

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y C

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REF: Expediente 09-081-847

**TÍTULO SOLICITADO: ECTOPARASITICIDA DE ACCION PROLONGADA
CON ALTA DOSIS PARA UN CONTROL
PROLONGADO.**

PUBLICACIÓN: Gaceta 621 de 20/10/2010, N° de publicación 774.

SOLICITANTE: WYETH.

APODERADO: ALVARO CORREA ORDOÑEZ.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 27 de Septiembre de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario. Por tal razón me permito presentar los argumentos anunciados en el escrito de oposición presentado en su momento:

En primer lugar, y ante la revelación textual de un “uso”, es relevante señalar que dicha pretensión resulta inaceptable a la luz de la Decisión 486, en tanto los “usos” son una categoría excluida del concepto de “Productos o Procedimientos” que establece el artículo 14 de la norma citada. Lo anterior, además, en consonancia con reiteradas interpretaciones de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que, aún si en gracia de discusión los usos o métodos terapéuticos fuesen permitidos en nuestro medio, éstos deberían cumplir necesariamente, y en forma simultánea, con los requisitos materiales de patentabilidad, es decir, novedad, nivel Inventivo y aplicación industrial. Además de anotar que respecto del pretendido “uso” el tercer requisito resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías sería del resorte de la profesión médica, y no, por supuesto, de las actividades industriales.

En este mismo orden de ideas cabe señalar que la solicitud colombiana en cuestión incurre en otra improcedencia de patentabilidad al mencionar en sus reivindicaciones un método para prevenir o tratar una infestación de ectoparásitos en un animal de sangre caliente, ya que va en contra de lo dispuesto por la Decisión 486 de 2000 que revela explícitamente en su artículo 20 literal d) que *“No serán patentables Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*.

En el mismo sentido, y ante la reivindicación textual de concentraciones (dosis) de los ectoparaticidas involucrados en la solicitud, es importante indicar que esto también contraviene lo dispuesto en la Decisión 486 de 2000 ya que dicha mención de dosificaciones tiene el mismo efecto que las reivindicaciones sobre métodos de tratamiento, dado que la concentración, en este caso directamente referido a la dosificación de la formulación ectoparacitida, no pertenece a la categoría de producto o proceso, sino que hace referencia la forma en la que un producto se utiliza terapéuticamente, y por lo tanto no hace parte de las actividades industriales sino de las actividades médicas veterinarias. En otras palabras la dosificación o los cambios en la dosificación dentro de un producto

farmacéutico no tiene naturaleza inventiva, ya que no cumplen con el estándar de aplicabilidad industrial, dado que dichas modificaciones solo tienen efectos en el organismo (verificables a nivel clínico) y no efectos técnicos.

En otro aspecto, y teniendo en cuenta que dentro del capítulo reivindicatorio de la solicitud en cuestión se refiere a las combinaciones entre agentes ectoparacitcidas es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich¹ en su opinión escrita a cerca de "Asociaciones y Patentes" en donde afirma que las asociaciones farmacológicas están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica, veamos:

"3.3.2. Lineamientos FDA:

A continuación se mencionarán lineamientos que la agencia sanitaria de EEUU ha establecido para el caso de los llamados "*Combination Drug Products*":

3.3.2.1. CFR

El CFR establece la política en relación a las combinaciones de drogas a dosis fija para humanos en 21CFR300.50. Allí se establece que dos o más drogas pueden ser combinadas en una única unidad posológica cuando cada componente hace una contribución al efecto propuesto y la dosis de cada componente es tal que la combinación es segura y efectiva (se consideran casos especiales cuando se busca aumentar la seguridad y eficacia del principal componente o minimizar su potencial abuso).

3.3.2.2. Guía "OTC Combination of Drug Products" [Docket No. 78D-0322]²:

Esta guía establece en detalle la política de la agencia para combinar dos o más ingredientes activos OTC, seguros y eficaces y caracteriza diferentes tipos de asociaciones de OTC:

- Ingredientes activos de diferentes categorías terapéuticas para tratar distintos síntomas simultáneamente: Sólo se acepta esta asociación si cada ingrediente está presente dentro de su rango de seguridad y eficacia.
- Ingredientes activos de la misma categoría terapéutica que tienen distintos mecanismos de acción para tratar los mismos síntomas o

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² Anunciada en el Federal Register (1978), Vol. 43, No. 229.

condición: Sólo se acepta esta asociación si es mejor o igual que cada ingrediente solo en su dosis terapéutica y también pueden usarse a dosis subterapéuticas si corresponde.

- Ingredientes activos de la misma categoría terapéutica que tienen el mismo mecanismo de acción: Estos no deberían ser combinados a menos que haya alguna ventaja con respecto a los ingredientes simples (mayor eficacia, seguridad, aceptación del paciente o calidad de la formulación).
- Ingredientes considerados adyuvantes, que aumenten o alteren el efecto de otro ingrediente activo, serán, considerados ingredientes activos.

3.3.2.3. Guía Draft "Current GMP for Combination Products":

Este documento provee una guía para la industria y para el *staff* de la FDA acerca de la aplicabilidad de la cGMP para las asociaciones (*combination products*) y define a un *combination product*, de acuerdo al CFR (21CFR3.2(e)), de forma que no sólo involucra drogas sino *devices*:

Un producto combinado es un producto compuesto de cualquier combinación de una droga y un dispositivo; un producto biológico y un dispositivo; una droga y un producto biológico; o una droga, dispositivo, y un producto biológico. Bajo 21 CFR 3.2 (e), un producto de combinación incluye:

- 1. Un producto que comprende dos o más componentes regulados (i.e., droga/dispositivo, biológico/dispositivo, droga/biológico, o droga/dispositivo/biológico) que son combinados físicamente, químicamente, o de otra forma, o mezclados y producidos como una entidad única;*
- 2. Dos o más productos separados, empaquetados juntos en un solo paquete, o como una unidad comprendiendo droga y productos del dispositivo, dispositivo y productos biológicos, o biológico y productos de droga;*
- 3. Una droga, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo a su plan de investigación o el etiquetado propuesto, es destinado para utilizarse únicamente con una droga, dispositivo, o producto biológico aprobada especificada individualmente, dónde al mismo tiempo ambos son deben estar aceptados para la indicación o efecto y donde, luego de la aprobación del producto propuesto, el etiquetado del producto aprobado necesitaría ser cambiado (e.g., para reflejar un cambio en la indicación, forma farmacéutica, dosis, ruta de administración, cambio significativo en la posología); ó*
- 4. Cualquier droga en investigación, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo al etiquetado propuesto es para utilizarse únicamente con otra droga en investigación especificada, dispositivo, o producto biológico, dónde a la vez se requiere que ambos sean aceptados para la misma indicación, uso y efecto.*

Además, dentro de esta guía es muy interesante el concepto de "parte constitutiva de un *combination product*" porque especifica su identidad regulatoria como droga, *device* o producto biológico.

3.3.2.4. Guía *Draft "Combination Products Timeliness of Premarket Reviews"*:

Esta guía provee información a un postulante a reclamar la resolución de una disputa acerca de la duración de la revisión de una postulación referida a un producto combinado. Es una guía referida simplemente a un problema administrativo que demuestra cuán regulado se halla este ámbito que tiene una oficina destinada, la Office of Combination Products.

3.3.3. Lineamientos EMEA: Guía "Fixed Combination Medicinal Products":

Esta guía propone evaluar las potenciales ventajas de la asociación en cuanto a mejoramiento de la relación riesgo/beneficio y a simplificación de la terapia. Asimismo, establece criterios a respetar y requisitos a cumplimentar, tanto generales como particulares. Dentro de los particulares hace especial referencia a:

- La indicación.
- Los estudios farmacodinámicos y farmacocinéticos.
- Eficacia y Seguridad: En este caso diferencia dos escenarios concretos:
 - a) *Cuando la combinación fija corresponde exactamente a combinaciones que están ya en uso difundido, un análisis de los datos bibliográficos bien fundamentados debería ser presentado. Con tal que los datos estén bien documentados, este análisis puede ser útil en reducir la cantidad de ensayos clínicos a ser realizada y podría facilitar la selección de dosis para cada sustancia y el rango de dosis propuesto en la combinación fija.*
 - b) *Cuando la combinación fija es esencialmente nueva (las sustancias activas no son usualmente combinadas, la composición cuantitativa es inusual entre sustancias usualmente combinadas o una sustancia enteramente nueva), los datos necesarios son similares a los de una nueva entidad química en la situación donde la combinación fija será propuesta (primero línea o segunda de la línea de terapia). La existencia de experiencia con las sustancias debería ser tenida en cuenta.*

y especifica Régimen de dosis y Composición, Ensayos Terapéuticos y Aspectos de Seguridad.

- Paquetes combinados de diferentes productos medicinales para administración simultánea o secuencial.

Conclusión:

Las diferentes agencias sanitarias a nivel internacional han regulado fuertemente el registro de asociaciones de forma de garantizar la seguridad y eficacia de las mismas y la buena calidad en su elaboración. Todo estudio, investigación o análisis derivados de estos requisitos representan procedimientos de rutina y no originales ideas llevadas a la práctica."

Además, se puede considerar que todo efecto sinérgico o terapéutico entre fármacos no se refiere propiamente a una invención, sino que corresponde mejor a la categoría de un descubrimiento, dado que dicho efecto sinérgico o terapéutico conseguido mediante la combinación de fármacos ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos por los que todo fármaco o combinación de fármacos se deben evaluar. Así mismo es importante volver a enfatizar en que la combinación de fármacos para tratar ciertas patologías, hace parte de las actividades de la profesión médica, y no de las actividades industriales.

