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(54) Title: METHOD OF TREATING PARASITES

(57) Abstract: The present invention provides a method of treating or preventing an infestation by a parasite in or on an animal. The method comprises providing an aqueous formulation comprising a macrocyclic lactone to the animal and allowing the animal to drink the aqueous formulation for an extended period.



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METHOD OF TREATING PARASITES

TECHNICAL FIELD

The invention relates to treating or preventing an
5 infestation by a parasite in or on an animal.

BACKGROUND ART

Macrocyclic lactones are used to treat infestations by
endoparasites and ectoparasites in or on animals.
10 Macrocyclic lactones include the LL-F28249 compounds, the
milbemycins and the avermectins.

The LL-F28249 family of compounds are natural endectocidal
agents isolated from the fermentation broth of
15 *Streptomyces cyaneogriseus subsp. noncyanogenus*. The LL-
F28249 family of compounds includes moxidectin.

The milbemycins, also known as the B-41 series of
antibiotics, are naturally occurring macrocyclic lactones
20 isolated from the microorganism *Streptomyces hygroscopicus*
subsp. aureolacrimosus. The milbemycins include
milbemycin A, milbemycin B, milbemycin D and others.

The avermectins, also known as the C-076 family of
25 compounds, are a family of closely related compounds
produced by *Streptomyces avermitilis* or by synthetic or
semisynthetic means. Members of the avermectin family
include avermectin A_{1a}, A_{2a}, B_{1a}, B_{2a}, A_{1b}, A_{2b}, B_{1b} and B_{2b}.
The avermectins include ivermectin, abamectin, doramectin,
30 eprinomectin and others.

Ivermectin is a semisynthetic derivative of abamectin.
Ivermectin contains at least 80% of 22,23-
dihydroavermectin B_{1a} and not more than 20% of 22,23-
35 dihydroavermectin B_{1b}.

Macrocyclic lactones, including ivermectin, have been used

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to treat endoparasites, such as worms, and ectoparasites, such as lice and mites, in or on animals.

5 The formulations containing ivermectin approved for use in Australia for the treatment of parasites in or on pigs are formulations that are administered in admixture with the animal's feed or administered by subcutaneous injection. Oral drenches containing ivermectin have been approved for use in Australia to treat parasites in or on horses, dogs, 10 cattle and sheep. Topical formulations containing a macrocyclic lactone have been approved for use in Australia to treat parasites in or on cattle.

DISCLOSURE OF INVENTION

15 In a first aspect, the present invention provides a method of treating or preventing an infestation by a parasite in or on an animal, the method comprising providing an aqueous formulation comprising a macrocyclic lactone to the animal and allowing the animal to drink the aqueous 20 formulation for an extended period.

The extended period during which the animal is allowed to drink the aqueous formulation is typically greater than about 6 days. In some embodiments, the extended period is 25 from about 7 to about 14 days. In other embodiments, the extended period is about 3 months or about 100 days.

The macrocyclic lactone is present in the aqueous formulation at a concentration such that by drinking the 30 aqueous formulation, the animal consumes a parasitocidally effective amount of the macrocyclic lactone.

In some embodiments, the aqueous formulation comprises the macrocyclic lactone at a concentration such that when the 35 aqueous formulation is drunk by the animal, the animal consumes about 50 to about 300 μg , for example, about 100 to about 300 μg , of the macrocyclic lactone per kg

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liveweight of the animal per day.

Typically the aqueous formulation is the only, or the principal, source of water available to the animal for
5 drinking.

Preferably, the macrocyclic lactone is in solution in the aqueous formulation.

10 The macrocyclic lactone may be any macrocyclic lactone. The macrocyclic lactone may be an LL-F28249 compound (for example, moxidectin), a milbemycin (for example, milbemycin A, milbemycin B or milbemycin D), or an avermectin (for example, ivermectin, abermectin,
15 doramectin or eprinomectin). In some embodiments, the macrocyclic lactone is ivermectin.

In some embodiments, the aqueous formulation comprises two or more macrocyclic lactones.

20

Typically the animal is an intensively farmed animal kept in a controlled environment. The animal may be a mammal or a bird. The animal may, for example, be a pig, poultry (e.g. a chicken, turkey, guinea fowl, duck or goose),
25 cattle (e.g. cattle kept in a feed lot) or sheep.

