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LANGWIRKENDE, INJIZIERBARE, FORMULIERUNGEN ENTHALTEND RIZINUSÖL

FORMULATIONS INJECTABLES A ACTION PROLONGEE RENFERMANT DE L’HUILE DE RICIN HYDROGENEE

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- EP-A- 0 413 538
- WO-A-97/11709
- DE-A- 2 548 413
- DE-A- 19 613 972
- GB-A- 1 060 632

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SUMMARY OF THE INVENTION

[0001] This invention is concerned with the unexpectedly long duration of activity which is observed when injectable formulations containing certain therapeutic agents are prepared using hydrogenated castor oil and a combination of hydrophobic or water immiscible carriers. Thus, it is an object of this invention to provide such a prolonged therapeutic effect. An additional object is to describe the therapeutic agents which may be employed in the long acting formulations. A still further object is to provide additional components which may be employed in the formulations. Additional objects will become apparent from a reading of the following description.

BACKGROUND OF THE INVENTION

[0002] The therapeutic agents which are used in the inventive formulations are well known to the practitioner to which this invention pertains. Classes of therapeutic agents contemplated by the inventive formulations include insecticides, acaricides, parasiticides, growth enhancers, and oil-soluble, nonsteroidal anti-inflammatory drugs (NSAIDS). Specific classes of compounds which fall within these classes include, for example, avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridymethyl derivatives, phenylpyrazoles, and COX-2 inhibitors.


[0004] European Patent Application 413,538 relates to an injectable formulation containing an avermectin compound and triacetin. European Patent Application 535,734 relates to an injectable formulation containing an avermectin compound and hydrogenated castor oil in a hydrophobic carrier such as triacetin. The formulations in both European Patent Applications are said to provide efficacy against external and internal parasites in animals only for up to 42 days. Neither of these applications suggests or teaches how to manipulate the composition of the formulation in order to achieve efficacy beyond 42 days.

[0005] Nodulisporic acid and its derivatives are a class of acaricidal, antiparasitic, insecticidal and anthelmintic agents known to a practitioner of the art. These compounds are used to treat or prevent infections in humans and animals. These compounds are described, for example, in U.S. Patent 5,399,582 and WO 96/29073. Additionally, the compounds can be administered in combination with other insecticides, parasiticides, and acaricides. Such combinations include anthelmintic agents, such as those discussed above which include ivermectin, avermectin, and emamectin, as well as other agents such as thiabendazole, fentanetor morantel; phenylpyrazoles such as fipronil; and insect growth regulators such as lufenuron. Such combinations are also contemplated in the present invention.

[0006] Generally, all classes of insecticides are provided for in this invention. One example of this class include substituted pyridymethyl derivatives such as imidacloprid. Agents of this class are described, for example, in U.S. Patent 4,742,060 or in EP 892,060. It would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulation to treat a particular infection of an insect.

[0007] Phenylpyrazoles are another class of insecticides which possess excellent insecticidal activity against all insect pests including blood-sucking pests such as ticks, fleas etc., which are parasites on animals. This class of agents kills insects by acting on the gammabutyric acid receptor of invertebrates. Such agents are described, for example, in U.S. Patent No. 5,567,429, U.S. Patent No. 5,122,530, and EP 295,117. It would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulations.

[0008] Insect growth regulators are another class of insecticides or acaricides, which are also provided for in the inventive formulations. Compounds belonging to this group are well known to the practitioner and represent a wide range of different chemical classes. These compounds all act by interfering with the development or growth of the...
insect pests. Insect growth regulators are described, for example, in U.S. Patent 3,748,356; U.S. patent 3,818,047; U.S. Patent 4,225,598; U.S. Patent 4,798,837; and U.S. Patent 4,751,225, as well as in EP 179,022 or U.K. 2,140,010. Again, it would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulation.

[0009] Estrogens, progestins, and androgens refers to classes of chemical compounds which are also well known to a practitioner in this art. In fact, estrogens and progestins are among the most widely prescribed drugs and are used, for example, alone or in combination for contraception or hormone replacement therapy in post menopausal women. Estrogens and progestins occur naturally or are prepared synthetically. This class of compounds also includes estrogens or progestosterone receptor antagonists. Antiestrogens, such as tamoxifen and clomiphene, are used to treat breast cancer and infertility. Antiprogestines are used as contraceptives and anticancer drugs, as well as to induce labor or terminate a pregnancy.

[0010] The androgens and antiandrogens structurally related to the estrogens and progestins as they are also biosynthesized from cholesterol. These compounds are based on testosterone. Androgens are used for hypogonadism and promote muscle development. Antiandrogens are used, for example, in the management of hyperplasia and carcinoma of the prostate, acne, and male pattern baldness as well as in the inhibition of the sex drive in men who are sex offenders. Estrogen, progestins, and androgens are described, for example, in "Goodman & Gilman's The Pharmacological Basis of Therapeutics," 9th ed., J.G. Handman and L. Elimbird, eds., Ch. 57 to 60, pp. 1411-1485, McGraw Hill, New York (1996) or in "Principles of Medicinal Chemistry," 2nd ed., W.O. Foye, ed., Ch. 21, pp. 495-559, Lea & Febiger, Philadelphia (1981).

[0011] Estrogens, progestins and androgens are also used in animal husbandry as growth promoters for food animals. It is known in the art that compounds of these classes act as growth-promoting steroids in animals such as cattle, sheep, pigs, fowl, rabbits, etc. Delivery systems to promote the growth of animals are described, for example, in U.S. Patent 5,401,507, U.S. Patent 5,288,469, U.S. Patent 4,758,435, U.S. Patent 4,686,092, U.S. Patent 5,072,716 and U.S. Patent 5,419,910.