Para finalizar, también se puede demostrar que con anterioridad se habían descrito en el estado de la técnica formulaciones del mismo tipo que la descrita en la solicitud colombiana en trámite, formulaciones ectoparacitcidas para la aplicación veterinaria que contienen en esencia las mismas características y son en esencia una clara guía para cualquier persona medianamente versada en la materia que decida realizar una composición como la descrita en la solicitud en cuestión, veamos:

La publicación internacional WO 2006/127399 publicada el 30 de noviembre de 2006 revela:

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

(...)

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 protection from fleas and ticks in companion animals, but it would be potentially useful for many other species if suitable formulations could be developed. Nonetheless, formulation of metaflumizone is made difficult by its insolubility in many solvents, and its instability in the presence of primary alcohols. (...)

Preferred high load concentrate compositions of this invention comprise on a 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. (...)

3. The composition according to Claim 1 or Claim 2 wherein the surfactant is a non-ionic low foam surfactant. (...)

5. The composition according to any one of Claims 1 to 4 wherein the bridging agent is dimethyl sulfoxide.

6. The composition according to any one of Claims 1 to 5 wherein the carrier solvent is γ -hexalactone. (...)

Por su parte la publicación internacional WO 2006/127487 publicada el 30 de noviembre de 2006 revela:

to the chemical stability of the actives. 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. It is particularly advantageous in that it can provide 4-6 weeks of protection from fleas and ticks in companion animals, but it would be potentially useful for many other species if suitable formulations could be developed. Nonetheless, formulation of metaflumizone is made difficult by its insolubility in many solvents, and its instability in the presence of primary alcohols.

(...)

It is also an object of the present invention to provide a versatile composition for topical administration which comprises a relatively high loading of metaflumizone in combination with an anti-parasitic macrolide compound, and which will provide protection from ecto- and endo-parasitic infestation. Most advantageously, the (...)

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

about 0.1 to about 10% of substantially water-insoluble anti-parasitic macrolide compound, especially, moxidectin:

about 5% to about 40% of metaflumizone;

about 0% to about 15% of a bridging or penetrating agent;

about 2 to about 8% of a surfactant and

about 50% to about 80% of a carrier solvent.

(...)

4. The composition according to any one of Claims 1 to 3 wherein the surfactant is a non-ionic low foam surfactant.

(...)

6. The composition according to any one of Claims 1 to 5 wherein the penetrating agent is dimethyl sulfoxide.

7. The composition according to any one of Claims 1 to 6 wherein the carrier solvent comprises gamma-hexalactone.

(...)

Finalmente la publicación internacional WO 2006/042099 publicada el 20 de Abril de 2006, revela:

The present invention provides a composition which comprises an effective amount of each of amitraz and at least one additional parasitocidal compound in a non-hydroxyl-group-containing solvent mixture comprising N,N-diethyl-m-toluamide and γ -hexalactone. In a preferred composition, the non-hydroxyl-group-containing solvent mixture additionally comprises: dimethyl sulfoxide; eucalyptol; and 1-methoxy-2-propyl acetate.

(...)

Surprisingly, it has now been found that amitraz and at least one additional parasitocidal compound may be formulated in a stable topical non-irritating composition by employing as a carrier a non-hydroxyl-group-containing solvent combination of N,N-diethyl-m-toluamide and γ -hexalactone, optionally, in further combination with dimethyl sulfoxide, eucalyptol, and 1-methoxy-2-propyl acetate.

(...)

Representative parasitocidal compounds suitable for use in the composition of the invention are: chitin synthesis inhibitors including benzoylphenylureas such as diflubenzuron, flufenoxuron, teflubenzuron; novaluron, fluazuron; or the like; juvenile hormone mimics such as methoprene, hydroprene, pyriproxyfen, fenoxycarb, or the like; pyrethroid insecticides such as permethrin, cypermethrin, α -cypermethrin or the like; phenylpyrazole insecticides such as fipronil; organophosphate insecticides such as chlorfenvinphos, diazinon, malathion, terbufos, or the like; oxime carbamate insecticides; avermectins such as abamectin, doramectin, ivermectin, selamectin or eprinomectin; imidacloprid; milbemycins such as moxidectin or milbemycin oxime; semicarbazones such as endoxcarb or R-28153, preferably R-28153 (also named as metaflumizone); and the like. R-28153 is especially preferred for use with amitraz, due to its complementary mode of parasitocidal activity, and its chemical compatibility with, and solubility in, non-hydroxyl-group-containing solvents. (...)

5. The composition according to any one of claims 1 to 3 wherein the additional parasitocidal compound is a benzoylphenylurea; a juvenile hormone mimic; a pyrethroid; an organophosphate; a semicarbazone, fipronil; imidacloprid; ivermectin; or moxidectin.

6. The composition according to any one of claims 1 to 4 which comprises about 10-30% w/v of amitraz and about 10-30% w/v of R-28153.

Como se puede apreciar claramente en estas tres anterioridades se revelan absolutamente todos los aspectos técnicos necesario para que una persona medianamente versada en la materia los tome como guía para elaborar formulaciones del mismo tipo que las reivindicadas en la solicitud colombiana en trámite, aspecto específicos como la aplicación tópica de la formulación, los mismos principios activos, los mismos sistemas solventes que resuelven los problemas de solubilidad de dichos principios activos, la proporciones de los componentes de la formulación e inclusive el mismo tiempo o periodo de efectividad de dichas formulaciones.

Así mismo, insistimos a este Despacho tenga en cuenta los otros documentos que se citaron en el escrito de oposición de fecha 18/01/2011, es decir, la publicación internacional WO 2006/127406 de 30/11/2006, la patente americana US 6,395,765 de 28/05/2002, la patente británica GB 2 318 512 de 29/04/1998 y la publicación europea EP 0 061 208 de 29/09/1982, ya que en todas ellas se hace referencia a composiciones para administración tópica de compuestos útiles como ectoparasitocidas como por ejemplo metaflumizone, en compañía de auxiliares de

formulaciones como disolventes, surfactantes, entre otros y su uso en la protección o tratamiento de infestación de parásitos en un animal, tal como se pretende en la solicitud colombiana en trámite.

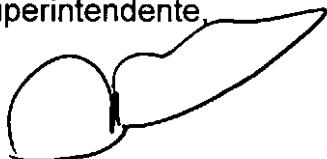
En conclusión, dicha solicitud colombiana carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia de patentabilidad directa al reivindicar usos y métodos de tratamiento; y en segundo lugar porque la esencia técnica de las composiciones que describe la composición ya se habían aplicado con anterioridad en el estado de la técnica para obtener formulaciones del mismo tipo, lo que hace irrefutable la carencia de novedad y de nivel inventivo.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

II. ANEXOS

- Todos los documentos mencionados en el acápite de Ratificación.

Señor Superintendente,



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International Bureau



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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,
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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).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished
upon receipt of that report

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

(54) Title: VERSATILE HIGH LOAD CONCENTRATE COMPOSITIONS 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.

WO 2006/127399 A2

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

 The present invention further provides a method for preventing or treating
10 ectoparasitic infection or infestation in a warm-blooded animal which method
 comprises 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 comprise metaflumizone; an optional bridging agent or penetration
15 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
 weight to volume basis:

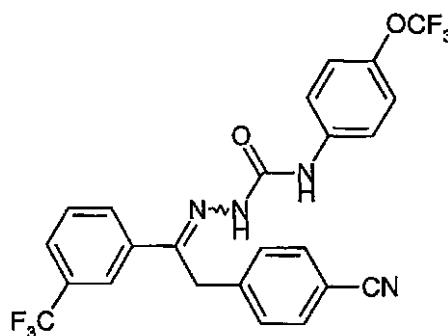
- 20 about 5% to about 25% of metaflumizone;
 about 0% to about 15% of a bridging agent;
 about 2 to about 15%, and especially about 2 to about 8%, of a surfactant
 and
 about 50% to about 80% of a carrier solvent.

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-blooded animals comprises, on a weight to volume basis, about 5% to about 25 %
10 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 METAFIUMIZONE 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 METAFIUMIZONE 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 METAFIUMIZONE 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.

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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.

WHAT IS CLAIMED IS:

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 a bridging agent;
about 2 to about 15 of a surfactant; and
about 50% to 80% of a carrier solvent.

2. The composition according to Claim 1 which comprises about 15% to 25% metaflumizone.

3. The composition according to Claim 1 or Claim 2 wherein the surfactant is a non-ionic low foam surfactant.

4. The composition according to any one of Claims 1 to 3 wherein the surfactant is present at a level of about 2% to about 8% w/v.

5. The composition according to any one of Claims 1 to 4 wherein the bridging agent is dimethyl sulfoxide.

6. The composition according to any one of Claims 1 to 5 wherein the carrier solvent is γ -hexalactone.

7. The composition according to any one of Claims 1 to 5 wherein the carrier solvent is 1-methoxy-2-propyl acetate.

8. The composition according to any one of Claims 1 to 7 which additionally contains up to 2% of one or more preservatives, colorants, antioxidants, or stabilizers.

9. A method for preventing or treating ectoparasitic infection or infestation in a warm-blooded animal which method comprises topically

administering to the animal effective amount of a composition according to any one of Claims 1 to 8.

10. The method according to Claim 9 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.

11. The method according to Claim 9 or Claim 10 wherein the composition comprises about 5% to 25% metaflumizone; about 10% of a bridging agent; about 2% to about 8% of a non-ionic low foam surfactant; and about 50-60% carrier solvent.

12. The method according to any one of Claims 9 to 11 wherein the composition comprises γ -hexalactone as the carrier solvent.

13. The method according to any one of Claims 9 to 12 wherein the composition is further diluted for use as a pour-on composition.

14. The method according to any one of Claims 9 to 11 wherein the composition comprises 1-methoxy-2-propyl acetate as the carrier solvent.

15. The method according to Claim 14 wherein the composition is further diluted for use as a spray or feed/water additive.