The parasite may be a worm, lice or mite. For example, if the animal is a pig, the parasite may be selected from one or more of gastrointestinal roundworms, kidney worms,
30 lungworms, lice and mange mites.

In some embodiments, the macrocyclic lactone is provided in a concentrate that is added to a source of water available to the animal for drinking, to produce the
35 aqueous formulation.

In one embodiment, the present invention provides a method

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of treating or preventing an infestation by a parasite in or on an animal, comprising mixing a formulation comprising:

- one or more macrocyclic lactones;
- 5 one or more co-solvents;
- one or more preservatives;
- one or more buffers; and
- water,

with a source of water available to the animal for
10 drinking to form an aqueous formulation comprising the one or more macrocyclic lactones, and allowing the animal to drink the aqueous formulation for an extended period.

In a second aspect, the present invention provides a
15 method of treating or preventing an infestation by a parasite in or on an animal, the method comprising administering a macrocyclic lactone in an amount of from about 50 to about 300 μg per kg liveweight of the animal per day to the animal in the animal's drinking water for
20 an extended period.

In a third aspect, the present invention provides a formulation comprising:

- one or more macrocyclic lactones;
- 25 one or more co-solvents;
- one or more preservatives;
- one or more buffers; and
- water,

when added to a source of water available to an animal for
30 drinking.

In a fourth aspect, the present invention provides a formulation comprising:

- one or more macrocyclic lactones;
- 35 one or more co-solvents;
- one or more preservatives;
- one or more buffers; and

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water,

when added to a source of water available to an animal for drinking to form the aqueous formulation used in the method of the first aspect of the present invention.

5

The formulation of the third or fourth aspect of the present invention may be added to the source of water available to the animal for drinking in an amount which results in the source of water comprising the one or more
10 macrocyclic lactones in an amount of from about 250 to about 10,000 $\mu\text{g/L}$.

In some embodiments, the one or more macrocyclic lactones is in solution in the formulation of the third or fourth
15 aspect of the present invention.

In some embodiments, the formulation of the third or fourth aspect of the present invention comprises:

the macrocyclic lactone(s) in an amount of 0.1 to
20 100 g/L;
the co-solvent(s) in an amount of 200 to 300 g/L;
the preservative(s) in an amount of 20 to 50 g/L; and
the buffer(s) in an amount of 8 to 15 g/L.

25 **MODE(S) FOR CARRYING OUT THE INVENTION**

It has been found that parasites in or on an animal can be treated by administering a macrocyclic lactone over an extended period of time in the water drunk by the animal. Surprisingly, administering macrocyclic lactones to the
30 animal via this route provides a number of advantages over administration of macrocyclic lactones in admixture with the animal's feed, by subcutaneous injection or by an oral drench.

35 In one aspect, the present invention provides a method of treating or preventing an infestation by a parasite in or

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on an animal, the method comprising providing an aqueous formulation comprising a macrocyclic lactone to the animal and allowing the animal to drink the aqueous formulation for an extended period.

5

Typically the aqueous formulation is prepared and provided to the animal by adding the macrocyclic lactone to a source of water available to the animal for drinking, that is, the macrocyclic lactone is added to the animal's

10 drinking water.

Typically the macrocyclic lactone is added to all sources of water available to the animal for drinking.

15 Typically the macrocyclic lactone is added to the source of water available to the animal for drinking in an amount such that the resultant aqueous formulation comprises from about 250 to about 10,000 $\mu\text{g/L}$ of the macrocyclic lactone. In some embodiments, the aqueous formulation comprises the
20 macrocyclic lactone in an amount of from about 250 to about 2,500 $\mu\text{g/L}$. In some embodiments, the concentration of the macrocyclic lactone in the aqueous formulation is from about 500 to about 2,500 $\mu\text{g/L}$. In some embodiments, the concentration is less than about 2,000 $\mu\text{g/L}$.

25

Typically, the aqueous formulation comprises the macrocyclic lactone at a concentration such that when the animal drinks the aqueous formulation, the animal consumes about 50 to about 300 μg of the macrocyclic lactone per kg
30 liveweight of the animal per day.

