

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2006249423 B2**

(54) Title
Versatile high load concentrate compositions comprising metaflumizone for control of ecto-parasites

(51) International Patent Classification(s)
A01N 47/34 (2006.01) **A61K 31/175** (2006.01)

(21) Application No: **2006249423** (22) Date of Filing: **2006.05.18**

(87) WIPO No: **WO06/127399**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/683,949	2005.05.24	US

(43) Publication Date: **2006.11.30**

(44) Accepted Journal Date: **2011.11.10**

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(56) Related Art
WO 2006/042099
WO 2006/002984
EP 1 413 201

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 November 2006 (30.11.2006)

PCT

(10) International Publication Number
WO 2006/127399 A3

(51) International Patent Classification:
A61K 31/175 (2006.01) A01N 47/34 (2006.01)

(21) International Application Number:
PCT/US2006/019284

(22) International Filing Date: 18 May 2006 (18.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/683,949 24 May 2005 (24.05.2005) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
11 January 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2006/127399 A3

(54) Title: VERSATILE HIGH LOAD CONCENTRATE COMPOSITIONS COMPRISING METAFUMIZONE FOR CONTROL OF ECTO-PARASITES

(57) Abstract: High load concentrate compositions comprising metaflumizone, an optional bridging agent, a surfactant, and a suitable carrier solvent. These compositions may be topically administered to animals, and are useful for preventing or treating ectoparasitic infestations in warm-blooded animals for prolonged periods of time. Additionally, they may be further diluted to provide other types of formulations useable for both topical and oral administration.

VERSATILE HIGH LOAD CONCENTRATE COMPOSITIONS FOR CONTROL OF
ECTO-PARASITES

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This application claims priority from copending provisional Application Number 60/683,949, filed May 24, 2005, the entire disclosure of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Arthropod ectoparasites commonly infecting warm-blooded animals include
10 ticks, mites, lice, fleas, blowfly, the ectoparasite *Lucilia* sp. of sheep, biting insects including keds (*Melophagus ovinus*) and migrating dipterous larvae such as *Hypoderma* sp. and *Dermataobia* in cattle, *Gastrophilus* in horses and *Cuterebra* sp. in rodents.

Metaflumizone is useful for the prevention and control of infestation by
15 ectoparasites in warm-blooded animals. Topical administration of this active is a preferred method for administering this compound.

To provide useful protection against ectoparasitic infection or infestation in warm-blooded animals it is desirable to use formulations having a relatively high loading of active agent, but such formulations must be stable, both with respect to
20 the physical formulation, and also, with respect to the chemical stability of the active. Metaflumizone is one of several useful insecticidal agents which have found particular application for the control of fleas and ticks on animals, particularly companion animals such as dogs, cats and horses, and livestock such as cattle, sheep and goats. It is particularly advantageous in that it can provide 4-6 weeks of
25 protection from fleas and ticks in companion animals, but it would be potentially useful for many other species if suitable formulations could be developed.

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Nonetheless, formulation of metaflumizone is made difficult by its insolubility in many solvents, and its instability in the presence of primary alcohols.

One or more embodiments of the present invention may provide a versatile composition for topical administration which comprises a relatively high loading of metaflumizone and which will provide protection from ectoparasitic infestation. Most advantageously, the formulation can function as a concentrate, which with simple modifications, can be extended to use for a wide variety of other animals. Thus, the concentrated formulation can be utilized as a small volume spot-on formulation, for instance, for protection of companion animals, while further dilutions can be utilized as conventional pour-on products for farm animals, with still further dilutions utilizable for emulsified sprays delivered through an aerosol spray or a pump spray with numerous volumes of dosage and/or application to the feed.

One or more embodiments of the present invention may provide a method for preventing or treating acarid or arthropod ectoparasitic infestation in animals, especially warm-blooded animals, using the compositions of the invention.