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(54) Title: USEFUL HIGH LOAD CONCENTRATE COMPOSITIONS FOR CONTROL OF ECTO-AND ENDO-PARASITES

(57) Abstract: High load concentrate compositions comprising metaflumizone, a substantially water-insoluble anti-parasitic macrolide compound,such as moxidectin, an optional bridging agent, a surfactant, and a suitable carrier solvent are prepared. 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.

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USEFUL HIGH LOAD CONCENTRATE COMPOSITIONS FOR CONTROL OF ECTO-AND ENDO-PARASITES

BACKGROUND OF THE INVENTION

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

Helminthiasis is a widespread disease found in many animals and is responsible for significant economic losses throughout the world. Among the
10 helminths most frequently encountered are the group of worms referred to as nematodes. The nematodes are found in the gastrointestinal tract, heart, lungs, blood vessels and other body tissues of animals and are a primary cause of anemia, weight loss and malnutrition in the infected animals. They do serious damage to the walls and tissue of the organs in which they reside and, if left untreated, may result in
15 death to the infected animals.

The nematodes most commonly found to be the infecting agents of ruminants include *Haemonchus* and *Ostertagia* generally found in the abomasum; *Cooperia*, *Trichostrongylus* and *Nematodirus* generally found in the intestinal tract, and *Dictyocaulus* found in the lungs. In non-ruminant animals, important nematodes
20 include *Toxocara* and *Ancylostoma* in the intestine and *Dirofilaria* in the heart of dogs and cats; *Ascaridae* in the intestine of swine; and large and small strongyles in equines.

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

Anti-parasitic macrolide compounds such as LL-F28249 α - λ compounds, 23-oxo or 23-imino derivatives of LL-F28249 α - λ compounds, including, but not limited to, moxidectin, milbemycin compounds, including but not limited to milbemycin
30 oxime, avermectin compounds, including, but not limited to abamectin, ivermectin, and mixtures thereof, are useful for the prevention and control of helminthiasis and

infection by acarids and arthropod endo- and ectoparasites in warm-blooded animals.

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

To provide useful protection against both endoparasitic infections and 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 the physical formulation, and also, with respect to the chemical stability of the actives. 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. It is particularly advantageous in that it can provide 4-6 weeks of protection from fleas and ticks in companion animals, but it would be potentially useful for many other species if suitable formulations could be developed. Nonetheless, formulation of metaflumizone is made difficult by its insolubility in many solvents, and its instability in the presence of primary alcohols.

It is the object of the present invention to provide a method for preventing, controlling or treating helminth, acarid or arthropod endo- or ectoparasitic infection or infestation in warm-blooded animals which method comprises topically administering to the warm-blooded animals an anthelmintically, acaricidally or arthropod endo- or ectoparasitically effective amount of a nonaqueous composition which comprises about 0.1 to 10% w/v of a substantially water-insoluble anti-parasitic macrolide compound, about 5% to about 40% of metaflumizone; about 0% to about 15% of a bridging or penetrating agent; about 2 to 8% of a surfactant, and about 50 to 80% w/v of a pharmaceutically acceptable water-miscible or water immiscible solvent or solvent system as the carrier.

It is also an object of the present invention to provide a versatile composition for topical administration which comprises a relatively high loading of metaflumizone in combination with an anti-parasitic macrolide compound, and which will provide protection from ecto- and endo-parasitic 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 sprays and application to the feed.

It is also an object of the present invention to provide a method for preventing or treating acarid or arthropod ectoparasitic infestation in warm-blooded animals, using the compositions of the invention.

It is another object of this invention to 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 objects 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 0.1 to about 10% of substantially water-insoluble anti-parasitic macrolide compound, especially, moxidectin:

about 5% to about 40% of metaflumizone;

about 0% to about 15% of a bridging or penetrating agent;

about 2 to about 8% of a surfactant and

about 50% to about 80% of a carrier solvent.

The present invention further provides a method for preventing or treating ectoparasitic and endoparasitic infection or infestation in a warm-blooded animal which method comprises 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 comprise a substantially water-insoluble anti-parasitic macrolide compound, especially, moxidectin, 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.

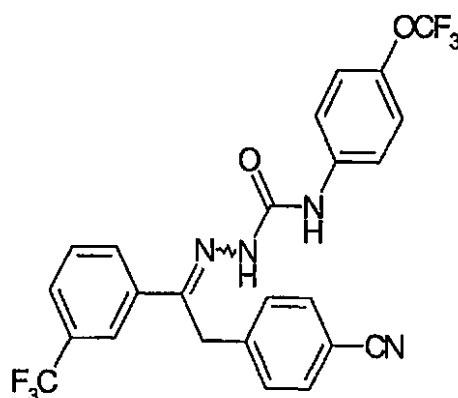
5 Preferred high load concentrate compositions of this invention comprise on a weight to volume basis:

About 0.1 to about 10% of a substantially water-insoluble anti-parasitic macrolide compound, especially, moxidectin
about 5% to about 40% of metaflumizone;
about 0% to about 15% of a bridging or penetrating agent;
10 about 2 to about 8% of a surfactant and
about 50% to about 80% of a carrier solvent.

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 the desired physical characteristics over time, without loss of potency of the active. Further, the formulation is sufficiently viscous to be retained upon the animal's skin, hair, and be released over the desired period of time.

20 Uniquely, it has been found these high load concentrate compositions can be further utilized to prepare more dilute compositions for application in various other 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 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
25 30 pour-on or in a spray, or with water, to provide the feed/water additive.

Metaflumizone is described in U.S. Patent No. 5,543,573, and U. S. Published Application 2004-0122075A1, both incorporated herein by reference



Chemically, metaflumizone is known as (E Z)-2-[2-(4-cyanophenyl)-1-[3-(trifluoromethyl)phenyl]ethylidene]-N-[4-(trifluoromethoxy)phenyl]hydrazinecarboxamide.

5 The substantially water-insoluble anti-parasitic macrolide compounds useful for the compositions of the present invention are well-known in the art, and are described in detail in, for instance, "Macrocyclic Lactones in Antiparasitic Therapy," edited by J. Vercruysse and R. S. Rew, CABI Publishing, London, 2002. Such macrolide compounds are subclassed into avermectins and milbemycins, with
10 avermectins being glycosylated milbemycins. Highly preferred, due to its persistency of activity, and its environmental friendliness, is the milbemycin moxidectin, sold in various forms for administration under the Cydectin® tradename.

Bridging agents or penetrating agents or 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);
15 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, tetrahydrofurfuryl alcohol, cineole, N,N-diethyl-3-methylbenzamide (DEET), isopropyl myristate (IPM) and dimethyl isosorbide. Other
20 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 penetrating agent 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
25 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
5 alkoxyate surfactants, with those such as nonylphenol ethoxylate (sold under the tradename Surfonic N-95), and alcohol alkoxyates (sold under the tradename Synperonic® NCA by Uniqema), and the polyethoxylated castor oil surfactants (also known as macrogolglycerol ricinoleate, and sold under the Cremaphor® EL tradename by BASF) being especially suitable. Also useful are ionic surfactants
10 such as sodium lauryl sulfate and dioctyl sodium sulfosuccinate.

Typically, the surfactant is utilized at a level of 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
15 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 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
20 formulation with the diluting solvent. Particularly useful surfactants for use with an organic solvent diluent are non-ionic surfactants such as polyethoxylated castor oil, sold under the tradename Cremophor® EL by BASF Corporation.

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
25 solvents, especially those such as γ -hexalactone (gamma-hexalactone). Optionally, other such solvents such as N,N-diethyl-m-toluamide, eucalyptol, dimethyl isosorbide, diisopropyl adipate and/or methoxypropyl acetate (1-methoxy-2-propyl acetate) can be utilized in combination with the γ -hexalactone to comprise the carrier solvent.

30 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-blooded animals comprises, on a weight to volume basis, about 20% to about 30%
35

metaflumizone; 0.5% moxidectin, about 10% of a bridging or penetrating agent, especially dimethyl sulfoxide, about 2 to-about 8%, and especially about 5%, of a non-ionic, low foam surfactant, and about 50-60% carrier solvent, especially γ -hexalactone.

5 The high load concentrate compositions of this invention may further 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.

10 When topically administered, the compositions of this invention are highly 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. Additionally, the composition is highly effective against endoparasitic infections.

15 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.

20 EXAMPLE 1

Preparation of metaflumizone/moxidectin High Load Concentrate, suitable for use as a Spot-on

25 A 100 gram weight of dimethyl sulfoxide (DMSO) is added to 400 grams γ -hexalactone. To this solvent system is added 200 grams metaflumizone. Dissolve metaflumizone in the solvent system. Weigh 10 grams of moxidectin and add it to the current solution containing metaflumizone. Allow the moxidectin to dissolve. To the resulting solution, add 60 grams alcohol alkoxylate surfactant (sold under the tradename Synperonic® NCA) and allow the surfactant to dissolve. Lastly, bring the solution to 1000 ml with γ -hexalactone

EXAMPLE 2

Preparation of metaflumizone/moxidectin 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. to 100 ml γ -hexalactone. This provides a pour-on formulation having sufficient metaflumizone and moxidectin and volume to treat 5 head of cattle weighed 200 Kg each at 5 mg/kg dose rate metaflumizone and 0.25 mg/kg dose rate moxidectin.

EXAMPLE 3

Preparation of High Load Concentrate for use as a Concentrate to prepare metaflumizone Spray or Feed/Water Supplement

12.59 grams of metaflumizone is added to methoxypropyl acetate using mild heating (approximately 40°C). To this solution is added 109.92 grams polyethoxylated castor oil (sold under the tradename Cremophor® EL), with stirring, followed by 1.0 grams moxidectin and then brought to volume with methoxypropyl 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 additive (in approximately the same ratio) or additionally, applied directly as a backline pour-on.