[0012] NSAIDS are well known in the art. The classes of compounds which belong to this group include salicylic acid derivatives, para-aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids (fenamates), enolic acids, and alkanones. NSAIDS exert their activity by interfering with prostaglandin biosynthesis by irreversibly or reversibly inhibiting cycloxygenase. Also included are COX-2 inhibitors which act by inhibiting the COX-2 receptor. Compounds of this group possess analgesic, antipyretic and nonsteroidal anti-inflammatory properties. Compounds belonging to these classes are described, for example, in Chapter 27 of Goodman and Gilman on pages 617 to 658 or in Ch. 22 of Foye on pages 561 to 590 as well as in U.S. Patents 3,896,145; U.S. Patent 3,337,570; U.S. Patent 3,904,682; U.S. Patent 4,009,197; U.S. Patent 4,223,299; and U.S. Patent 2,562,830, as well as the specific agents listed in The Merck Index. This invention contemplates those compounds that are oil-soluble.

[0013] These and other embodiments are disclosed or are obvious from and encompassed by the following Detailed Description of the Invention.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention relates to a long acting injectable formulation for use in human and veterinary medicine, depending on the selected specific therapeutic agent and the indication being treated. The inventive formulation comprises:

(a) a therapeutic agent selected from the group consisting of, e.g., insecticides, acaricides, parasiticides, growth enhancers, and oil-soluble NSAIDS,
(b) hydrogenated castor oil, and
(c) a hydrophobic carrier comprising:

(i) triacetin, benzyl benzoate, or ethyl oleate or a combination thereof,
(ii) acylated monoglycerides, propyl dicaprylates/dicaprates and caprylic acid/capric triglycerides.

[0015] More preferred, are long-acting injectable formulations wherein

(a) a therapeutic agent selected from the group consisting of, e.g., avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, phenylpyrazoles and COX-2 inhibitors,
(b) hydrogenated castor oil, and
(c) a hydrophobic carrier comprising:
(i) triacetin, benzyl benzoate, or ethyl oleate or a combination thereof,
(ii) acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric acid triglycerides or a combination thereof.

The formulations of the present invention considerably prolong the duration of activity. By the term "acyl" Applicants mean an organic acid group in which the OH of the carboxyl group is replaced by some other substituent; i.e., RCO wherein R is, for example a C1-C10-alkyl group or a carbocyclic aromatic or a heteroaromatic group. Examples of such groups include acetyl, propionyl, butyryl, isobutyryl, and benzoyl. The term "prolonged duration of activity" means that the activity of the therapeutic agent is extended beyond the time period normally achieved when the therapeutic agent is injected into a host using a conventional, prior art carrier. As conventional injectable formulations are well known in the art, a skilled practitioner could readily understand the meaning of this term. Generally, depending upon the agent, host, and disease state, activity can be prolonged for a period from up to 120 days to up to 180 days. Preferable time periods in which the duration of the agent is prolonged includes from 14 days to 180 days, 30 days to 150 days, 42 days to 120 days; and 60 days to 90 days. While not wishing to be bound by theory, it is believed this increase in activity is achieved because the inventive formulations significantly increase the plasma concentration in tissue for an extended period of time by up to about 2 weeks to about 24 weeks, with time periods of up to about 6, 8, 10, 12, 16 and 20 weeks being observed. With respect to avermectins and milbemycins, the present formulations have been found to have a considerably prolonged duration against internal and external parasites over prior injectable formulation of avermectins or milbemycins. In addition, the present formulations for avermectin and milbemycin provide significantly higher plasma levels at day 42 than prior long-acting formulations thereby producing efficacy for all relevant parasitic species.

Preferred long-acting injectable formulations comprise:

(a) about 1.0 to about 10.0% w/v of a therapeutic agent,
(b) about 1 to about 3% w/v of hydrogenated castor oil, and
(c) a hydrophobic carrier comprising:

(i) about 30 to about 45% v/v of triacetin; benzyl benzoate or ethyl oleate; and
(ii) about 55 to 70% of v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

Even more preferred are the above formulations wherein about 1.0 to about 5.0% w/v of a therapeutic agent is present. Especially preferred are the inventive formulations wherein about 2.5 to about 5.0% w/v of a therapeutic agent is present.

Especially preferred long-acting formulation of the present invention comprises:

(a) an avermectin or milbemycin compound,
(b) hydrogenated castor oil, and
(c) triacetin and acetylated monoglycerides.

In an especially preferred embodiment, the long-acting formulation comprises:

(a) about 1.0 to about 5.0% w/v of an avermectin or milbemycin compound,
(b) about 0.5 to about 3.5% w/v of hydrogenated castor oil, and
(c) about 30 to about 45% v/v of triacetin and about 55 to about 70% v/v of acetylated monoglycerides.

In a most preferred embodiment, the long-acting formulation comprises:

(a) 3.15% w/v of ivermectin,
(b) 1% w/v of hydrogenated castor oil, and
(c) 40% v/v of triacetin and up to 60% v/v of acetylated monoglycerides.

Another aspect of the invention is to provide a method for the prevention or treatment of parasite or insect infestations in a host in need thereof for an extended period of time by administering a single dose of a long-acting injectable formulation comprising the appropriate therapeutic agent. That duration typically, for example, lasts from up to about 1 month to about six months, depending upon the agent, host and indication being treated. Extensions of activity lasts from up to about 2 months to about 5 months and especially from up to 3 months to up to 4 months are observed. A further aspect of this invention is to promote the growth in animals by administering a single long-acting
formulation according to the present invention wherein the therapeutic agent is an estrogen, progestin, or androgen. Another aspect of the present invention is a method to treat inflammation, pain or fever for an extended period of time in a host in need thereof by administering a single-dose of a formulation according to the present invention wherein the therapeutic agents are oil-soluble NSAIDS. An especially preferred aspect of the invention is to provide a method for the prevention or treatment of parasitic infestation in cattle for a minimum of 42 days which comprises administering to said cattle a single dose of a long-acting injectable formulation according to the present invention wherein the therapeutic agent is an avermectin or milbemycin.

