localised pathology. The wounds may evolve to cover significantly larger areas than the original size of the tumour.

<u>Very common</u>
Mild to moderate:
Pain upon injection.
Wound formation at the injection site, associated with pain and lameness.
Vomiting and tachycardia.

<u>Common</u>

Severe:
Lameness, pain, wound formation at the injection site and scar contraction.
Lethargy.

Mild to moderate:
Enlargement of the draining lymph node, wound infection, bruising, erythema and oedema.
Diarrhoea, anorexia, weight loss, tachypnoea, lethargy, pyrexia, cystitis, reduced appetite, new neoplastic mass, personality/behaviour changes, pruritis, tremor and skin ulceration.
Anaemia, neutrophilia, increased band neutrophils, hypoalbuminemia, leucocytosis, monocytosis, and elevated creatine kinase.

Uncommon
Severe:
Infection/cellulitis, wound slough.
Anorexia, reduced appetite, somnolence, tachycardia, neuropathy and pruritis.
Leucocytosis, increased band neutrophils, thrombocytopenia and elevated ALT.
Seizures.

Mild to moderate:
Formation of a transient peri-wound nodule.
Dehydration, haemorrhage, cholestasis, polydipsia, polyuria, regurgitation, melaena, flatulence, urinary incontinence, inappropriate defecation, maculopapular rash, abrasion, dermatitis, licking, restlessness.
Proteinuria, thrombocytosis, elevated ALT and ALP, elevated bilirubin, elevated BUN, elevated GGT, elevated triglyceride, and hyperkalaemia.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established in dogs during pregnancy or lactation or in dogs intended for breeding. The use of the veterinary medicinal product is therefore not recommended in these animals.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

No specific interaction studies have been performed with the veterinary medicinal product, but in field trials no interactions were observed when administered concomitantly with corticosteroids (prednisone / prednisolone) and H1 and H2 receptor blocking agents (e.g. diphenhydramine / chlorpheniramine and famotidine), or with opioid analgesics (e.g. tramadol hydrochloride).

The concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) has not been investigated in the pivotal clinical trial, as they are not recommended for concomitant use with corticosteroids.

4.9 Amount(s) to be administered and administration route

Intratumoral use.

STELFONTA is provided as a single use vial for intratumoral (IT) injection.

The surface of the mast cell tumour (MCT) to be treated must be intact, in order to minimize the leakage of the product after IT injection.

Before administering this veterinary medicinal product, it is essential that concomitant treatments (corticosteroids, H1 and H2 receptor blocking agents) are initiated to address the risk of mast cell degranulation. See 'concomitant treatment' below.

Administer the veterinary medicinal product as a single dose of 0.5 ml per cm^3 of tumour volume, as determined on the day of dosing (following initiation of concomitant treatments) by the equations below:

Calculate the tumour size: Tumour Volume (cm^3) = ½ (length (cm) x width (cm) x height (cm))
Calculate the dose: Dose volume of STELFONTA (ml) to inject = Tumour Volume (cm^3) x 0.5

The **maximum dose** of the veterinary medicinal product is 0.15 ml/kg body weight (corresponding to 0.15 mg tigilanol tiglate/kg bw), with no more than 4 ml administered per dog, regardless of the number of tumours treated, the tumour volume or the dog's body weight.

The **minimum dose** of the veterinary medicinal product is 0.1 ml, regardless of the tumour volume or the dog's body weight.

Appropriate hygienic measures (such as clipping of the treated area) should be performed prior to treatment.

Once the correct dose of the veterinary medicinal product has been determined, draw up the required volume into a sterile Luer lock syringe with a 23-27 gauge needle.

Caution should be used to avoid manipulation of the tumour to minimise the risk of degranulation. To inject, insert the needle into the tumour mass through a single injection site. Whilst applying even pressure on the syringe plunger, move the needle back and forth in a fanning manner to inject the veterinary medicinal product into different locations within the tumour. Care should be taken to restrict injections to the tumour mass only (no injection into the margins or beyond the periphery of the tumour).