EXAMPLE 4

Preparation of various formulations of a metaflumizone/moxidectin High Load Concentrate, suitable for use as a Spot-on treatment

Formulation:	1	2	3	4	5	6	7	8	9
Moxidectin	0.1	0.5	2.5	0.1	0.5	2.5	0.1	0.5	2.5
Metaflumizone	30	30	30	20	20	20	5	5	5
Nonylphenol ethoxylate	5					5	5		
alcohol ethoxylate, e.g.		5			5			5	

Synperonic® NCA									
Diethyl sodium sulfosuccinate			5	5					5
Cineole	10								
DEET		10							
IPM			10						
Methoxypropyl acetate					10	10	10	10	10
DMSO	10	10	10	10					
γ-hexalactone	qs	qs	qs	qs	qs	qs	qs	qs	qs

The preceding formulations are prepared using essentially the same procedures as are listed in Example 1.

EXAMPLE 5

Preparation of various formulations of a metaflumizone/macrolide High Load Concentrate, suitable for use as a Spot-on

Formulation:	10	10B	10C
Ivermectin			5
Abamectin		5	
Moxidectin	5		
Metaflumizone	30	30	20
alcohol ethoxylate, e.g. Synperonic NCA	5	5	5
Methoxypropyl acetate	10	10	10
γ-hexalactone	qs	qs	qs

The preceding formulations are prepared using essentially the same procedures as are listed in Example 1.

Example 6

Preparation of various formulations of a metaflumizone/moxidectin High Load
Concentrate, suitable for use as a Spot-on

Formulation:	11	12	14	15	16	17	18	19	20
Moxidectin	0.1	0.5	0.1	1	10	0.25	5	0.1	0.1
Metaflumizone	30	30	20	20	20	5	5	5	5
Cineole									
DEET									
Isopropyl myristate	5				1				
polyethoxylated castor oil		5		1		5	5	5	5
Sodium lauryl sulfate			1						
Methoxypropyl acetate			5	5	5				
DMSO	30	30							
Dimethyl isosorbide						30	30	30	30
γ -hexalactone	qs	qs	qs	qs	qs	qs	qs	qs	qs

The preceding formulations are prepared using essentially the same procedures as are listed in Example 1.

WHAT IS CLAIMED IS:

1. A composition for topical administration which comprises on a weight to volume basis from about 0.1 to about 10% of a substantially water-insoluble anti-parasitic macrolide compound, about 5% to about 40% of metaflumizone; about 0% to about 15% of a penetrating agent; about 2 to about 8%
5 of a surfactant; and about 50% to about 80% of a carrier solvent.
2. The composition according to Claim 1 which comprises from about 20% to about 30% of the metaflumizone.
- 10 3. The composition in Claim 1 or Claim 2 wherein the macrolide compound is moxidectin, abamectin or ivermectin.
4. The composition according to any one of Claims 1 to 3 wherein the surfactant is a non-ionic low foam surfactant.
15
5. The composition according to any one of Claims 1 to 4 wherein the macrolide compound is moxidectin.
6. The composition according to any one of Claims 1 to 5 wherein the
20 penetrating agent is dimethyl sulfoxide.
7. The composition according to any one of Claims 1 to 6 wherein the carrier solvent comprises gamma-hexalactone.
- 25 8. The composition according to any one of Claims 1 to 7 wherein the carrier solvent comprises dimethyl isosorbide.
9. The composition according to any one of Claims 1 to 8 which additionally contains up to about 2% of one or more preservatives, colorants,
30 antioxidants, or stabilizers.

10. A method for preventing or treating endoparasitic and ectoparasitic infection or infestation in a warm-blooded animal which method comprises topically administering to the animal an effective amount of a composition according to any one of Claims 1 to 9.

5

11 The method according to Claim 10 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.

10

12. The method according to Claim 10 or 11 wherein the composition comprises about 20% to 30% of the metaflumizone; about 10% of a bridging agent, about 2% to about 8% of a non-ionic low foam surfactant, and about 50-60% carrier solvent.

15

13. The method according to any one of Claims 10 to 12 wherein the composition comprises a gamma-hexalactone as the carrier solvent.

14. The method according to Claim 13 wherein the composition is further diluted for use as a pour-on composition.

20

15. The method according to any one of Claims 10 to 12 wherein the composition comprises dimethyl isosorbide as the carrier solvent.

16. The method according to Claim 15 wherein the composition is further diluted for use as a spray or feed/water additive.

25

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A01P5/00 A01P7/02 A01P7/04 A01N43/90
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B. FIELDS SEARCHED

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Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 413 201 A (WYETH) 28 April 2004 (2004-04-28) paragraphs [0002] - [0006], [0022], [0023], [0027], [0028], [2935] examples 1-4 claims 15,21,22,28,32,35	1-16
Y	EP 1 334 661 A (NIHON NOHYAKU CO., LTD) 13 August 2003 (2003-08-13) paragraph [0009]; example 44 claims 1,2,6 paragraphs [0001], [0006], [0011], [0014], [0016], [0017] ----- -/--	1-16

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2006/042099 A (WYETH; SABNIS, SHOBHAN, SHASHI; ZUPAN, JACOB, A; ALBRIGHT, ROBERT, BRU) 20 April 2006 (2006-04-20) claims 1,4,5 page 5, lines 1,2 examples 1-3	1-16
Y	WO 2004/089239 A (MERIAL LTD; SOLL, MARK, D; KUMAR, KRISHAN; WARANIS, ROBERT, P; SHUB, N) 21 October 2004 (2004-10-21) page 1, paragraph 2 page 3, paragraph 2 page 6, last paragraph - page 7, paragraph 2 page 9, paragraph 1 page 9, last paragraph - page 10, paragraph 1 page 19, paragraph 4 claims 1-26	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/019513

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10-16 are directed to a method of treatment of the animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/019513

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 2006042099	A	20-04-2006	NONE	
WO 2004089239	A	21-10-2004	AU 2004228041 A1 BR PI0409185 A CA 2521268 A1 EP 1610613 A2 MX PA05010659 A	21-10-2004 11-04-2006 21-10-2004 04-01-2006 12-12-2005

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- *as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))*

Published:

- *with international search report*
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*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: AMITRAZ COMPOSITIONS

(57) Abstract: The present invention provides a stable composition which comprises a non-hydroxyl-group-containing solvent mixture comprising N,N-diethyl-m-toluamide and γ-hexalactone, optionally with dimethyl sulfoxide, eucalyptol and 1-methoxy-2-propyl acetate; and an effective amount of each of amitraz and at least one additional parasitocidal compound, such as R-28153. Said composition allows for high concentrations of a mixture of parasitocidal agents in a single application and is useful for treating and controlling parasitocidal infection and infestation in a homeothermic animal.

WO 2006/042099 A1

Many topical veterinary compositions require relatively high concentrations of active ingredients to ensure effective and long-lasting protection to the host animal and administration in sufficiently small volumes so as to avoid loss of the composition from run-off or licking by the animal. Typical "spot-on" applications of such compositions to the base of the neck of the animal aid in making the applied composition difficult for the animal to remove, but require that a relatively small volume be applied. Frequently, highly polar solvents containing active hydroxyl groups such as water, alcohol, glycol or the like are utilized to prepare such compositions due to their compatibility with animal skin, hide and/or hair, and their ability to dissolve relatively high concentrations of active. Topical veterinary compositions containing amitraz as one of the active ingredients are highly desirable due to the effective and persistent activity of amitraz against a wide variety of ticks, including ticks resistant to other parasitocidal actives. Heretofore, veterinary compositions containing amitraz and an additional parasitocidal compound have been limited by the instability of amitraz in the presence of hydroxyl-group-containing solvents.

Surprisingly, it has now been found that amitraz and at least one additional parasitocidal compound may be formulated in a stable topical non-irritating composition by employing as a carrier a non-hydroxyl-group-containing solvent combination of N,N-diethyl-m-toluamide and γ -hexalactone, optionally, in further combination with dimethyl sulfoxide, eucalyptol, and 1-methoxy-2-propyl acetate. Accordingly, the present invention provides a topical veterinary parasitocidal composition which comprises a non-hydroxyl-group-containing solvent mixture comprising N,N-diethyl-m-toluamide and γ -hexalactone, optionally with dimethyl sulfoxide, eucalyptol, and 1-methoxy-2-propyl acetate; and an effective amount of each of amitraz and at least one additional parasitocidal compound.

Solvent mixtures suitable for the composition of the invention include those non-hydroxyl-group-containing solvent mixtures containing about 2-30% w/v, preferably about 5-25% w/v of N,N-diethyl-m-toluamide; about 2-30% w/v, preferably about 5-25% w/v, of dimethyl sulfoxide; about 2-30% w/v, preferably about 5-25% w/v, of eucalyptol; about 2-40% w/v, preferably about 10-30% w/v, of γ -hexalactone, and about 2-40% w/v, preferably about 15-35% w/v, of 1-methoxy-2-propyl acetate.

The effective amounts of amitraz and at least one additional parasitocidal compound may be up to as high as 30% w/v of the total composition. For example, amitraz may be present at about 10-30% w/v, preferably 13-20% w/v, and the additional parasitocidal compounds may be present at about 10-30% w/v, preferably 13-20% w/v. The effective amounts of the additional parasitocidal compounds may vary according to the potency of the compounds, the method of application, the host animal, the target parasite, the degree of infestation, or the like. It is understood that effective amounts of less than 10% of the additional parasitocidal compounds may be suitable for the composition of the invention. For example when the composition is administered in the form of a pour-on, spray or any topical administration suitable for use in large animals such as swine, sheep, horses or cattle, amounts of about 3-9% w/v, preferably 5-7% w/v, of amitraz may be suitable and amounts of about 3-9% w/v, preferably 5-7% w/v, of the additional parasitocidal compound may be suitable.