[0023] Therapeutic agents used in the invention formulations include all known avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, oil-soluble NSAIDS, phenylpyrazoles, substituted pyridylmethyl compounds, and agents which act as insect growth regulators, which are compatible in the inventive formulations for their intended use. The ester and amide derivatives of these compounds, where applicable, as well as their salt forms are also contemplated. Specific compounds which belong to these classes of therapeutic agents are well known to the practitioner of this art. Likewise, the specific disease state as well as the particular dose would be well known to the practitioner.

[0024] Avermectins and milbemycins share the same common 16-membered macrocyclic lactone ring; however milbemycins do not possess the disaccharide substituent on the 13-position of the lactone ring.

[0025] While many avermectin compounds are known in the art, a representative structure of the class of compounds is as follows:

where the broken line indicates a single or a double bond at the 22,23-positions;

\[ R_1 \text{ is hydrogen or hydroxy provided that } R_1 \text{ is present only when the broken line indicates a single bond;} \]
\[ R_2 \text{ is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;} \]
\[ R_3 \text{ is hydroxy, methoxy or } = \text{NOR}_5 \text{ where } R_5 \text{ is hydrogen or lower alkyl;} \text{ and} \]
\[ R_4 \text{ is hydrogen, hydroxy or} \]

where \( R_6 \) is hydroxy, amino, mono- or di-lower alkylamino or lower alkanoylamino.

[0026] The preferred compounds are avermectin Bla/Blb (abamectin), 22,23-dihydro avermectin Bla/Blb (ivermectin) and the 4"-acetylamino-5-ketoximino derivative of avermectin Bla/Blb. Both abamectin and ivermectin are approved
as broad spectrum antiparasitic agents. The structures of abamectin and ivermectin are as follows:

![Abamectin Structure](image1)

wherein for abamectin the broken line represents a double bond and R₁ is not present and for ivermectin the double bond represents a single bond and R₁ is hydrogen; and R₂ is isopropyl or sec-butyl.

[0027] The 4''-acetylamino-5-ketoximino derivatives of avermectin Bla/Blb has the following structural formula:

![Avermectin Structure](image2)

where R₂ is isopropyl or sec-butyl.

[0028] The avermectin products are generally prepared as a mixture of at least 80% of the compound where R₂ is sec-butyl and no more than 20% of the compound where R₂ is isopropyl. Other preferred avermectins, include eme-mectin, epinomectin and doramectin. Doramectin is disclosed in U.S. Patent 5,089,490 and EP 214738. This compound has the following structure:
In the present formulations, ivermectin is especially preferred. A representative structure for a milbemycin is that for milbemycin α₁:

[0029] An especially preferred milbemycin is moxidectin, whose structure is as follows:
The compound is disclosed in U.S. Patent No. 5,089,490.

Insecticides contemplated by this invention are also well known in the art and such compounds include substituted pyridymethyl derivatives and phenylpyrazoles. An especially preferred substituted pyridymethyl derivative is imidaclorop. An especially preferred phenylpyrazole is fipronil, whose chemical name is 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylpyrazole. Fipronil is well known in the art as a flea and tick agent. Additional insecticides included by the invention include insect growth regulators. Especially preferred insect growth regulators include diflubenzuron, lufenuron, methoprene, phenoxy carb, pyriproxyfen, and cyromazine.

Specific estrogen, progestin and androgen compounds are well known to the practitioner. Especially preferred compounds belonging to this class include progesterone, estradiol benzoate and trenbolone acetate.

Oil-soluble NSAIDS are also well known to the practitioner. Classes of NSAIDS which are preferred are indole and indecene acetic acids and heteroaryl acetic acids. Especially preferred compounds include indomethacin, ketorolac, caprofen, flunixin, ketoprofen, meloxicam, naproxen, and phenylbutazone.

Hydrogenated castor oil is refined, hydrogenated, and deodorized castor oil, consisting mainly of the triglyceride of hydroxystearic acid. The hydrogenated castor oil is readily prepared using normal techniques known to those skilled in the art of preparing hydrogenated castor oils and one suitable form of hydrogenated castor oil is available commercially under the trade name "Thixcin R" from NL Industries. While not wishing to be bound by theory, it appears that hydrogenated castor oil, being a waxy hydrophobic solid, is left at the injection site entrapping the therapeutic agent after the hydrophobic carrier has diffused from the injection site; it is this hydrophobic hydrogenated castor oil/therapeutic agent matrix that forms a "depot" of the active material which slowly diffuses from the injection site over a prolonged period of time. The hydrogenated castor oil constitutes approximately 1% w/v of the present formulation.

The hydrophobic carrier of the present formulation comprises a mixture of

(i) triacetin, benzyl benzoate, ethyl oleate or a combination thereof; and
(ii) acylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides or a combination thereof.