One or more embodiments of this invention may reduce or control the proliferation of such insects in warm-blooded animals for prolonged periods of time by a topically applied active, with the formulation being mild and gentle enough to avoid adverse skin reactions upon administration, yet with the ability to be retained in the animal's skin and/or coat over the time needed for protection.

These and other embodiments of the present invention will become more apparent from the description thereof set forth below and the appended claims.

SUMMARY OF THE INVENTION

The present invention provides high-load concentrate compositions for topical administration which comprise on a weight to volume basis:

- about 5% to 25% of metaflumizone;
- about 0% to about 15% of dimethyl sulfoxide;
- about 2% to about 15% of an alcohol alkoxylate surfactant or nonylphenol ethoxylate surfactant or polyoxyl 35 castor oil; and
- about 50% to 80% of a non-hydroxyl-group-containing carrier solvent.

The present invention further provides a composition for topical administration which comprises on a weight to volume basis:

- about 5% to 25% of metaflumizone;

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about 0% to about 15% of dimethyl sulfoxide;
 about 2% to about 15% of a non-ionic surfactant; and
 about 50% to 80% of γ -hexalactone or 1-methoxy-2-propyl acetate and, optionally,
 dimethyl isosorbide.

5 The present invention further provides a use of a composition of the invention for
 the preparation of a pharmaceutical composition for preventing or treating ectoparasitic
 infection or infestation in a warm-blooded animal.

The present invention further provides a method for preventing or treating
 ectoparasitic infection or infestation in a warm-blooded animal which method comprises
 10 topically administering to the animal an acaricidally or arthropod ectoparasitically
 effective amount of the composition of this invention.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, the high load concentrate compositions
 15 comprise metaflumizone; an optional bridging agent or penetration enhancer, a surfactant,
 and a carrier solvent. The invention also provides a method for preventing or treating
 acarid or arthropod ectoparasitic infection or infestation in warm-blooded animals by
 topical application of the aforesaid formulations.

Preferred high load concentrate compositions of this invention comprise on a
 20 weight to volume basis:

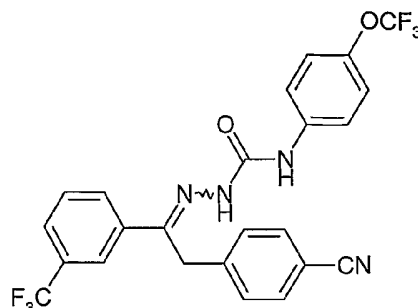
about 5% to about 25% of metaflumizone;
 about 0% to about 15% of a bridging agent;
 about 2 to about 15%, and especially about 2 to about 8%, of a surfactant and
 about 50% to about 80% of a carrier solvent.

25 In certain embodiments about 15% to about 25% metaflumizone is included in the
 composition, e.g. about 20%. In certain embodiments about 5% to about 15% bridging
 agent is included, e.g. about 10% is included. In certain embodiments about 50% to about
 60% carrier solvent is included.

5 While not wishing to be bound by any particular theory, it is believed that the compositions of the present invention have the requisite stability by virtue of physical and/or chemical interactions between the surfactant and the metaflumizone. The exact nature of the interactions is unknown, but apparently the surfactant stabilizes the metaflumizone in solution so as to ensure that the resultant formulation retains
10 the desired physical characteristics over time, without loss of potency of the active. Further, the formulation is sufficiently viscous to be retained upon or in the animal's skin and/or hair, and be released over the desired period of time.

 Uniquely, it has been found these high load concentrate compositions can be further utilized to prepare more dilute compositions for application in various other
15 manners, *i.e.*, for use as a pour-on for large animals, as a spray for large animals or for outdoor use, and as a water-dilutable formulation for addition to the feed and/or water supply of animals under treatment. This has the dual advantage of providing a concentrated formulation that can be shipped to the end-user for dilution and use, or to an intermediate formulator to prepare the compositions. The high loading of
20 metaflumizone in the formulation thus provides a small volume of formulation to use as a "spot-on" formulation, for instance, for companion animals, especially felines. The concentrate can then be diluted by an appropriate organic solvent for use as a pour-on or in a spray, or with water, to provide the feed/water additive.