Examples of non-hydroxyl-group-containing solvents include: N,N-diethyl-m-toluamide, γ -hexalactone, dimethyl sulfoxide, eucalyptol, D-limonene or similar terpenes, 1-methoxy-2-propyl acetate, diethylene glycol monobutyl ether acetate, diethylene glycol monoethyl ether acetate, propylene glycol diacetate, ethylene glycol butyl ether acetate, N-methyl-2-pyrrolidone, benzyl acetate, dimethyl formamide, diethyl succinate, diethyl adipate, diethyl sebacate, 2,6-dimethyl-4-heptanone, dipropylene glycol dimethyl ether, heptyl acetate, 2-butoxyethyl acetate, isopropyl myristate, lauryl pyrrolidone, methyl butanone, methyl pentanone, alkylethers of ethylene glycol, γ -butyrolactone, benzyl benzoate, and the like; preferably N,N-diethyl-m-toluamide, γ -hexalactone, dimethyl sulfoxide, eucalyptol, 1-methoxy-2-propyl acetate, or a mixture thereof.

Representative parasitocidal compounds suitable for use in the composition of the invention are: chitin synthesis inhibitors including benzoylphenylureas such as diflubenzuron, flufenoxuron, teflubenzuron, novaluron, fluazuron, or the like; juvenile hormone mimics such as methoprene, hydroprene, pyriproxyfen, fenoxycarb, or the like; pyrethroid insecticides such as permethrin, cypermethrin, α -cypermethrin or the like; phenylpyrazole insecticides such as fipronil; organophosphate insecticides such as chlorfenvinphos, diazinon, malathion, terbufos, or the like; oxime carbamate insecticides; avermectins such as abamectin, doramectin, ivermectin, selamectin or eprinomectin; imidacloprid; milbemycins such as moxidectin or milbemycin oxime;

semicarbazones such as endoxcarb or R-28153, preferably R-28153 (also named as metaflumizone); and the like. R-28153 is especially preferred for use with amitraz, due to its complementary mode of parasitocidal activity, and its chemical compatibility with, and solubility in, non-hydroxyl-group-containing solvents.

5 As used in the specification and claims, the term R-28153 designates the compound 2-[2-(4-cyanophenyl)-1-[3-(trifluoromethyl) phenyl] ethylidene]-N-[4-(trifluoromethoxy) phenyl]-hydrazinecarboxamide. R-28153 and a method for the preparation thereof are described in U. S. Patent 5,543,573. The animal health uses of R-28153 are described in U. S. Patent Publication number US2004-0116419A1.

10 As used herein, the term "w/w" designates weight/weight, the term "w/v" designates weight/volume, and the term "mg/kg" designates milligrams per kilogram of body weight.

Advantageously, the stable topical parasitocidal veterinary composition of the invention allows for high concentrations of the active ingredients and demonstrates
15 no irritation to the skin/hide/hair of the host animal. Accordingly, the present invention provides a method for the treatment and control of ectoparasitocidal infection or infestation in an animal, particularly a homeothermic animal, which comprises topically administering to said animal a composition which comprises a non-hydroxyl-group-containing solvent mixture comprising N,N-diethyl-m-toluamide
20 and γ -hexalactone; optionally with dimethyl sulfoxide; eucalyptol; and 1-methoxy-2-propyl acetate; and an effective amount of each of amitraz and at least one additional parasitocidal compound.

Examples of topical administrations suitable for use in the method of the invention include spot-on, pour-on, dip, wash, shampoo, foam, gel, lotion, or any of
25 the conventional means of topically applying a liquid veterinary composition. The topical mode or administration will vary with the species and size of the host animal. As an example, for companion animals such as dogs or cats, a spot-on, shampoo or wash, and most preferably a spot-on, may be suitable. For large agronomic animals such as cattle, horses or sheep, a pour-on or spray, most preferably a pour-on, may
30 be suitable.

Homeothermic animals suitable for treatment using the composition and method of the present invention include: swine, cattle, sheep, horses, goats, camels, water buffalos, donkeys, rabbits, fallow deer, reindeer, minks, chinchillas, raccoons,

chicken, geese, turkeys, ducks, dogs, cats, or the like, preferably dogs, cats, swine, cattle, horses or sheep.

Ectoparasitic infection or infestations suitable for treatment by the method of the invention include fleas, ticks, lice, mites, or flies, preferably fleas or ticks.

5 In actual practice, the composition of the invention may be administered in dose rates of mg of active ingredient per kg of body weight of the host animal. Dose rates suitable for use in the method of invention will vary depending upon the mode of administration, the species and health of the host animal, the target parasite, the degree of infection or infestation, the breeding habitat, the potency of the additional
10 parasitocidal compound, and the like. In general, a dose of at least 20 mg/kg of amitraz is suitable and, in the case wherein the additional parasitocidal compound is R-28153, at least 1.0 mg/kg of R-28153, preferably 20-45 mg/kg of amitraz and 20-45 mg/kg of R-28153.

In one embodiment of the invention, a dose rate of about 0.1-100 mg/kg, preferably about 1.0-50 mg/kg, of amitraz may be suitable and about 0.1-100 mg/kg, preferably about 1.0-50 mg/kg of an additional parasitocidal compound, such as R-2813. Such doses may be particularly applicable to large animals such as swine, cattle, horses or sheep.

The present invention also provides a process for the preparation of a topical
20 veterinary parasitocidal composition which comprises: admixing N,N-diethyl-m-toluamide and γ -hexalactone, optionally with dimethyl sulfoxide, eucalyptol, and 1-methoxy-2-propyl acetate to form a non-hydroxyl-group-containing solvent mixture; and treating said solvent mixture with amitraz and at least one additional parasitocidal compound to form a homogeneous solution, optionally passing said
25 solution through a solid dehydrating agent.

Parasitocidal compounds suitable for use in the process of the invention may be chitin synthesis inhibitors including benzoylphenylureas such as diflubenzuron, flufenoxuron, teflubenzuron, novaluron, fluazuron, or the like; juvenile hormone mimics such as methoprene, hydroprene, pyriproxyfen, fenoxycarb, or the like;
30 pyrethroid insecticides such as permethrin, cypermethrin, α -cypermethrin or the like; phenylpyrazole insecticides such as fipronil; organophosphate insecticides such as chlorfenvinphos, diazinon, malathion, terbufos, or the like; oxime carbamate insecticides; avermectins such as abamectin, doramectin, ivermectin, selamectin or

What is claimed is:

1. A parasitocidal composition which comprises amitraz and at least one additional parasitocidal compound, in a non-hydroxyl-group-containing solvent mixture comprising N,N-diethyl-m-toluamide and γ -hexalactone, and optionally one or more of dimethyl sulfoxide, eucalyptol and 1-methoxy-2-propyl acetate.
2. The composition according to claim 1 wherein the solvent mixture comprises about 2-30% w/v of N,N-diethyl-m-toluamide; 2-30% w/v of dimethyl sulfoxide; 2-30% w/v of eucalyptol; 2-40% w/v of γ -hexalactone, and 2-40% w/v of 1-methoxy-2-propyl acetate.
3. The composition according to claim 1 wherein the solvent mixture comprises about 5-25% w/v of N,N-diethyl-m-toluamide; 5-25% w/v of dimethyl sulfoxide; 5-25% w/v of eucalyptol; 10-30% w/v of γ -hexalactone; and 15-35% w/v of 1-methoxy-2-propyl acetate.
4. The composition according to any one of claims 1 to 3 wherein the additional parasitocidal compound is R-28153.
5. The composition according to any one of claims 1 to 3 wherein the additional parasitocidal compound is a benzoylphenylurea; a juvenile hormone mimic; a pyrethroid; an organophosphate; a semicarbazone, fipronil; imidacloprid; ivermectin; or moxidectin.
6. The composition according to any one of claims 1 to 4 which comprises about 10-30% w/v of amitraz and about 10-30% w/v of R-28153.
7. The composition according to any one of claims 1 to 4 comprising about 3-9% w/v of amitraz and about 3-9% w/v of R-28153.
8. The composition according to any one of claims 1 to 4 comprising about 13-20% w/v of amitraz and about 13-20% w/v of R-28153.

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9. The composition according to any one of claims 1 to 4 wherein the effective amount is about 5-7% w/v of amitraz and about 5-7% w/v of R-28153.

5 10. A method for the treatment and control of ectoparasiticial infection or infestation in a homeothermic animal which comprises topically administering to said animal a composition according to any one of claims 1 to 9.

10 11. The method according to claim 10 wherein said composition is administered as a spot-on, pour-on, dip, wash, shampoo, spray, foam, gel or lotion.

12. The method according to claim 10 or claim 11 wherein said animal is selected from the group consisting of dogs; cats; swine, cattle; horses; and sheep.

15 13. The method according to any one of claims 10 to 12 wherein said ectoparasiticial infection or infestation is caused by fleas, ticks, lice, mites, or flies.

20 14. A process for the preparation of a composition according to claim 1 which comprises: admixing N,N-diethyl-m-toluamide and γ -hexalactone, optionally with one or more of eucalyptol, dimethyl sulfoxide and 1-methoxy-2-propyl acetate to form a solvent mixture; and treating said solvent mixture with amitraz and an additional parasiticial compound to form a homogeneous solution, optionally passing said solution through a solid dehydrating agent.

25 15. The process according to claim 14 wherein the additional parasiticial compound is R-28153.

30 16. The process according to claim 14 or claim 15 wherein the solid dehydrating agent is 4Å molecular sieves.

EXAMPLE 1

Preparation of Ectoparasitcidal Compositions

<u>Component Description</u>	<u>A</u>		<u>B</u>	
	<u>w/w%</u>	<u>w/v%</u>	<u>w/w%</u>	<u>w/v%</u>
amitraz	14.6	15.3	14.6	15.3
R-28153	14.6	15.3	14.6	15.3
N,N-diethyl-m-toluamide	9.6	10.0	9.6	10.0
dimethyl sulfoxide	9.6	10.0	9.6	10.0
eucalyptol	9.6	10.0	9.6	10.0
1-methoxy-2-propyl acetate	28.7	30.0	19.1	20.0
γ-hexalactone	13.3	9.4	22.9	19.4

5

Method of Preparation

The following solvents are introduced sequentially into a jacketed vessel at 25°C with stirring: N,N-diethyl-m-toluamide, dimethyl sulfoxide, eucalyptol,
10 1-methoxy-2-propyl acetate and γ-hexalactone. This solvent mixture is slowly treated with R-28153 and amitraz; stirring is continued until solution is complete. The resultant solution is passed through a bed of activated 4/ molecular sieves.