These compounds as well as their sources are well known in the art. For example, triacetin (glyceryl triacetate or glycerol triacetate) and acetylated monoglycerides (available under the tradename "Myvacet 9-45" from Quest International). The ratio of component (i) to component (ii) used in the present formulation is generally from 45:55 to 70; preferably the ratio is approximately 40:60. In addition to the hydrogenated castor oil, the therapeutic agent and the hydrophobic carrier, the formulation can contain other inert ingredients such as antioxidants or preservatives. Antioxidants such as a propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like may be added to the present formulation. The antioxidants are generally added to the formulation in amounts of from about 0.01 to about 2.0% (w/v). Preservatives such as the parabens (methylparaben and/or propylparaben) are suitably used in the formulation in amounts ranging from about 0.01 to about 2.0 w/v.

The long-acting injectable formulation of the present invention may be prepared by adding a dispersion of hydrogenated castor oil in acetylated monoglycerides, propyl dicaprylates/dicaprates or caprylic/capric triglycerides to a solution comprising the therapeutic agent, and any other inert ingredients, in triacetin benzyl benzoate or ethyl oleate,
and mixing the liquids until uniform. Since the long acting formulation is intended for injection, it is necessary that it be sterilized. Heat sterilization is generally to be avoided in the situation where avermectin or milbemycin compounds are used since these compounds are unstable at autoclave temperatures. Rather, membrane sterilization is preferred in those situations with dissolved solids and gamma sterilization for the hydrogenated castor oil. The sterile hydrogenated castor oil is dispersed in the product aseptically and then aseptically packaged.

[0037] The instant formulation is equally applicable to other compounds used for injection as long as such compounds are soluble in the mixture of the hydrogenated castor oil and hydrophobic carrier. Additional compounds that can be used in this formulation are other antiparasitic agents and antibiotics, therapeutic vitamin and mineral supplements, and other agents that are assisted in their therapeutic effect by having their effects extended over a prolonged period of time. Again, such compounds would be well known to the practitioner.

[0038] The instant long-acting formulations are administered to a warm-blooded animals such as humans, cattle, sheep, pigs, cats, dogs, horses, and the like by intramuscular or subcutaneous injection. The amount of therapeutic agent depends on the individual therapeutic agent, the animal being treated, the disease state, and the severity of the disease state. The determination of those factors is well within the skill level of the practitioner. Generally, such preparation normally contains about 0.0005 to about 50% w/v of therapeutic agent. Preferred formulations are those containing about 0.01 to 10% w/v of therapeutic agent and especially preferred formulations are those containing about 2.5 to about 5% w/v of therapeutic agent. For the avermectins and milbemycins, the formulations will generally be prepared to administer from about 0.1 to about 2 mg/kg, preferably from about 0.4 to about 0.85 mg/kg and most preferably from about 0.6 to about 0.7 mg/kg of the active ingredient. At a preferred dose volume of about 1 ml to treat 50 kg of animal body weight the formulation contains from about 5 to about 50 mg of the active agent per ml of solution or about 0.5 to about 10%, w/v preferably about 2.5 to about 5% w/v. However, depending upon the activity of the compound and the animal being treated, doses as low as about 0.3% w/v of the active ingredient are usable. For nodulisporic acid and its derivatives, a formulation containing about 0.0005 to about 5% w/v of the active compound is preferred.

[0039] The present formulation provides for an extended period of treatment. For avermectins and milbemycins a minimum of 42 days of activity against endo- and ectoparasites is obtained without causing tissue irritation. The extended period of time for the other therapeutic agents is readily determined by one skilled in the art and is determined by such factors as the therapeutic agent, disease state, host and severity of the infection. While the previously reported avermectin formulation containing hydrogenated castor oil in triacetin did produce prolonged plasma level compared to a formulation without hydrogenated castor oil, it did not achieve a plasma level efficacious against all relevant parasitic species at the 42 day target. In contrast the present formulation using avermectins or milbemycins surprisingly provides a significantly higher plasma at day 42 and beyond. The present formulation is also efficacious against ticks and Dermatobia hominis for up to 75 and 140 days, respectively.

[0040] The following example is provided in order that the invention might be more fully understood. It is not to be construed as a limitation of the invention.

### EXAMPLE 1

<table>
<thead>
<tr>
<th>Material</th>
<th>%</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>3.15%</td>
<td>17.6 gm</td>
</tr>
<tr>
<td>n-propyl gallate</td>
<td>0.02%</td>
<td>0.10 gm</td>
</tr>
<tr>
<td>Thixcin R</td>
<td>1.0%</td>
<td>5.0 gm</td>
</tr>
<tr>
<td>triacetin</td>
<td>40.0%</td>
<td>200.0 gm</td>
</tr>
<tr>
<td>Myvacet 9-45</td>
<td>qs 100%</td>
<td>qs to 500.0 gm</td>
</tr>
</tbody>
</table>

### EXAMPLE 2

<table>
<thead>
<tr>
<th>Material</th>
<th>%</th>
<th>Amount/2000 L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>3.15%</td>
<td>63.0 kg</td>
</tr>
</tbody>
</table>

[0041] Triacetin was added to n-propyl gallate and ivermectin in an Erlenmeyer flask and mixed until all of the n-propyl gallate dissolved. Myvacet 9-45 was placed in a non-glass beaker in a 50°C water bath, and mixed at a low speed with a dispersator mixer until the temperature of the content reached 50°C. Thixcin R was then added slowly to the vortex of the mixing Myvacet 9-45. When all the Thixcin R was added, the speed of the mixer was slowly increased to 60 rpm and mixing continued for 20 minutes. The beaker was removed from the water bath and allowed to cool to 30°C, while mixing continued at about 25 rpm. The triacetin solution was added to the Thixcin R/Myvacet 9-45 mixture and the liquids were mixed until uniform.
Ivermectin, BHT, methyl and propyl paraben were dissolved in 800 L of triacetin, and the solution was sterile filtered into a 2000 L tank equipped with an agitator. Myvacet 9-45 was sterile filtered into a 150 L tank capable of maintaining a batch temperature of 60°C and equipped with an agitator and with an aseptic addition of sterile powder capability. The gamma sterilized hydrogenated castor oil was dispersed in the Myvacet 9-45, and the dispersion was heated to 50°C, then transferred to the triacetin solution through a microfluidizer. The liquids were mixed until uniform and then aseptically packaged in low density polyethylene containers.