When the total dose of the veterinary medicinal product has been administered, pause for up to 5 seconds to allow tissue dispersion before removing the needle from the tumour.
The site of application should be covered for the first day after treatment in order to prevent direct contact with residual or leaking product. Handle the cover with gloves to avoid contact with the product. In case of severe leakage of wound debris, which may occur in the first weeks following administration of the product, the wound should be covered.

If tumour tissue remains 4 weeks after the initial treatment and the surface of the residual mass is intact, a second dose may be administered. The size of the residual tumour should be measured and the new dose calculated before the second dose is administered.

Concomitant treatment

The following medications must be given concurrently with each treatment with STELFONTA to address the potential for mast cell degranulation:

Corticosteroids (oral prednisone or prednisolone): start treatment 2 days prior to the treatment with STELFONTA at a total dose of 1 mg/kg, administered at 0.5 mg/kg orally, twice a day (PO BID), and continue daily until 4 days post-treatment (i.e. for 7 days in total). Then reduce the corticosteroid dose to a single dose of 0.5 mg/kg orally, once a day (PO OID) for a further 3 days.

H1 and H2 receptor blocking agents: start treatment on the day of administration of STELFONTA and continue for 8 days (see section 5.1).

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

In a laboratory safety study conducted in young healthy male Beagle dogs, overdose signs such as vomiting were observed following a 15 minute intravenous infusion of 0.05 mg tigilanol tiglate/kg b.w. Further signs such as swaying gait, tachypnoea and lateral position occurred following a 15 minute intravenous infusion at a dose rate of 0.10-0.15 mg/kg b.w. These signs were severe, but self-limiting. Apathy, mydriasis, seizures and finally death were seen following a 15 minute intravenous infusion at 0.225 mg/kg b.w.

There is no known antidote for overdosage of STELFONTA. In case of adverse events during or following overdosage, supportive treatment should be administered at the discretion of the attending veterinarian.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agent – Protein kinase C activator, tigilanol tiglate
ATC Vet Code: QL01XX91

5.1 Pharmacodynamic properties

The pharmacodynamic effects of tigilanol tiglate have been investigated in several *in vitro* and *in vivo* mice model studies; no pharmacodynamic studies were performed in dogs or on mast cell tumour cells. In these non-clinical pharmacology studies, it was demonstrated that tigilanol tiglate activates the protein kinase C (PKC) signalling cascade. In addition, necrosis is induced in cells that are in direct contact with tigilanol tiglate.

A single intratumoral injection of tigilanol tiglate was shown to elicit a rapid and localised inflammatory response, via activation of PKC, loss of integrity of the tumour vasculature and induction of tumour cell death. These processes led to haemorrhagic necrosis and destruction of the tumour mass.

In dogs treated with tigilanol tiglate, treatment results in an acute inflammatory response with swelling and erythema extending to the tumour margins and immediate surrounds. This acute inflammatory response generally resolves within 48 to 96 hours. Necrotic destruction of the tumour is seen within 4 to 7 days of treatment, but sometimes takes longer. In dogs, this is characterised by blackening, shrinkage and ‘softening’ of the tumour and by a leakage of a thick discharge composed of the tumour remnants and dried blood. The necrotic tumour mass will begin to fall away through the ischaemic surface forming a wound with a pocket or crater-like defect. Healthy granulation tissue then rapidly fills the newly-created wound bed, with full wound closure occurring typically within 4 to 6 weeks.

The efficacy and safety of the veterinary medicinal product was evaluated in a multi-centre, clinical study using 123 client owned dogs with a single mast cell tumour that measured up to 10 cm^3 at the time of initial treatment.

Dogs aged 1 year or older were included in the study if they were diagnosed with a subcutaneous MCT located at or distal to the elbow or the hock, or with a cutaneous MCT, at WHO stage Ia or IIIa without regional lymph node involvement, or clinical signs of systemic disease. Dogs included had a measurable tumour less than 10 cm^3 that was not excoriated or abraded, and which was not a recurrence following surgery, radiation therapy or systemic therapy.