15

EXAMPLE 2

Preparation of Ectoparasitcidal Compositions

Using essentially the same procedure described in Example 1 hereinabove,
20 the compositions shown below are prepared.

<u>Component Description</u>	<u>C</u> w/w%	<u>D</u> w/w%
amitraz	14.5	14.5
R-28153	14.5	14.5
N,N-diethyl-m-toluamide	19.3	9.6
dimethyl sulfoxide	--	9.6
eucalyptol	9.6	19.3
1-methoxy-2-propyl acetate	22.8	32.5
γ -hexalactone	14.5	--
Silwet®-560 organosilicone	4.8	--

EXAMPLE 3**5 Preparation of Ectoparasiticide Compositions**

Using essentially the same procedure described in Example 1 hereinabove, the compositions shown below are prepared.

<u>Component Description</u>	<u>E</u> w/v%	<u>F</u> w/v%
amitraz	6.0	6.0
R-28153	6.0	6.0
N,N-diethyl-m-toluamide	10.0	10.0
eucalyptol	10.0	10.0
1-methoxy-2-propyl acetate	30.0	20.0
γ -hexalactone	38.8	48.0

10

EXAMPLE 4**Evaluation of the Efficacy of Test Composition B**

- In this evaluation sixteen dogs are each infested with 100 unfed adult fleas (*Ctenocephalides felis*) and 50 adult brown dog ticks (*Rhipicephalus sanguineus*).
- 15 Each dog is assessed for its ability to retain fleas and ticks by examination and

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(54) Title: GEL COMPOSITIONS FOR CONTROL OF ECTO-PARASITES

(57) Abstract: Semi-solid compositions comprising metaflumizone, a gelling agent and a non-aqueous solvent. The semi-solid compositions of this invention may be topically administered to animals, and are useful for preventing or treating, ectoparasitic infestations in warm-blooded animals for prolonged periods of time.

WO 2006/127406 A2

WHAT IS CLAIMED IS:

1. A composition for topical administration which comprises on a weight
to weight basis
from about 5% to about 30% of metaflumizone;
5 from about 1% to about 15% of a gelling agent;
from about 0% to about 8% of a surfactant; and
from about 45% to about 80% of a non-aqueous solvent system.
2. The composition according to Claim 1 which comprises from about
10 5% to about 20% of the metaflumizone compound.
3. The composition according to Claim 1 or Claim 2 which comprises
from about 2% to 15% of the gelling agent.
- 15 4. The composition according to any one of Claims 1 to 3 wherein the
gelling agent is selected from the group consisting of colloidal silicone dioxide, ethyl
cellulose, methyl cellulose, methacrylic esters copolymers, carboxylated vinyl acetate
terpolymer, PVP/Vinyl acetate copolymers or an equivalent non-aqueous solvent
soluble polymer.
20
5. The composition according to any one of Claims 1 to 4 wherein the
surfactant is a non-ionic surfactant.
6. The composition according to any one of Claims 1 to 4 wherein the
25 surfactant is polyoxyethylene 20 sorbitan monooleate.

7. The composition according to any one of Claims 1 to 6 wherein the amount of the surfactant is about 3% to about 5%.

5 8. The composition according to any one of Claims 1 to 7 wherein the solvent system comprises a mixture of approximately 7:1:2 ratio by weight of γ -hexalactone:N,N-diethyl-m-toluamide:Miglyol 840.

9. The composition according to any one of Claims 1 to 8 which
10 additionally contains up to about 8% by weight of one or more preservatives, colorants, antioxidants, or stabilizers.

10. The composition according to any one of Claims 1 to 9 which additionally includes an anti-syneresis agent.

15

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

20

12. The method according to Claim 11 wherein the animal is selected from the group consisting of, a cows, a sheep, a horse, a camel, a deer, a swine, a goat, a dog, a cat, and a bird.

25



US006395765B1

(12) **United States Patent**
Etchegaray

(10) **Patent No.:** **US 6,395,765 B1**
(45) **Date of Patent:** ***May 28, 2002**

- (54) **ANTIPARASITIC COMPOSITION FOR THE TREATMENT AND PROTECTION OF PETS**
(75) **Inventor:** Jean Pierre Etchegaray, Toulouse (FR)
(73) **Assignee:** Merial, Lyons (FR)
(*) **Notice:** This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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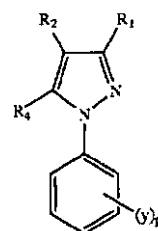
Primary Examiner—John Pak

(74) *Attorney, Agent, or Firm*—Frommer Lawrence & Haug LLP; William S. Frommer; Thomas J. Kowalski

(57) **ABSTRACT**

Composition which is useful in particular for the treatment and protection of domestic animals which are infested with parasites or are likely to be infested with them, these compositions comprising, in the form of a ready-to-use solution:

- a) an insecticidal active substance of formula (I),



(I)

- b) a crystallization inhibitor,
c) an organic solvent having a dielectric constant of between 10 and 35, preferably of between 20 and 30,
d) an organic co-solvent having a boiling point below 100° C., preferably below 80° C., and a dielectric constant of between 10 and 40, preferably of between 20 and 30.

- (21) **Appl. No.:** 08/719,942
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33 Claims, No Drawings

-continued											
	Example No.										
	1	2	3	4	5	6	7	8	9	10	11 12
Butylated hydroxy-toluene (g)	0.01	0.01	0.01	0.01	0.01	0	0.01	0.01	0.01	0.01	0.01 0
Diethylene glycol monoethyl ether (cm ³)		qs	100 cm ³						0		
Dipropylene glycol monomethyl ether (cm ³)			0						qs	100 cm ³	

By way of example, the volume of diethylene glycol monoethyl ether represented by qs is about 75 cm³ for the formula of Example 1.

The following are mixed together, by stirring:
10 g of active principle 1-[4-CF₃ 2, 6-Cl₂ phenyl] 3-cyano 4-[CF₃—SO—] 5-NH₂ pyrazole, all of the ethanol, 60 cm³ of diethylene glycol monoethyl ether or of dipropylene glycol monomethyl ether (solvents), all of the polyvinylpyrrolidone (Kollidono® 17PF from BASF, Germany), all of the polysorbate 80 (Tween® from ICI), all of the butylated hydroxyanisole (if present), all of the butylated hydroxytoluene (if present).

The mixture is made up to 100 cm³ with diethylene glycol monoethyl ether or with dipropylene glycol monomethyl ether (for Example 1, this corresponds to a remaining volume of about 15 cm³).

Each mixture constitutes a concentrated solution S.
3 dogs, weighing about 7, 14 and 28 kg respectively, are infested with 100 fleas each. Two days later, they are treated by cutaneous application of a solution S in a proportion of 0.1 ml/kg, in localized form over about 5 cm² between the shoulders in the area of the withers. After 24 hours, the time required for complete drying, the appearance of the dogs' coat in the area of the deposition on the skin and elsewhere is identical to the initial appearance. In particular, the animal's coat is neither tacky nor sticky when touched and the coat contains no bristled tufts.

24 hours after treatment, the dogs are combed in order to remove and count any fleas which may be present. Then, at weekly intervals after the treatment, the animals are reinfested in the same way as before. 24 hours after each experimental reinfestation, the animals are again combed in order to remove and count any fleas which may still be present. Over a period of 13 weeks, it was observed that there was a percentage reduction in the population of fleas which was maintained above 95% when compared with a control group which had not received the treatment according to the invention. Examples 12 to 24:

For Examples 12 to 24, it suffices to replace, in the above table, Examples 1 to 12 by 12 to 24 respectively, with 12.5 g of active principle. The amounts of the other constituents are unchanged, apart from the amount of solvent required for the complement to 100 cm³.

The following ingredients are mixed together, by simple stirring:

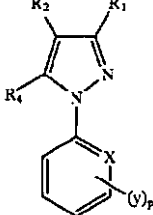
12.5 g of the compound of Example 1 all of the ethanol 60 cm³ of diethylene glycol monoethyl ether or of dipropylene glycol monomethyl ether

all of the polyvinylpyrrolidone
all of the polysorbate 80
all of the butylated hydroxyanisole (if present)
all of the butylated hydroxytoluene (if present).
The mixture is made up to 100 cm³ with diethylene glycol monoethyl ether or with dipropylene glycol monomethyl ether.

When used under the conditions described in Example 1, these mixtures lead to comparable results. A greater than 95% reduction in the population of fleas is observed in less than 24 h when compared with the control group.