EXAMPLE 3

The plasma levels of ivermectin administered once subcutaneously at a dose of 630 mcg/kg bodyweight were determined in cattle for two formulations: formulation I contains ivermectin 3.15%, n-propyl gallate 0.02%, Thixcin R 1.5% and triacetin qs to 100%; formulation II has the composition given in Example 2. Ten animals were used for formulation I and six were used for formulation II. Mean plasma levels (ng/ml) are shown in the following Table:

<table>
<thead>
<tr>
<th>Days post dosing</th>
<th>3</th>
<th>14</th>
<th>21</th>
<th>28</th>
<th>35</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation I</td>
<td>80</td>
<td>18</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Formulation II</td>
<td>21</td>
<td>25</td>
<td>22</td>
<td>16</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

The mean plasma level for formulation II was greater than 3 ng/ml on day 70.

The 42-day plasma level of formulation I (2 ng/ml) is not sufficient to produce efficacy against Cooperia oncophora and Nematodirus which require an ivermectin plasma level of 3 to 4 ng/ml.

EXAMPLE 4

To facilitate the manufacture of large scale batches the following process was developed which results in a product that meets the same release specifications as the product manufactured in Example 2. The formula is also the same as used in Example 2. Ivermectin, BHT, methyl and propyl paraben are dissolved a mixture of the triacetin and Myvacet 9-45. The solution is sterile filtered. The gamma sterilized hydrogenated castor is aseptically dispersed in sterile solution using an in-line educator/homogenizer system. Such in-line system can be a Flashblend system. The product is heated and recirculated through the system until the product temperature is from 42 to 50°C. Then the product is aseptically packaged.

Claims

1. A long-acting injectable formulation comprising:

   (a) a therapeutic agent selected from the group consisting of insecticides, acaricides, parasiticides, growth enhancers and oil-soluble NASIDS,
   (b) hydrogenated castor oil, and
   (c) a hydrophobic carrier comprising:

      (i) triacetin, benzyl benzoate or ethyl oleate or a combination thereof; and
(ii) acylated monoglycerides, propyl dicaprylates/dicaprates, caprylic/capric acid triglycerides, or a combination thereof.

2. A long-acting injectable formulation comprising:

(a) a therapeutic agent selected from the group consisting of avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridylmethyl derivatives, phenylpyrazoles, and COX-2 inhibitors,
(b) hydrogenated castor oil, and
(c) a hydrophobic carrier comprising:

(i) triacetin, benzyl benzoate or ethyl oleate or a combination thereof; and
(ii) acetylated monoglycerides, propyl dicaprylates/dicaprates, caprylic/capric triglycerides, or a combination thereof.

3. The long-acting injectable formulation according to claim 1 comprising

(a) 1.0 to 10.0 w/v of a therapeutic agent;
(b) 0.3 to 5% w/v of hydrogenated castor oil;
(c) a hydrophobic carrier comprising:

(i) 30 to 45% v/v of triacetin; benzyl benzoate or ethyl oleate; and
(ii) 55 to 70% of v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

4. The long-acting injectable formulation according to claim 2 comprising

(a) 1.0 to 10.0 w/v of a therapeutic agent;
(b) 0.3 to 5% w/v of hydrogenated castor oil;
(c) a hydrophobic carrier comprising:

(i) 30 to 45% v/v of triacetin; benzyl benzoate or ethyl oleate; and
(ii) 55 to 70% of v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

5. The long-acting injectable formulation according to claim 2 wherein 2.5 to 5.0% w/v of a therapeutic agent is present.

6. The long-acting injectable formulation according to claim 2 wherein the therapeutic agent is an avermectin or a milbemycin.

7. The long-acting injectable formulation according to claim 6, wherein the avermectin is ivermectin, abamectin, eme- mectin, eprinomectin, or doramectin and the milbemycin is moxidectin.

8. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is an estrogen, progestin or androgen.

9. The long-acting injectable formulation according to claim 8, where the estrogen, progestin or androgen is estradiol benzoate, progesterone, or trenbolone acetate.

10. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is nodulisporic acid or its derivatives.

11. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is a substituted pyridyl- methyl derivative or a phenylpyrazole.

12. The long-acting injectable formulation according to claim 11, wherein the therapeutic agent is imidacloprid or fipronil.
13. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is a COX-2 inhibitor.

14. The long-acting injectable formulation according to claim 1, wherein the therapeutic agent is an oil-soluble, nonsteroidal anti-inflammatory drug.

15. The long-acting injectable formulation according to claim 14, wherein the therapeutic agent is carprofen, flunixin, ketoprofen, meloxicam, naproxen or phenylbutazone.

16. The long-acting injectable formulation according to claim 1, wherein the therapeutic agent is an insect growth regulator.

17. The long-acting injectable formulation according to claim 16, wherein the therapeutic agent is diflubenzuron, lufenuron, methoprene, phenoxy carb, pyriproxyfen, and cyromazine.

18. The long-acting injectable formulation according to claim 1, which further comprises an antioxidant or a preservative.