 Metaflumizone, as well as its use in veterinary applications, is described in
25 U.S. Patent No. 5,543,573, and U. S. Published Application 2004-0122075A1, both incorporated herein by reference. Chemically, it is known as (E Z)-2-[2-(4-cyanophenyl)-1-[3-(trifluoromethyl)phenyl]ethylidene]-N-[4-(trifluoromethoxy)phenyl]hydrazinecarboxamide.



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Bridging agents or penetration enhancers suitable for use in the compositions of this invention include, but are not limited to, alkyl methyl sulfoxides (such as dimethyl sulfoxide, decylmethyl sulfoxide and tetradecylmethyl sulfoxide); pyrrolidones (such as 2-pyrrolidone, N-methyl-2-pyrrolidone and N-(2-hydroxyethyl) pyrrolidone); laurocapram; and miscellaneous solvents such as acetone, dimethyl acetamide, dimethyl formamide, and tetrahydrofurfuryl alcohol. Other bridging agents include amphiphiles such as L-amino acids, and fatty acids. Additional bridging agents are disclosed in *Remington: The Science and Practice of Pharmacy*, 19th Edition (1995) on page 1583. Typically, the bridging agents is used at a level of about 10% w/v of the formulation where the end use is for a topical application, but this may vary, especially when the end use of the composition is for oral administration.

The surfactant utilized in the present invention may be a single surfactant, or a mixture of two or more surfactants, again, in part dependent upon whether the end use of the composition is topical or oral. The surfactant should be non-irritating, and non-toxic. Preferred are non-ionic, low foaming surfactants, such as the alcohol alkoxylate surfactants, with those sold by Uniqema under the tradename Synperonic® NCA 810, 830 and 850 being especially suitable. Other useful surfactants are the nonylphenol ethoxylates, with those sold under the tradename

5 Tergitol® NP by the Dow Chemical Company being preferred. Additional surfactants, including appropriately chosen anionic and cationic surfactants, can also be utilized in the formulations of the present invention. Especially useful properties are found in anionic surfactants, such as dioctylsulfosuccinate salts.

Typically, the surfactant is utilized at a level of about 2 to about 15% w/v,
10 especially about 2 to about 8% w/v, of the composition, but this may vary somewhat depending upon the end use of the composition. In the case where the end use of the concentrate is as a spray formulation, or as a water-dispersible feed /water additive, it may be desirable to add a further surfactant to ensure that the diluted formulation will be a unitary phase. This ensures that the spray will not block the
15 spray nozzle, and that the active will be dispersed equally throughout the diluted product. In such cases, the additional surfactant may be added to the concentrate formulation, or added to the end use formulation with the diluting solvent.

Particularly useful surfactants for use with an organic solvent diluent are non-ionic surfactants such as polyoxyl 35 castor oil sold under the Cremophor® tradename.

20 The carrier solvent for the compositions of the present invention may be a single solvent, or a mixture of solvents. Due to the instability of metaflumizone in the presence of primary alcohols, preferred solvents are non-hydroxyl-group-containing solvents, especially those such as γ -hexalactone (also known as γ - caprolactone; ethyl butyrolactone; γ -ethyl-n-butyrolactone; hexanolide-1, 4; 4-hydroxy hexanoic
25 acid γ -lactone or tonkalide). Optionally, other such solvents such as N,N-diethyl-m-toluamide, eucalyptol, dimethyl isosorbide, diisopropyl adipate and/or 1-methoxy-2-propyl acetate can be utilized in combination with the γ -hexalactone to comprise the carrier solvent.