What is claimed is:
1. A composition for the treatment or protection of a domestic animal against parasitic infestation by topical application to a localized region with a surface area of less than 10 cm² and diffusion therefrom over the animal's body, the composition comprising, in the form of a ready-to-use solution:

(a) an insecticidal active substance of the formula (I)



in which:
R₁ is a halogen atom, CN or methyl;
R₂ is S(O)_nR₃ or 4,5 dicyanoimidazol-2-yl or haloalkyl;
R₃ is alkyl or haloalkyl;
R₄ represents a hydrogen or halogen atom; NR₅R₆, S(O)_mR₇, C(O)R₇, C(O)OR₇, alkyl, haloalkyl, OR₈ or —N=C(R₉)(R₁₀);
R₅ and R₆ independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl, S(O),CF₃, acyl or alkoxy-carbonyl radical; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms;
R₇ represents an alkyl or haloalkyl radical;
R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;
R₉ represents an alkyl radical or a hydrogen atom;
R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms;

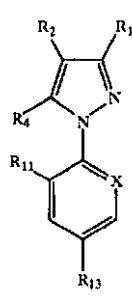
9

X represents carbon, a trivalent nitrogen atom or a radical C—R₁₂;
R₁₂ represents a hydrogen or halogen atom, CN or NO₂;
Y represents SF₅, a hydrogen, CN, NO₂, S(O)_rCF₃, a halogen atom or a haloalkyl or haloalkoxy radical;
m, n, and r represent, independently of each other, an integer equal to 0, 1 or 2; and
p is an integer equal to 1, 2, 3, 4 or 5;
with the proviso that when R₁ is methyl, then either R₃ is haloalkyl, R₄ is NH₂, p is 2, Y in position 6 is Cl, Y in position 4 is CF₃ and X is N; or R₂ is 4,5-dicyanomidazol-2-yl, R₄ is Cl, p is 3, Y in position 6 is Cl, Y in position 4 is CF₃ and X is C—Cl;
(b) a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone, copolymers of vinyl acetate and vinylpyrrolidone, polyoxyethylenated sorbitan esters and mixtures thereof;
(c) an organic solvent selected from the group consisting of acetone, benzyl alcohol, butyl diglycol, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, dipropylene glycol monomethyl ether, propylene glycol, diethylene glycol monoethyl ether, ethylene glycol, and a mixture of at least two of these solvents; and
(d) an organic co-solvent selected from the group consisting of ethanol, isopropanol, and methanol; wherein the compound of formula (I) is present in a proportion from 1 to 20% (W/V);
the crystallization inhibitor is present in a proportion from 1 to 20% (W/V), and meets the following test: a 0.3 ml solution comprising 10% (W/V) of the compound of formula (I) in the organic solvent defined in (c), and 10% (W/V) of said crystallization inhibitor, placed on a glass slide at 20° C. for 24 hours results in fewer than 10 crystals observed on the glass slide with the naked eye;
the organic solvent (c) is present in the overall composition in a proportion representing the complement to 100% of the composition, with the organic co-solvent also present in a (d)/(c) weight/weight (W/W) ratio of between 1/15 and 1/2; and
the organic co-solvent is miscible with water and/or solvent (c).
2. The composition of claim 1 wherein X is carbon or the radical C—R₁₂, Y is CN or NO₂ in positions 2 and 6 of the phenyl ring.
3. The composition of claim 1 X is carbon or the radical C—R₁₂, wherein Y is in position 4 on the phenyl ring and is selected from the group consisting of S(O)_rCF₃, haloalkyl, haloalkoxy and SF₅, wherein r represents an integer equal to 0, 1 or 2.
4. The composition according to claim 1 wherein alkyl radicals in compounds of formula (I) comprise from 1 to 6 carbon atoms.
5. The composition according to claim 1 wherein R₅ and R₆ form the divalent alkylene radical, which, along with the nitrogen atom to which R₅ and R₆ are attached, comprises a 5-, 6- or 7-membered ring.
6. The composition according to claim 1, wherein the compound of formula (I) is 1-[4-CF₃, 2,6-Cl₂ phenyl] 3-cyano 4-[CF₃—SO] 5-NH₂ pyrazole.
7. A composition for the treatment or protection of a domestic animal against parasitic infestation by topical application to a localized region with a surface area of less

10

than 10 cm² and diffusion therefrom over the animal's body, the composition comprising, in the form of a ready-to-use solution:
(a) an insecticidal active substance of the formula (II):

(II)



in which:
R₁ is a halogen atom, CN or methyl;
R₂ is S(O)_mR₃ or 4,5 dicyanoimidazol-2-yl or haloalkyl;
R₃ is alkyl or haloalkyl;
R₄ represents a hydrogen or halogen atom; NR₅R₆, S(O)_mR₇, C(O)R₇, C(O)OR₇, alkyl, haloalkyl, OR₈ or —N=C(R₉)(R₁₀);
R₅ and R₆ independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl, S(O)_rCF₃, or alkoxy-carbonyl radical; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms;
R₇ represents an alkyl or haloalkyl radical;
R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;
R₉ represents an alkyl radical or a hydrogen atom;
R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or one or more OH groups, —O-alkyl groups, —S-alkyl groups, cyano groups, or alky groups;
R₁₁ represents a hydrogen or halogen atom, CN or NO₂;
R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃, or SF₅ group;
m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2;
X represents a trivalent nitrogen atom or a radical C—R₁₂, the other three valencies of the carbon atom forming part of the aromatic ring;
R₁₂ represents a hydrogen or halogen atom, CN or NO₂;
with the proviso that when R₁ is methyl, then either R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N; or R₂ is 4,5 dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl, R₁₃ is CF₃ and X is C—Cl;
(b) a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone, copolymers of vinyl acetate and vinylpyrrolidone, polyoxyethylenated sorbitan esters and mixtures thereof;
(c) an organic solvent selected from the group consisting of acetone, benzyl alcohol, butyl diglycol, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, dipropylene glycol monomethyl ether, propylene glycol, diethylene glycol monoethyl ether, ethylene glycol, and a mixture of at least two of these solvents; and

(d) an organic co-solvent selected from the group consisting of ethanol, isopropanol, and methanol; wherein the compound of formula (II) is present in a proportion from 1 to 20% (W/V);

the crystallization inhibitor is present in a proportion from 1 to 20% (W/V), and meets the following test: a 0.3 ml solution comprising 10% (W/V) of the compound of formula (II) in the organic solvent defined in (c), and 10% (W/V) of said crystallization inhibitor, placed on a glass slide at 20° C. for 24 hours results in fewer than 10 crystals observed on the glass slide with the naked eye;

the organic solvent (c) is present in the overall composition in a proportion representing the complement to 100% of the composition, with the organic co-solvent also present in a (d)/(c) weight/weight (W/W) ratio of between 1/15 and 1/2; and

the organic co-solvent is miscible with water and/or solvent (c).

8. The composition of claim 7 wherein X is a trivalent nitrogen atom.

9. The composition according to claim 7 wherein R₁ is CN, R₂ is haloalkyl, R₄ is NH₂, R₁₁ and R₁₂ are independently of each other a halogen atom, and R₁₃ is a haloalkyl.

10. The composition according to claim 7 wherein X is C—R₁₂.

11. The composition according to claim 7 wherein alkyl radicals in compounds of formula (II) comprise from 1 to 6 carbon atoms.

12. The composition according to claim 7 wherein R₅ and R₆ form the divalent alkylene radical, which, along with the nitrogen atom to which R₅ and R₆ are attached, comprises a 5-, 6- or 7-membered ring.

13. The composition of any one of claims 1-12, wherein the compound of part (a) present in a proportion from 5 to 15% (W/V).

14. The composition of any one of claims 1-12, wherein the crystallization inhibitor is present in a proportion from 5 to 15% (W/V).

15. The composition of claim 13, wherein the crystallization inhibitor is present in a proportion from 5 to 15% (W/V).

16. The composition of any one of claims 1-12, further comprising water present to 30% V/V.

17. The composition of claim 16, wherein the water is present to 5% V/V.

18. The composition of any one of claims 1-12, further comprising an antioxidant present in a proportion from 0.005-1% W/V.

19. The composition of claim 18, wherein the antioxidant is present in a proportion from 0.01-0.05% W/V.

20. The composition of any one of claims 1-12, wherein the crystallization inhibitor meets the following test: a 0.3 ml solution comprising 10% (W/V) of the compound of part (a)

in the organic solvent defined in (c), and 10% (W/V) of said crystallization inhibitor, placed on a glass slide at 20° C. for 24 hours results in 0 crystals observed on the glass slide with the naked eye.

21. The composition according to any one of claims 1-12, wherein the polyoxyethylenated sorbitan ester is polysorbate.

22. The composition according to claim 21, wherein the polysorbate is polysorbate 80.

23. The composition according to any one of claims 1-12, wherein the crystallization inhibitor comprises a mixture of polyvinylpyrrolidone and polysorbate.

24. The composition according to any one of claims 1-12, wherein the organic solvent is a glycol ether selected from the group consisting of dipropylene glycol n-butyl ether, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, diethylene glycol monoethyl ether, dipropylene glycol monomethyl ether and mixtures thereof.

25. The composition according to claim 24, wherein the glycol ether is selected from the group consisting of diethylene glycol monoethyl ether and dipropylene glycol monomethyl ether.

26. The composition according to claim 18, wherein the antioxidant is selected from the group consisting of butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, sodium metabisulphite, propyl gallate, sodium thiosulfate, and a mixture of not more than two of these antioxidants.

27. The composition of any one of claims 1-12, wherein the crystallization inhibitor comprises a mixture of at least one copolymer of vinyl acetate and vinyl pyrrolidone and polysorbate.

28. A method for the treatment or the elimination of a parasitic infestation in a domestic animal which comprises topically applying to a localized region with a surface area of less than 10 cm² and diffusion therefrom over the animal's body an effective amount of the composition according to any one of claims 1-12.

29. The method according to claim 28, wherein the animal is a cat or dog and the parasite is a flea or tick.

30. A method for distributing an active agent over a domestic animal's body and thereby treating or eliminating a parasitic infestation in said animal, which method comprises topically applying to a localized region with a surface area of 5-10 cm² on the animal's skin an effective amount of a composition according to any one of claims 1-12.

31. The method according to claim 30, wherein the animal is a cat or dog and the parasite is a flea or tick.

32. The method according to claim 30, wherein the animal is a cat.

33. The method according to claim 30, wherein the animal is a dog.

* * * * *

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Research Disclosure, No. 380, page 802

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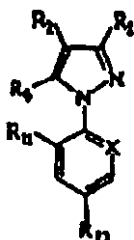
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(54) **Solution for direct application on the skin for controlling cattle and sheep parasites**

(57) A solution for direct application on the skin to eliminate cattle and sheep parasites, particularly *Boophilus microplus*, including 0.05-25 %, preferably 0.05-10 % and particularly 0.1-2 % w/v relative to the total solution, of a compound of formula (I), in a low-volume formulation designed to release the compound of formula (I) onto the skin and hair for contact activity against parasites.