19. The long-acting injectable formulation according to claim 2 where 1 to 3.0 % w/v of hydrogenated caster oil is present and hydrophobic carrier comprises about 40% v/v of triacetin, benzybenzoate or ethyl oleate and about 60% v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

20. The long-acting injectable formulation of claim 2 which comprises:
   (a) 1.0 to 5.0% w/v of an avermectin compound,
   (b) 1 to 3% w/v of hydrogenated castor oil, and
   (c) 30 to 45% v/v of triacetin and 55 to 70% v/v of acetylated monoglycerides.

21. The long-acting injectable formulation of claim 2 which comprises:
   (a) 3.15% w/v of ivermectin,
   (b) 1% w/v of hydrogenated castor oil, and
   (c) 40% of triacetin and up to 60% v/v of acetylated monoglycerides.

22. The long-acting injectable formulation of claim 2 which further comprises an antioxidant.

23. The long acting injectable formulation of claim 2 which further comprises a preservative.

24. The long acting injectable formulation of claim 22 wherein said antioxidant is selected from n-propyl gallate, BHA, BHT and monothioglycerol.

25. The long-acting injectable formulation of claim 23 wherein said preservative is selected from the parabens.

26. The long-acting injectable formulation of claim 21 which further comprises an antioxidant selected from n-propyl gallate, BHA, BHT and monothioglycerol.

27. The long-acting injectable formulation of claim 26 which further comprises a preservatives selected from the parabens.

28. The long acting injectable formulation of claim 21 which further comprises BHT and one or more preservatives from the parabens.

29. A long acting injectable formulation according to any previous claim for use in therapy of the human or animal body.

30. A long acting injectable formulation according to claim 1 or claim 2 for use in treatment or prevention of parasitic infestation in a host.

31. A long acting injectable formulation according to claim 21 for use in treatment or prevention of parasitic infestation in cattle.
32. A long acting injectable formulation according to claim 10 or claim 11 for use in treatment or prevention of insect infestation in a host.

33. A long acting injectable formulation according to claim 32 wherein said insects are fleas.

34. A long acting injectable formulation according to claim 8 for use in promoting growth in animals.

35. A long acting injectable formulation according to claim 14 for use in treating inflammation, pain or fever in an animal.

**Patentansprüche**

1. Eine langwirkende injizierbare Formulierung, die enthält:

   (a) ein therapeutisches Mittel, ausgewählt aus der Gruppe, bestehend aus Insektiziden, Akariziden, Parasitika, Wachstumsförderern und öllöslichen NSAIDs,
   (b) hydriertes Rizinusöl und
   (c) einen hydrophoben Träger, der enthält:

   (i) Triacetin, Benzylbenzoat oder Ethyloleat oder eine Kombination davon und
   (ii) acylierte Monoglyceride, Propyldicaprylate/-dicaprate, Caprylsäure-/Caprinsäuretriglyceride oder eine Kombination davon.

2. Eine langwirkende injizierbare Formulierung, die enthält:

   (a) ein therapeutisches Mittel, ausgewählt aus der Gruppe, bestehend aus Avermectinen, Milbemycinen, Nodulisponsäure und deren Derivate, Östrogenen, Progestinen, Androgenen, substituierten Pyridylmethyl derivaten, Phenylpyrazolen und COX-2-Inhibitoren,
   (b) hydriertes Rizinusöl und
   (c) einen hydrophoben Träger, der enthält:

   (i) Triacetin, Benzylbenzoat oder Ethyloleat oder eine Kombination davon und
   (ii) acylierte Monoglyceride, Propyldicaprylate/-dicaprate, Caprylsäure-/Caprinsäuretriglyceride oder eine Kombination davon.

3. Die langwirkende injizierbare Formulierung gemäß Anspruch 1, die enthält

   (a) 1,0 bis 10,0% Gew./Vol. eines therapeutischen Mittels,
   (b) 0,3 bis 5% Gew./Vol. hydriertes Rizinusöl,
   (c) einen hydrophoben Träger, der enthält:

   (i) 30 bis 45% Vol./Vol. Triacetin, Benzylbenzoat oder Ethyloleat und
   (ii) 55 bis 70% Vol./Vol. acylierte Monoglyceride, Propyldicaprylate/-dicaprate oder Caprylsäure-/Caprinsäuretriglyceride.

4. Die langwirkende injizierbare Formulierung gemäß Anspruch 2, die enthält

   (a) 1,0 bis 10,0% Gew./Vol. eines therapeutischen Mittels,
   (b) 0,3 bis 5% Gew./Vol. hydriertes Rizinusöl.
   (c) einen hydrophoben Träger, der enthält:

   (i) 30 bis 45% Vol./Vol. Triacetin, Benzylbenzoat oder Ethyloleat und
   (ii) 55 bis 70% Vol./Vol. acylierte Monoglyceride, Propyldicaprylate/-dicaprate oder Caprylsäure-/Caprinsäuretriglyceride.

5. Die langwirkende injizierbare Formulierung gemäß Anspruch 2, wobei 2,5 bis 5,0% Gew./Vol. eines therapeutischen Mittels vorliegen.
6. Die langwirkende injizierbare Formulierung gemäß Anspruch 2, wobei das therapeutische Mittel ein Avermectin oder ein Milbemycin ist.


8. Die langwirkende injizierbare Formulierung gemäß Anspruch 2, wobei das therapeutische Mittel ein Östrogen, Progestin oder Androgen ist.


11. Die langwirkende injizierbare Formulierung gemäß Anspruch 2, wobei das therapeutische Mittel ein substituiertes Pyridylmethylderivat oder ein Phenylpyrazol ist.

12. Die langwirkende injizierbare Formulierung gemäß Anspruch 11, wobei das therapeutische Mittel Imidacloprid oder Fipronil ist.