The following concomitant medication was given. Prednisone or prednisolone was initiated 2 days prior to study treatment at a dose of 0.5 mg/kg orally twice daily for 7 days (2 days before, on the day of treatment, and 4 days post treatment), then 0.5 mg/kg once daily for an additional 3 days. Famotidine (0.5 mg/kg orally twice daily) and diphenhydramine (2 mg/kg orally twice daily) were initiated on the day of study treatment and continued for 7 days. Treatment with the veterinary medicinal product was given once on treatment day and again 4 weeks later if any residual tumour was detected. Tumour response was measured via RECIST scores: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Four weeks after first treatment, 60/80 (75%) achieved a complete response (CR), and another four weeks later CR was observed in 8/18 (44.4%) of remaining dogs that were treated twice. Therefore, overall 68/78 (87.2%) of dogs achieved a CR result after one to two doses of the veterinary medicinal product. Of the treated dogs with CR, which were available for follow up 8 and 12 weeks after the last injection, 59/59 (100%) and 55/57 (96%), respectively, remained disease free at the site of the treated tumour.

Efficacy of the product in high grade tumours (as determined by cytological grading) was only evaluated in a limited number of cases. Ten out of 13 tumours in the study that were categorised as either "high grade" or "suspected high grade" received STELFONTA. Of these, 5 achieved a complete response after 1 or 2 treatments, four of which were still tumour free after 84 days after their final treatment. From the 5 complete response cases, 3 were confirmed being "high grade", and 2 were of "suspected high grade".

In this multi-centre clinical study, 98% of dogs treated with the veterinary medicinal product developed a wound at the site of the treated tumour (an intended reaction to treatment). 56.5% of these wounds were fully healed at 28 days post treatment. By 42 days post treatment, 76.5% of wounds were fully healed. By 84 days post treatment, 96.5% of wounds were fully healed.

5.2 Pharmacokinetic particulars

Pharmacokinetic parameters of tigilanol tiglate were evaluated in a study monitoring systemic plasma levels of 10 dogs following intratumoral injection into 5 cutaneous and 5 subcutaneous MCTs with the recommended treatment dose. A dose of 0.5 mg/cm^3 (= 0.5 ml/cm^3) tumour volume was used in animals with tumour volumes ranging from 0.1 to 6.8 cm^3, resulting in dose rates ranging from 0.002 to 0.145 mg/kg bodyweight (mean 0.071 mg/kg bodyweight).

Due to varying dose rates and limitations in sampling timepoints, a reliable determination of C_{max} and AUC values could not be obtained, but measurements indicated a mean C_{max} of 5.86 ng/ml (range: 0.36─11.1 ng/ml) and a mean AUC_{last} of 14.59 h*ng/ml (range: 1.62─28.92 h*ng/ml). Large inter-individual variability has been observed when determining half-life following intratumoral injection ranging from 1.24─10.8 hours. Tigilanol tiglate appears to exhibit flip-flop kinetics (sustained release rate) since a considerable shorter half-life of 0.54 hours was determined after intravenous infusion of 0.075 mg/kg in 12 dogs.

In vitro metabolite screening in canine liver microsomes demonstrated a half-life of tigilanol tiglate in hepatocytes of 21.8 minutes and a total of thirteen metabolites. Metabolic products were more polar and oxygenated than the parent compound. Studies have shown some functional group substitutions of

this nature resulting in reduced *in vitro* biological activity (>60X reduction of activity on PKC compared with parent compound).

The route of excretion of tigilanol tiglate or its metabolites has not been determined. Analysis of urine, faeces and saliva samples from dogs treated with the veterinary medicinal product show the appearance of tigilanol tiglate in isolated samples with no trend or consistency at levels of 11─44 ng/g (ml).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Sodium acetate trihydrate
Acetic acid, glacial
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 48 months.
Shelf life after first opening the immediate packaging: use immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Colourless glass vial with coated chlorobutyl rubber stopper, aluminium seal and flip-off polypropylene top button, containing 2 ml.