5 To manufacture the high load concentrate composition of the present invention, the metaflumizone is dissolved in the carrier solvent or solvents, and the surfactant and bridging agent, if desired added to the mixture. This composition can then be utilized as a high load spot-on, or further diluted for additional uses.

 An especially preferred composition for topical administration to warm-
10 blooded animals comprises, on a weight to volume basis, about 5% to about 25 % metaflumizone; about 10% of a bridging agent, especially dimethyl sulfoxide, about 2-about 8% of a non-ionic, low foam surfactant; and about 50-60% carrier solvent, especially γ -hexalactone.

 The high load concentrate compositions of this invention may further
15 comprise other agents known in the art, such as preservatives (e.g., methylparaben and propylparaben), colorants, antioxidants, and the like. Generally, these agents would be present in the compositions in an amount up to about 2% on a weight to volume basis.

 When topically administered, the compositions of this invention are highly
20 effective for preventing or treating ectoparasitic infection and infestation for prolonged periods of time in warm-blooded animals such as cows, sheep, horses, camels, deer, swine, goats, dogs, cats, birds, and the like. Representative dosages for application to companions are, for instance, 20 mg/kg for dogs, and 40 mg/kg for cats, but lower dosages down to 5 mg/kg show efficacy on large animals such as
25 horses and cattle.

 In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating specific embodiments thereof. The invention is not to be deemed limited thereby, except as defined in the claims.

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EXAMPLE 1

PREPARATION OF METAFUMIZONE HIGH LOAD CONCENTRATE, SUITABLE
FOR USE AS A SPOT-ON

To 10 grams of DMSO is added to 40 grams of γ -hexalactone. To this solvent mixture is added 20 g. of metaflumizone. Mild heat (40°C) may be used to facilitate the process of dissolution. To the resulting solution, 6 grams of Synperonic® NCA 830 brand of alcohol alkoxylate surfactant is added with stirring. Bring to 100 ml with γ -hexalactone.

Thus formulated, the composition can be applied as a "spot-on" (topical small dose) treatment for cats.

The efficacy of such a formulation is given in the efficacy table below:

Days after treatment	2	15	29	57
Untreated Control group, number of fleas /cat	53.9	83.9	62.9	65.2
20% metaflumizone spot-on 40mg/kg % Efficacy	100.0	100.0	100.0	97.1

EXAMPLE 2

PREPARATION OF METAFUMIZONE POUR-ON FROM HIGH LOAD
CONCENTRATE OF EXAMPLE 1

To 25 ml of the high load concentrate prepared in Example 1 is added q.s. 100 ml γ -hexalactone. This provides a pour-on formulation having sufficient metaflumizone and volume to treat 5 head of cattle weighing 200 Kg each at 5 mg/kg dose rate.

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EXAMPLE 3

PREPARATION OF HIGH LOAD CONCENTRATE FOR USE AS A
CONCENTRATE TO PREPARE METAFUMIZONE SPRAY OR FEED/WATER
SUPPLEMENT

12.59 grams of metaflumizone is added to dimethyl isosorbide using mild
10 heating (approximately 40°C). To this solution is added 109.92 grams Cremophor®
EL (polyethoxylated castor oil, sold by Basf Aktiengesellschaft), with stirring, followed
by q.s. 200 ml 1-methoxy-2-propyl acetate. The resultant solution is stored until
ready for use, whereupon it can be diluted with water for use as a spray (17 ml of
concentrate diluted to 3500 ml with water), or with water for use as a feed/water
15 additive (in approximately the same ratio).