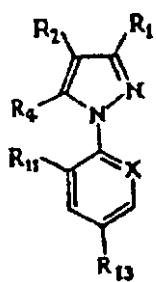
(I)

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CLAIMS

1. Direct pour-on skin solution intended to eliminate parasites from cattle and sheep, most particularly ticks, especially *Boophilus microplus* in cattle and lice and blowfly in sheep, comprising from 0.05 to 25% weight/volume, relative to the total solution, of a compound of formula (I):

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(I)

in which:

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R₁ is CN or methyl or a halogen atom;
R₂ is S(O)_nR₃ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R₃ is alkyl or haloalkyl;

25

R₄ represents a hydrogen or halogen atom; or a radical NR₅R₆, S(O)_nR₇, C(O)R₇, C(O)O-R₇, alkyl, haloalkyl or OR₈ or a radical -N=C (R₉) (R₁₀);

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R₅ and R₆ independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl, alkoxycarbonyl, or S(O)_nCF₃ radical; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms, such as oxygen or sulphur;

R₇ represents an alkyl or haloalkyl radical;

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R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

8. Solution according to one of claims 1 to 7, characterized in that the compound of formula (I) is chosen from those in which R_1 is CN, R_2 is haloalkyl, R_3 is NH_2 , R_{11} and R_{12} are, independently of each other, a halogen atom and/or R_{13} is haloalkyl.
9. Solution according to one of claims 1 to 3, characterized in that the compound of formula (I) is: 1-[2,6-Cl₂, 4-CF₃phenyl]3-CN 4-[SO-CF₃] 5-NH₂pyrazole.
10. Solution according to any one of claims 1 to 9, characterized in that it comprises from 0.05 to 10% weight/volume, preferably from 0.1 to 2%, of compound of formula (I).
11. Solution according to any one of claims 1 to 10, characterized in that it comprises from 0.25 to 1.5%, preferably about 1%, of compound of formula (I).
12. Solution according to any one of claims 1 to 11, characterized in that it comprises a solvent for the compound (I) and a diluent, optionally an emollient.
13. Solution according to claim 12, characterized in that the solvent is selected from the group consisting of:
- acetyl tributyl citrate, fatty acid esters such as the dimethyl ester, diisobutyl adipate, acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, in particular N-methylpyrrolidone, diethylene glycol monoethyl ether, ethylene glycol and diethyl phthalate, or a mixture of at least two of these solvents.
14. Solution according to claim 12 or 13, characterized in that the diluent is selected from the group

consisting of:

plant oils such as soybean oil, groundnut oil, castor oil, corn oil, cotton oil, olive oil, grape seed oil, sunflower oil, etc.; mineral oils such as petrolatum, paraffin, silicone, etc.; aliphatic or cyclic hydrocarbons or alternatively, medium-chain (C8 to C12 in particular).

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15. Solution according to one of claims 12 to 14, characterized in that the emollient is selected from the group consisting of:

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- polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters; lecithin, sodium carboxymethylcellulose, silicone oils,

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- anionic surfactants such as alkaline stearates, in particular sodium, potassium or ammonium stearates; calcium stearate, triethanolamine stearate; sodium abietate; alkyl sulphates, in particular sodium lauryl sulphate and sodium cetyl sulphate; sodium dodecylbenzenesulphonate, sodium dioctylsulphosuccinate; fatty acids, in particular those derived from coconut oil,

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- cationic surfactants such as water-soluble quaternary ammonium salts of formula $N^+R'R''R'''R''''$, Y^- in which the radicals R are optionally hydroxylated hydrocarbon radicals, and Y^- is an anion of a strong acid such as the halide, sulphate and sulphonate anions; cetyltrimethylammonium bromide is among the cationic surfactants which can be used,

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- amine salts of formula $N^+R'R''R'''$ in which the radicals R are optionally hydroxylated hydrocarbon radicals; octadecylamine hydrochloride is among the cationic surfactants which can be used,

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- nonionic surfactants such as sorbitan esters, which are optionally polyoxyethylenated, in particular

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haloalkyl, R_4 is NH_2 , R_{11} is Cl, R_{13} is CF_3 and X is N.

21. Use according to one of claims 18 to 20, characterized in that the compound of formula (I) is such that R_1 is CN.

5 22. Use according to one of claims 18 to 21, characterized in that the compound of formula (I) is such that R_{11} is haloalkyl, preferably CF_3 .

23. Use according to one of claims 18 to 22, characterized in that the compound of formula (I) is such that
10 R_2 is $S(O)_nR_3$, preferably with $n = 1$, R_3 preferably being CF_3 or alkyl, in particular methyl or ethyl, or $n = 0$, R_3 preferably being CF_3 .

24. Use according to one of claims 18 to 23, characterized in that the compound of formula (I) is such that
15 X is $C-R_{12}$ with R_{12} being a halogen atom.

25. Use according to one of claims 18 to 20, characterized in that the compound of formula (I) is such that
20 R_1 is CN, R_3 is haloalkyl, R_4 is NH_2 , R_{11} and R_{12} are, independently of each other, a halogen atom and/or R_{13} is haloalkyl.

26. Use according to one of claims 18 to 20, characterized in that the compound of the formula (I) is:
1-[2,6-Cl₂, 4- CF_3 ,phenyl]3-CN 4-[SO- CF_3] 5- NH_2 pyrazole.

27. Use according to any one of claims 18 to 26,
25 characterized in that it is applied at a rate of 0.1 to 2 mg/kg, preferably 0.25 to 1.5 mg/kg, in particular about 0.1 mg/kg.

28. Use according to any one of claims 18 to 27, characterized in that when applied topically locally
30 onto the animal's skin, the solution is designed to ensure protection for at least two months, in particular against *Boophilus microplus*.

29. Use according to any one of claims 18 to 28, characterized in that the solution is designed to ensure
35 total elimination of *Boophilus microplus* in less than 2

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days.

30. Use according to any one of claims 18 to 29, characterized in that it is directed towards the preparation of such a skin solution for application to the animal before the animal enters into the "feed lots".

31. Use according to claim 30, for the preparation of such a skin solution which is intended to be applied every month, preferably every two months, to the animal, preferably with the applications being stopped 1 to 3 months before slaughter.

32. Process for the treatment of cattle and sheep essentially against *Boophilus microplus* in cattle and blowfly and lice in sheep, using a direct pour-on skin solution as described, and under the conditions indicated, in any one of the preceding claims.

EUROPEAN PATENT APPLICATION

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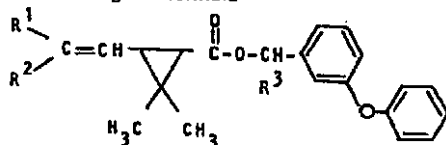
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Insecticidal control of ectoparasites.

A pour-on or spot-on method of eradicating or controlling ectoparasites and myiasis in non-human animals by the direct application of an ectoparasitocidal amount of a pyrethroid, having the formula



or a stereochemically isomeric form thereof, wherein:

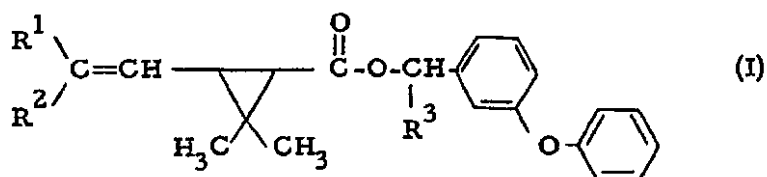
R¹ and R² are, each independently, selected from the group consisting of fluoro, chloro, bromo and iodo; and

R³ is a member selected from the group consisting of hydrogen and cyano,

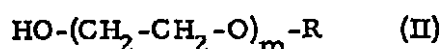
to a specific skin area of the non-human animal, compositions for use in such method and a process of preparing such compositions.

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5 or a stereochemically isomeric form thereof, in a liquid medium,
 6 said medium comprising at least 50% of a solvent consisting of one
 7 or more alcohols, having the formula



8 wherein m is the integer 1, 2 or 3; and
 9 R is lower alkyl.

1 6. A pour-on or spot-on composition for eradicating or con-
 2 trolling ectoparasites and myiasis in non-human animals, said
 3 composition comprising from 1 to 30% by weight of cypermethrin
 4 or a stereochemically isomeric form thereof in a liquid medium,
 5 said medium comprising at least 50% by weight of 2-(2-butoxy-
 6 ethoxy)ethanol.

1 7. A pour-on or spot-on composition according to claim 14
 2 wherein said medium comprises at least 80% by weight of 2-(2-
 3 butoxyethoxy)ethanol.

1 8. A pour-on or spot-on composition according to claim 14
 2 wherein said medium essentially consists of 2-(2-butoxyethoxy)-
 3 ethanol.

1 9. A method of preparing a pour-on or spot-on composition
 2 for eradicating or controlling ectoparasites and myiasis in non-
 3 human animals, characterized in that from 1 to 30 parts by weight
 4 of a pyrethroid of formula (I) as defined in claim 1 or a stereochemi-
 5 cally isomeric form thereof are intimately mixed with 70 to 99
 6 parts by weight of a liquid medium, said medium comprising at
 7 least 50% of a solvent consisting of one or more alcohols having
 8 the formula (II) as defined in claim 5.

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1 10. A method of preparing a pour-on or spot-on com-
2 position for eradicating or controlling ectoparasites and myiasis in
3 non-human animals, characterized in that form 1 to 30 parts by
4 weight of cypermethrin or a stereochemically isomeric form thereof
5 are intimately mixed with a liquid medium said medium comprising
6 at least 50% of 2-(2-butoxyethoxy)ethanol.