Pack size:
1 vial per cardboard box.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

QBiotics Netherlands B.V.
Prinses Margrietplantsoen 33
2595 AM The Hague
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/19/248/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15/01/2020

10. DATE OF REVISION OF THE TEXT

<{DD month YYYY}>

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Virbac
1ère avenue
2065m L I D
06516 Carros
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

· CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

For use by veterinary surgeons only.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

STELFONTA 1 mg/ml solution for injection for dogs
tigilanol tiglate

2. STATEMENT OF ACTIVE SUBSTANCES

tigilanol tiglate 1 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

2 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intratumoral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.
Accidental injection is dangerous.

10. EXPIRY DATE

EXP {month/year}
Once broached use immediately.

11. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

QBiotics Netherlands B.V.
Prinses Margrietplantsoen 33
2595 AM The Hague
Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/19/248/001

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 2 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

STELFONTA 1 mg/ml solution for injection for dogs
tigilanol tiglate

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

tigilanol tiglate 1 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

2 ml

4. ROUTE OF ADMINISTRATION

Intratumoral use.

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once broached use immediately.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
STELFONTA 1 mg/ml solution for injection for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
QBiotics Netherlands B.V.
Prinses Margrietplantsoen 33
2595 AM The Hague
Netherlands

Manufacturer responsible for batch release:
Virbac
1ère avenue
2065m L I D
06516 Carros
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

STELFONTA 1 mg/ml solution for injection for dogs
Tigilanol tiglate

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each ml contains:

Active substance:
Tigilanol tiglate 1 mg

4. INDICATION(S)

For the treatment of non-resectable, non-metastatic (WHO staging) subcutaneous mast cell tumours located at or distal to the elbow or the hock, and non-resectable, non-metastatic cutaneous mast cell tumours in dogs. Tumours must be less than or equal to 8 cm^3 in volume, and must be accessible to intratumoral injection.

5. CONTRAINDICATIONS

In order to minimise product leakage from the tumour surface upon injection, do not use in mast cell tumours with a broken surface.
Do not administer the product directly into the surgical margins following the surgical removal of a tumour.

6. ADVERSE REACTIONS

Manipulation of mast cell tumours may cause the tumour cells to degranulate. Degranulation can result in swelling and redness at and around the tumour site as well as systemic clinical signs, including stomach ulceration and bleeding and potentially life-threatening complications, including hypovolemic shock and/or a systemic inflammatory response. In order to reduce the occurrence of

local and systemic adverse events related to mast cell degranulation and histamine release, all treated dogs must be provided with concomitant supportive therapies, consisting of corticosteroids and H1 and H2 receptor blocking agents, both before and after treatment.

Formation of wounds is an intended reaction to treatment and is expected following the use of this veterinary medicinal product in all cases. In the pivotal field study, a maximum wound surface area was observed at 7 days after treatment for most patients, although in a small number of cases wound size increased up to 14 days post treatment. Most wounds were completely re-epithelised within 28 to 42 days of treatment (with individual cases that healed by day 84. In most cases, the wound area will increase with increasing tumour size. . However, this is not a reliable predictor for wound size or severity and duration of healing. These wounds resolve by second intention healing with minimal intervention. Wound management measures may be required as deemed necessary by the responsible veterinarian. The speed of healing is related to the size of the wound.

Commonly reported local adverse events, such as pain, injection site bruising/erythema/oedema, lameness in a treated limb and wound formation, are related to localised pathology. The wounds may evolve to cover significantly larger areas than the original size of the tumour.

Very common
Mild to moderate:
Pain upon injection.
Wound formation at the injection site, associated with pain and lameness.
Vomiting and tachycardia.

Common
Severe:
Lameness, pain, wound formation at the injection site and scar contraction.
Lethargy.