14. Die langwirkende injizierbare Formulierung gemäß Anspruch 1, wobei das therapeutische Mittel ein öllösliches nichtsteroidales Antiphlogistikum ist.

15. Die langwirkende injizierbare Formulierung gemäß Anspruch 14, wobei das therapeutische Mittel Carprofen, Flunixin, Ketoprofen, Meloxicam, Naproxen oder Phenylbutazon ist.

16. Die langwirkende injizierbare Formulierung gemäß Anspruch 1, wobei das therapeutische Mittel ein Insektenwachstumsregulator ist.

17. Die langwirkende injizierbare Formulierung gemäß Anspruch 16, wobei das therapeutische Mittel Diflubenzuron, Lufenuron, Methoprene, Phenoxy carb, Pyriproxyfen und Cyromazine ist.

18. Die langwirkende injizierbare Formulierung gemäß Anspruch 1, die ferner ein Antioxidationsmittel oder ein Konserverungsmittel enthält.


20. Die langwirkende injizierbare Formulierung nach Anspruch 2, die enthält:
   (a) 1,0 bis 5,0% Gew./Vol. einer Avermectinverbindung,
   (b) 1 bis 3% Gew./Vol. hydriertes Rizinusöl und
   (c) 30 bis 45% Vol./Vol. Triacetin und 55 bis 70% Vol./Vol. acetylierte Monoglyceride.

21. Die langwirkende injizierbare Formulierung nach Anspruch 2, die enthält:
   (a) 3,15% Gew./Vol. Ivermectin,
   (b) 1% Gew./Vol. hydriertes Rizinusöl und
   (c) 40% Triacetin und bis zu 60% Vol./Vol. acetylierte Monoglyceride.

22. Die langwirkende injizierbare Formulierung nach Anspruch 2, die ferner ein Antioxidationsmittel enthält.
23. Die langwirkende injizierbare Formulierung nach Anspruch 2, die ferner ein Konservierungsmittel enthält.

24. Die langwirkende injizierbare Formulierung nach Anspruch 22, wobei das Antioxidationsmittel ausgewählt ist aus n-Propylgallat, BHA, BHT und Monothioglycerin.


26. Die langwirkende injizierbare Formulierung nach Anspruch 21, die ferner ein Antioxidationsmittel enthält, ausgewählt aus n-Propylgallat, BHA, BHT und Monothioglycerin.

27. Die langwirkende injizierbare Formulierung nach Anspruch 26, die ferner ein Konservierungsmittel enthält, ausgewählt aus den Parabenen.


32. Eine langwirkende injizierbare Formulierung gemäß Anspruch 10 oder Anspruch 11 zur Verwendung bei der Behandlung oder Prävention eines Insektenbefalls bei einem Wirt.

33. Eine langwirkende injizierbare Formulierung gemäß Anspruch 32, wobei die Insekten Flöhe sind.

34. Eine langwirkende injizierbare Formulierung gemäß Anspruch 8 zur Verwendung bei der Wachstumsförderung bei Tieren.


Revendications

1. Formulation injectable à longue durée d'action comprenant :

   (a) un agent thérapeutique choisi dans le groupe constitué par les insecticides, les acaricides, les parasiticides, les agents stimulant la croissance et les médicaments anti-inflammatoires non-stéroïdiens solubles dans les huiles,

   (b) de l'huile de ricin hydrogénée et

   (c) un support hydrophobe comprenant :

      (i) de la triacétine, du benzoate de benzyle ou de l'oléate d'éthyle ou une combinaison de ceux-ci ; et

      (ii) des monoglycérides acétylés, des diaprylates/dicaprates de propyle, des triglycérides d'acide caprylique/acide caprique ou une combinaison de ceux-ci.

2. Formulation injectable à longue durée d'action comprenant :

   (a) un agent thérapeutique choisi dans le groupe constitué par les avermectines, les milbémycines, l'acide nodulisporique et ses dérivés, les oestrogènes, les progestatifs, les androgènes, les dérivés de pyridylméthyle substitués, les phénoxyprazoles et les inhibiteurs de la COX-2,

   (b) de l'huile de ricin hydrogénée et
(c) un support hydrophobe comprenant :

   (i) de la triacétine, du benzoate de benzyle ou de l’oléate d’éthyle ou une combinaison de ceux-ci ; et
   (ii) des monoglycérides acétylés, des dicaprylates/dicaprates de propyle, des triglycérides d’acide caprylique/acide caprique ou une combinaison de ceux-ci.

3. Formulation injectable à longue durée d’action selon la revendication 1 comprenant :

   (a) 1,0 à 10,0 % en masse/volume d’un agent thérapeutique ;
   (b) 0,3 à 5 % en masse/volume d’huile de ricin hydrogénée ;
   (c) un support hydrophobe comprenant :

       (i) 30 à 45 % en volume/volume de triacétine, de benzoate de benzyle ou d’oléate d’éthyle ; et
       (ii) 55 à 70 % en volume/volume de monoglycérides acétylés, de dicaprylates/dicaprates de propyle ou de triglycérides d’acide caprylique/acide caprique.

4. Formulation injectable à longue durée d’action selon la revendication 2 comprenant :

   (a) 1,0 à 10,0 % en masse/volume d’un agent thérapeutique ;
   (b) 0,3 à 5 % en masse/volume d’huile de ricin hydrogénée ;
   (c) un support hydrophobe comprenant :

       (i) 30 à 45 % en volume/volume de triacétine, de benzoate de benzyle ou d’oléate d’éthyle ; et
       (ii) 55 à 70 % en volume/volume de monoglycérides acétylés, de dicaprylates/dicaprates de propyle ou de triglycérides d’acide caprylique/acide caprique.