This formulation was diluted with water to a metaflumizone concentration of
10 mg/kg bodyweight, and applied to sheep at 1500 ml/animal to test the effect of
metaflumizone on biting lice

Days after treatment	7	14	21	28
Untreated Control group, number of lice/animal	140.2	293.2	542.2	824.8
10mg/kg metaflumizone dosed as a body spray % Efficacy	100	100	100	100

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EXAMPLE 4

PREPARATION OF SPOT-ON FORMULATIONS USING VARIOUS SURFACTANT
CHEMISTRIES AND SOLVENT SYSTEMS, % W/V

Ingredient	Formulation 5	Formulation 6	Formulation 7	Formulation 8
Metaflumizone	25	25	25	25
DMSO	35	0	0	0
Tergitol® NP13	5	5	0	10
Synperonic® NCA 830	0	0	0	0
Aerosol OT® (dioctyl sodium sulfosuccinate)	0	0	12.5	0
ethanol	0	0	0	10
Ethylene glycol propylene ether	0	35	0	0
γ -hexalactone	q.s	q.s.	q.s.	q.s.

10

Ingredient	Formulation 9	Formulation 10	Formulation 11	Formulation 12
Metaflumizone	20	20	20	20
Tergitol® NP13	0	0	0	5
N,N- Diethyltoluamide	10	10	10	0
Cineole	10	10	10	0
DMSO	0	0	0	10
Crodamol® PMP (polyoxypropylene (2) myristyl ether propionate)	0	1	0	0
Isopropyl myristate	0	0	1	0
γ -hexalactone	q.s	q.s.	q.s	q.s.

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5 The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

10 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

- 5 1. A composition for topical administration which comprises on a weight to volume basis:
about 5% to 25% of metaflumizone;
about 0% to about 15% of dimethyl sulfoxide;
about 2% to about 15% of an alcohol alkoxyate surfactant or nonylphenol ethoxylate surfactant or polyoxyl 35 castor oil; and
10 about 50% to 80% of a non-hydroxyl-group-containing carrier solvent.
2. The composition of Claim 1 which comprises about 15% to 25% metaflumizone.
- 15 3. The composition of Claim 1 or 2 wherein the surfactant is present at a level of about 2% to about 8% w/v.
4. The composition of any one of Claims 1 to 3, comprising an alcohol alkoxyate surfactant.
20
5. The composition of any one of Claims 1 to 3, comprising a nonylphenol ethoxylate surfactant.
6. The composition of any one of Claims 1 to 3, comprising a polyoxyl 35
25 castor oil.
7. The composition according to any one of Claims 1 to 6 wherein the carrier solvent is γ -hexalactone.
- 30 8. The composition according to any one of Claims 1 to 6 wherein the carrier solvent is 1-methoxy-2-propyl acetate.
9. The composition of any one of Claims 1 to 6 which additionally contains up to 2% of one or more preservatives, colorants, antioxidants, or stabilizers.
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10. A composition for topical administration which comprises on a weight to volume basis:

about 5% to 25% of metaflumizone;

about 0% to about 15% of dimethyl sulfoxide;

5 about 2% to about 15% of a non-ionic surfactant; and

about 50% to 80% of γ -hexalactone or 1-methoxy-2-propyl acetate and, optionally, dimethyl isosorbide.

10 11. Use of a composition of any one of Claims 1 to 10 for the preparation of a pharmaceutical composition for preventing or treating ectoparasitic infection or infestation in a warm-blooded animal.

12. A method for preventing or treating ectoparasitic infection or infestation in a warm-blooded animal which method comprises topically administering to the animal
15 effective amount of a composition according to any one of Claims 1 to 10.

13. The use of Claim 11 or method of Claim 12, wherein the animal is selected from the group consisting of a cow, a sheep, a horse, a camel, a deer, a swine, a goat, a dog, a cat, and a bird.
20

14. The use of Claim 11 or 13, or the method of Claim 12 or 13, wherein the composition is further diluted for use as a pour-on composition.

15. The use of Claim 11 or 13, or the method of Claim 12 or 13, wherein the
25 composition is further diluted for use as a spray or feed/water additive.

16. The composition of Claim 1 or Claim 10; the use of Claim 11 or the method of Claim 12 substantially as hereinbefore described with reference to the Examples.