Mild to moderate:
Enlargement of draining lymph node, wound infection, bruising, erythema and oedema.
Diarrhoea, anorexia, weight loss, tachypnoea, lethargy, pyrexia, cystitis, reduced appetite, new neoplastic mass, personality/behaviour changes, pruritis, tremor and skin ulceration.
Anaemia, neutrophilia, increased band neutrophils, hypoalbuminemia, leucocytosis, monocytosis, and elevated creatine kinase.

Uncommon
Severe:
Infection/cellulitis, wound slough.
Anorexia, reduced appetite, somnolence, tachycardia, neuropathy and pruritis.
Leucocytosis, increased band neutrophils, thrombocytopenia and elevated ALT.
Seizures.

Mild to moderate:
Formation of a transient peri-wound nodule.
Dehydration, haemorrhage, cholestasis, polydipsia, polyuria, regurgitation, melaena, flatulence, urinary incontinence, inappropriate defecation, maculopapular rash, abrasion, dermatitis, licking, restlessness.
Proteinuria, thrombocytosis, elevated ALT and ALP, elevated bilirubin, elevated BUN, elevated GGT, elevated triglyceride, and hyperkalaemia.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

STELFONTA is provided as a single use vial for intratumoral (IT) injection.

The surface of the mast cell tumour (MCT) to be treated must be intact, with the expectation of minimal product leakage from the tumour surface after IT injection.

Before administering this veterinary medicinal product, it is essential that concomitant treatments (corticosteroids, H1 and H2 receptor blocking agents) are initiated to address the risk of mast cell degranulation. See 'concomitant treatment' below.

Administer the veterinary medicinal product as a single dose of 0.5 ml per cm^3 of tumour volume, as determined on the day of dosing (following initiation of concomitant treatments) by the equations below:

Calculate the tumour size: Tumour Volume (cm^3) = ½ (length (cm) x width (cm) x height (cm))
Calculate the dose: Dose volume of STELFONTA (ml) to inject = Tumour Volume (cm^3) x 0.5

The **maximum dose** of the veterinary medicinal product is 0.15 ml/kg body weight (corresponding to 0.15 mg tigilanol tiglate/kg bw), with no more than 4 ml administered per dog, regardless of the number of tumours treated, the tumour volume or the dog's body weight.

The **minimum dose** of the veterinary medicinal product is 0.1 ml, regardless of the tumour volume or the dog's body weight.

9. ADVICE ON CORRECT ADMINISTRATION

Appropriate hygienic measures (such as clipping of the treated area) should be performed prior to treatment.

Once the correct dose of the veterinary medicinal product has been determined, draw the required volume into a sterile Luer lock syringe with a 23-27 gauge needle.

Caution should be used to avoid manipulation of the tumour to minimise the risk of degranulation. To inject, insert the needle into the tumour mass through a single injection site. Whilst applying even pressure on the syringe plunger, move the needle back and forth in a fanning manner to inject the veterinary medicinal product into different locations within the tumour. Care should be taken to restrict injections to the tumour mass only (no injection into the margins or beyond the periphery of the tumour).

When the total dose of the veterinary medicinal product has been administered, pause for up to 5 seconds to allow tissue dispersion before removing the needle from the tumour.

The site of application should be covered for the first day after treatment in order to prevent direct contact with residual or leaking product. Handle the cover with gloves to avoid contact with the product. In case of severe leakage of wound debris, which may occur in the first weeks following administration of the product, the wound should be covered.

If tumour tissue remains 4 weeks after the initial treatment and the surface of the residual mass is intact, a second dose may be administered. The size of the residual tumour should be measured and the new dose calculated before the second dose is administered.

Concomitant treatment

The following medications must be given concurrently with each treatment with STELFONTA to address the potential for mast cell degranulation:

Corticosteroids (oral prednisone or prednisolone): start treatment 2 days prior to the treatment with STELFONTA at a total dose of 1 mg/kg, administered at 0.5 mg/kg orally, twice a day (PO BID), and continue daily until 4 days post-treatment (i.e. for 7 days in total). Then reduce the corticosteroid dose to a single dose of 0.5 mg/kg orally, once a day (PO OID) for a further 3 days.