5. Formulation injectable à longue durée d’action selon la revendication 2, dans laquelle sont présents 2,5 à 5,0 % en masse/volume d’un agent thérapeutique.

6. Formulation injectable à longue durée d’action selon la revendication 2, dans laquelle l’agent thérapeutique est une avermectine ou une milbémycine.

7. Formulation injectable à longue durée d’action selon la revendication 6, dans laquelle l’avermectine est l’iverméctine, l’abamectine, l’éprinomectine ou la doramectine et la milbémycine est la moxidectine.

8. Formulation injectable à longue durée d’action selon la revendication 2, dans laquelle l’agent thérapeutique est un oestrogène, un progestatif ou un androgène.

9. Formulation injectable à longue durée d’action selon la revendication 8, dans laquelle l’oestrogène, le progestatif ou l’androgène est le benzoate d’estradiol, la progestérone ou l’acétate de trenbolone.

10. Formulation injectable à longue durée d’action selon la revendication 2, dans laquelle l’agent thérapeutique est l’acide nodulisporique ou ses dérivés.

11. Formulation injectable à longue durée d’action selon la revendication 2, dans laquelle l’agent thérapeutique est un dérivé de pyridylméthyle substitué ou un phénylpyrazole.

12. Formulation injectable à longue durée d’action selon la revendication 11, dans laquelle l’agent thérapeutique est l’imidacloprid ou le fipronil.


14. Formulation injectable à longue durée d’action selon la revendication 1, dans laquelle l’agent thérapeutique est un médicament anti-inflammatoire non-stéroïdien soluble dans les huiles.

15. Formulation injectable à longue durée d’action selon la revendication 14, dans laquelle l’agent thérapeutique est le carprofène, la flunixin, le kétoprofène, le méloxicam, le naproxène ou la phénylbutazone.
16. Formulation injectable à longue durée d'action selon la revendication 1, dans laquelle l'agent thérapeutique est un régulateur de la croissance des insectes.

17. Formulation injectable à longue durée d'action selon la revendication 16 dans laquelle l'agent thérapeutique est le diflubenzuron, le lufenuron, le méthoprène, le phénoxycarb, le pyriproxyfen et la cyromazine.

18. Formulation injectable à longue durée d'action selon la revendication 1, comprenant en outre un antioxydant ou un conservateur.

19. Formulation injectable à longue durée d'action selon la revendication 2, dans laquelle sont présents 1 à 3,0 % en masse/volume d'huile de ricin hydrogénée et dans laquelle le support hydrophobe comprend environ 40 % en volume/volume de triacétine, de benzoate de benzyle ou d'oléate d'éthyle et environ 60 % en volume/volume de monoglycérides acétylés, de diéaprylates/diéaprates de propyle ou de triglycérides d'acide caprylique/acide caprique.

20. Formulation injectable à longue durée d'action selon la revendication 2 comprenant :
   (a) 1,0 à 5,0 % en masse/volume d'un composé d'avermectine ;
   (b) 1 à 3 % en masse/volume d'huile de ricin hydrogénée ; et
   (c) 30 à 45 % en volume/volume de triacétine et 55 à 70 % en volume/volume de monoglycérides acétylés.

21. Formulation injectable à longue durée d'action selon la revendication 2 comprenant :
   (a) 3,15 % en masse/volume d'ivermectine;
   (b) 1 en masse/volume d'huile de ricin hydrogénée ; et
   (c) 40 % en volume/volume de triacétine et jusqu'à 60 % en volume/volume de monoglycérides acétylés.

22. Formulation injectable à longue durée d'action selon la revendication 2, comprenant en outre un antioxydant.

23. Formulation injectable à longue durée d'action selon la revendication 2, comprenant en outre un conservateur.

24. Formulation injectable à longue durée d'action selon la revendication 22, dans laquelle ledit antioxydant est choisi parmi le gallate de n-propyle, le BHA, le BHT et le monothioglycérol.

25. Formulation injectable à longue durée d'action selon la revendication 23, dans laquelle ledit conservateur est choisi parmi les parabens.

26. Formulation injectable à longue durée d'action selon la revendication 21, comprenant en outre un antioxydant choisi parmi le gallate de n-propyle, le BHA, le BHT et le monothioglycérol.

27. Formulation injectable à longue durée d'action selon la revendication 26, comprenant en outre des conservateurs choisis parmi les parabens.

28. Formulation injectable à longue durée d'action selon la revendication 21, comprenant en outre du BHT et un ou plusieurs conservateurs parmi les parabens.

29. Formulation injectable à longue durée d'action selon l'une quelconque des revendications précédentes pour une utilisation dans la thérapie de l'organisme humain ou d'un organisme animal.

30. Formulation injectable à longue durée d'action selon la revendication 1 ou la revendication 2 pour une utilisation dans le traitement ou la prévention d'une infestation parasitaire chez un hôte.

31. Formulation injectable à longue durée d'action selon la revendication 21 pour une utilisation dans le traitement ou la prévention d'une infestation parasitaire chez le bétail.

32. Formulation injectable à longue durée d'action selon la revendication 10 ou la revendication 11 pour une utilisation dans le traitement ou la prévention d'une infestation par insectes chez un hôte.
33. Formulation injectable à longue durée d'action selon la revendication 32, lesdits insectes étant des mouches.

34. Formulation injectable à longue durée d'action selon la revendication 8 pour une utilisation comme stimulant de la croissance chez des animaux.

35. Formulation injectable à longue durée d'action selon la revendication 14 pour une utilisation dans le traitement de l'inflammation, de la douleur ou de la fièvre chez un animal.