H1 and H2 receptor blocking agents: start treatment on the day of administration of STELFONTA and continue for 8 days.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of sight and reach of children.

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Once broached, use immediately.

Do not use this veterinary medicinal product after the expiry date which is stated on the label or carton after "EXP". The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

Special warnings for each target species:

The effect of STELFONTA on mast cell tumours is restricted to the location of injection, as it is not systemically active. STELFONTA should therefore not be used in case of metastatic disease. Treatment does not prevent the development of *de novo* mast cell tumours. Treatment causes a change in the tissue architecture. It is therefore unlikely that an accurate histological tumour grading can be obtained after treatment.

Special precautions for use in animals:

The product must strictly be administered intratumorally, as other routes of injections are associated with adverse reactions. Unintentional intravenous (IV) administration should be avoided at all times, since this is expected to cause severe systemic effects.

After injection of tigilanol tiglate into the subcutaneous tissues, even at low concentrations/doses, treated dogs exhibited restlessness and vocalisation, as well as severe local reactions at the injection sites. Injection into non-neoplastic tissues can cause a transient, local response resulting in localised inflammation, oedema, redness and pain. Cases of wound formation have been observed following subcutaneous injection of tigilanol tiglate.

Treatment induces a substantial local inflammatory reaction, generally lasting up to approximately 7 days. Consideration should be given to providing additional analgesia if required, based on clinical assessment by the veterinarian. Any bandaging used must be loose to allow for anticipated local oedema.

Treating tumours in mucocutaneous locations (eyelids, vulva, preputial opening, anus, mouth) and at the extremities (e.g. paws, tail) could impair functionality due to the loss of tissue associated with the treatment.

The product is an irritant; therefore, use of the product in the proximity of sensitive tissues, in particular the eye, should be avoided.

In order to reduce the occurrence of local and systemic adverse events related to mast cell degranulation and histamine release, all treated dogs must be provided with concomitant supportive therapies, consisting of corticosteroids and H1 and H2 receptor blocking agents, both before and after treatment.

Owners should be advised to check for signs of potential mast cell degranulation reactions. These include vomiting, anorexia, severe pain, lethargy, inappetence or extensive swelling. If signs of degranulation are observed, the treating veterinarian should be contacted straight away, so that appropriate treatment can be started immediately.

Following treatment, drinking water should always be available.

The safety of the product has not been established in dogs that are less than 12 months of age.

Tumours that lie completely in the subcutaneous tissue with no dermal involvement may have difficulty in creating an exit site for necrotic tissue removal. This may necessitate an incision to allow for drainage of necrotic tissue.

The product is to be administered only by a veterinarian.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Special precautions to be taken by the professional user (veterinarian):

Veterinarians should inform the pet owner about the special precautions to be taken at home.

People with known hypersensitivity to tigilanol tiglate or to propylene glycol should avoid contact with the product. The product is an irritant and potentially a skin sensitiser.

Accidental self-injection may result in severe local inflammatory reactions, including pain, swelling, redness and potential wound formation/necrosis, which may take several months to resolve. Caution is required during treatment to avoid self-injection. Dogs undergoing treatment with the product should be adequately restrained, including by sedation if necessary. Use a Luer lock syringe to administer the product. In case of accidental self-injection, seek medical advice immediately and show the package insert to the physician.

Accidental exposure to skin, eye, or by ingestion should be avoided. Leakage of the product from the site of injection may occur directly after administration. Personal protective equipment consisting of disposable impervious gloves and protective eye glasses should be worn when handling the product and/or touching the site of injection. In case of dermal or ocular exposure, repeatedly wash the exposed skin or eye 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 leaflet.

The safety of the veterinary medicinal product has not been established during pregnancy or lactation. Pregnant women and breastfeeding women should take care to avoid accidental self-injection, contact with the injection site, leaking product and tumour debris.

Special precautions to be taken by the animal owner:

Low levels of tigilanol tiglate residues might be present in the wound debris. In case of severe leakage of wound debris, which may occur in the first weeks following administration of the product, the wound should be covered. If however covering the wound is contraindicated due to its healing, the dog must be kept away from children. Wound debris should only be handled with protective equipment (disposable gloves).

In case of any contact with wound debris, the affected area(s) on the person should be thoroughly washed. Contaminated areas or bedding should be thoroughly cleaned/washed.

The safety of the veterinary medicinal product has not been established during pregnancy or lactation. Pregnant women and breastfeeding women should take care to avoid contact with the injection site, leaking product and tumour debris.

Pregnancy, lactation and fertility:

The safety of the veterinary medicinal product has not been established during pregnancy or lactation or in dogs intended for breeding. The use of the veterinary medicinal product is therefore not recommended in these animals.

Interaction with other medicinal products and other forms of interaction:

None known.

No specific interaction studies have been performed with the veterinary medicinal product, but in field trials no interactions were observed when administered concomitantly with corticosteroids (prednisone / prednisolone) and H1 and H2 receptor blocking agents (e.g. diphenhydramine / chlorpheniramine and famotidine), or with opioid analgesics (e.g. tramadol hydrochloride).

The concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) has not been investigated in the pivotal clinical trial, as they are not recommended for concomitant use with corticosteroids.

Overdose (symptoms, emergency procedures, antidotes):

In a laboratory safety study conducted in young healthy male Beagle dogs, overdose signs such as vomiting were observed following a 15 minute intravenous infusion of 0.05 mg tigilanol tiglate/kg b.w. Further signs such as swaying gait, tachypnoea and lateral position occurred following a 15 minute intravenous infusion at a dose rate of 0.10-0.15 mg/kg b.w. These signs were severe, but self-limiting. Apathy, mydriasis, seizures and finally death were seen following a 15 minute intravenous infusion with 0.225 mg/kg b.w.

There is no known antidote for overdosage of STELFONTA. In case of adverse events during or following overdosage, supportive treatment should be administered at the discretion of the attending veterinarian.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

15. OTHER INFORMATION

Pack size: 2 ml vial

Mechanism of action
The pharmacodynamic effects of tigilanol tiglate have been investigated in several *in vitro* and *in vivo* mice model studies; no pharmacodynamic studies were performed in dogs or on mast cell tumour cells. In these non-clinical pharmacology studies, it was demonstrated that tigilanol tiglate activates protein kinase C (PKC) signalling cascade. In addition, necrosis is induced in cells that are in direct contact with tigilanol tiglate.

A single intratumoral injection of tigilanol tiglate was shown to elicit a rapid and localised inflammatory response, via activation of PKC, loss of integrity of the tumour vasculature and induction of tumour cell death. These processes led to haemorrhagic necrosis and destruction of the tumour mass.

In dogs treated with tigilanol tiglate, treatment results in an acute inflammatory response with swelling and erythema extending to the tumour margins and immediate surrounds. This acute inflammatory response generally resolves within 48 to 96 hours. Necrotic destruction of the tumour is seen within 4 to 7 days of treatment but sometimes takes longer. In dogs, this is characterised by blackening, shrinkage and ‘softening’ of the tumour and by a leakage of a thick discharge composed of the tumour remnants and dried blood. The necrotic tumour mass will begin to fall away through the ischaemic surface forming a wound with a pocket or crater-like defect. Healthy granulation tissue then rapidly fills the newly-created wound bed, with full wound closure occurring typically within 4 to 6 weeks.

Effectiveness
The efficacy and safety of the veterinary medicinal product was evaluated in a multi-centre, clinical study using 123 client owned dogs with a single mast cell tumour that measured up to 10 cm^3 at the time of initial treatment.

Dogs aged 1 year or older were included in the study if they were diagnosed with a subcutaneous MCT located at or distal to the elbow or the hock, or with a cutaneous MCT, at WHO stage Ia or IIIa

without regional lymph node involvement, or clinical signs of systemic disease. Dogs included had a measurable tumour less than 10 cm^3 that was not excoriated or abraded, and which was not a recurrence following surgery, radiation therapy or systemic therapy.

The following concomitant medication was given. Prednisone or prednisolone was initiated 2 days prior to study treatment at a dose of 0.5 mg/kg orally twice daily for 7 days (2 days before, on the day of treatment, and 4 days post treatment), then 0.5 mg/kg once daily for an additional 3 days. Famotidine (0.5 mg/kg orally twice daily) and diphenhydramine (2 mg/kg orally twice daily) were initiated on the day of study treatment and continued for 7 days. Treatment with the veterinary medicinal product was given once on treatment day and again 4 weeks later if any residual tumour was detected. Tumour response was measured via RECIST scores: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Four weeks after first treatment, 60/80 (75%) achieved a complete response (CR), and another four weeks later CR was observed in 8/18 (44.4%) of remaining dogs that were treated twice. Therefore, overall 68/78 (87.2%) of dogs achieved a CR result after one to two doses of the veterinary medicinal product. Of the treated dogs with CR, which were available for follow up 8 and 12 weeks after the last injection, 59/59 (100%) and 55/57 (96%), respectively, remained disease free at the site of the treated tumour.

Efficacy of the product in high grade tumours (as determined by cytological grading) was only evaluated in a limited number of cases. Ten out of 13 tumours in the study that were categorised as either "high grade" or "suspected high grade" received STELFONTA. Of these, 5 achieved a complete response after 1 or 2 treatments, four of which were still tumour free after 84 days after their final treatment. From the 5 complete response cases, 3 were confirmed being "high grade", and 2 were of "suspected high grade".

In this multi-centre clinical study, 98% of dogs treated with the veterinary medicinal product developed a wound at the site of the treated tumour (an intended reaction to treatment). 56.5% of these wounds were fully healed at 28 days post treatment. By 42 days post treatment, 76.5% of wounds were fully healed. By 84 days post treatment, 96.5% of wounds were fully healed.

Pharmacokinetics
Pharmacokinetic parameters of tigilanol tiglate were evaluated in a study monitoring systemic plasma levels of 10 dogs following intratumoral injection into 5 cutaneous and 5 subcutaneous MCTs with the recommended treatment dose. A dose of 0.5 mg/cm^3 (= 0.5 ml/cm^3) tumour volume was used in animals with tumour volumes ranging from 0.1 to 6.8 cm^3, resulting in dose rates ranging from 0.002 to 0.145 mg/kg bodyweight (mean 0.071 mg/kg bodyweight).

Due to varying dose rates and limitations in sampling timepoints, a reliable determination of C_{max} and AUC values could not be obtained, but measurements indicated a mean C_{max} of 5.86 ng/ml (range: 0.36-11.1 ng/ml) and a mean AUC_{last} of 14.59 h*ng/ml (range: 1.62-28.92 h*ng/ml). Large inter-individual variability has been observed when determining half-life following intratumoral injection ranging from 1.24–10.8 hours. Tigilanol tiglate appears to exhibit flip-flop kinetics (sustained release rate) since a considerable shorter half-life of 0.54 hours was determined after intravenous infusion of 0.075 mg/kg in 12 dogs.

In vitro metabolite screening in canine liver microsomes demonstrated a half-life of tigilanol tiglate in hepatocytes of 21.8 minutes and a total of thirteen metabolites. Metabolic products were more polar and oxygenated than the parent compound. Studies have shown some functional group substitutions of this nature resulting in reduced *in vitro* biological activity (>60X reduction of activity on PKC compared with parent compound).

The route of excretion of tigilanol tiglate or its metabolites has not been determined. Analysis of urine, faeces and saliva samples from dogs treated with the veterinary medicinal product show the

appearance of tigilanol tiglate in isolated samples with no trend or consistency at levels of 11-44 ng/g (ml).

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

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