The extended period is typically a period of more than about 6 days. In some embodiments, the extended period is a period of more than about 7 days, for example, a period
35 of from about 7 to about 100 days (e.g. from about 7 to

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about 14 days). In other embodiments, for example where the animal is infected with a very persistent parasite, it may be more appropriate to treat the animal for a period of 14 to 21 days or longer. In some embodiments, the
5 extended period is 7 days, 10 days, 14 days, 21 days or 28 days. In some embodiments, the extended period is 60 days, 90 days, 3 months or 100 days.

In some embodiments, the macrocyclic lactone is
10 ivermectin. However, other macrocyclic lactones may be used. In some embodiments, the aqueous formulation comprises two or more macrocyclic lactones.

Typically the macrocyclic lactone is in solution in the
15 aqueous formulation.

The methods of the present invention may be used to treat or prevent an infestation by any parasite that is killed or whose growth or reproduction is inhibited by a
20 macrocyclic lactone.

For example, ivermectin and other macrocyclic lactones can be used to treat or prevent infestations by worms, lice and mange mites in or on an animal. When the macrocyclic
25 lactone is ivermectin, the methods of the present invention can, for example, be used to treat or prevent infestations by large round worm (*Ascaris suum*), small brown stomach worm (*Hyoststrongylus rubidus*), nodule worm (*Oesophagostomum spp*), stomach worm (*Ascarops*
30 *strongylina*), intestinal thread worm (*Strongyloides ransomi*), kidney worms (*Stephanurus dentatus*), lung worms (*Metastrongylus spp*), lice (*Haematopinus suis*) and mange mites (*Sarcoptes scabiei* var. *suis*) in or on pigs. When the macrocyclic lactone is ivermectin, the methods of the
35 present invention can, for example, be used to treat or prevent infestations by round worm (*Ascaridia galli*), caecal worm (*Heterakis gallinae*), hairworm (*Capillaria*

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spp.), lice (*Manacanthus stramineus*; *Menocan gallinae* L.) and mites (*Acarina* spp.) in or on poultry. The methods of the present invention can be used to treat or prevent infestations by these or similar parasites in or on other animals.

The animal may be any mammal or bird. The animal may, for example, be a companion animal such as a dog or cat, a domestic animal such as a horse, pony, mule, llama, alpaca, pig, cow or sheep, or a zoo animal such as a primate, felid, canid, bovid or ungulate. In some embodiments, the animal is a pig, camel, deer, cow, sheep, goat, antelope, llama, alpaca, monkey, horse, donkey, mule, mouse, rat, rabbit, guinea pig or buffalo. In some embodiments, the animal is a chicken, turkey, guineafowl, duck or goose.

In the methods of the present invention, the macrocyclic lactone is present in the aqueous formulation at a concentration such that when the aqueous formulation is drunk by the animal, the animal consumes a parasitically effective amount of the macrocyclic lactone.

As used herein, by a "parasitically effective amount" it is meant an amount effective to reduce the number of parasites in or on an animal or to prevent an infestation by a parasite in or on an animal. As used herein, the phrase "infestation by a parasite" includes a single parasite, that is, an animal has an infestation by a parasite if one or more individuals of that parasite species are present in or on the animal.

The parasitically effective amount of a macrocyclic lactone will vary with factors such as the type of animal treated, the particular parasite, the extent of the parasitic infestation, the age, weight and condition of the animal, the particular macrocyclic lactone used, and

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the duration of treatment. A parasitically effective amount of a macrocyclic lactone would readily be able to be determined by a veterinarian. A parasitically effective amount of a macrocyclic lactone may, for example, be determined by reference to conventional doses of the macrocyclic lactone used for the prevention or treatment of infestations by the parasite when the macrocyclic lactone is administered by another means, e.g. when administered as an oral drench.

10

A parasitically effective amount of ivermectin for the treatment of infestations by large round worm (*Ascaris suum*), small brown stomach worm (*Hyostrogylus rubidus*), nodule worm (*Oesophagostomum spp*), stomach worm (*Ascarops strongylina*), intestinal thread worm (*Strongyloides ransomi*), kidney worms (*Stephanurus dentatus*), lung worms (*Metastrongylus spp*), lice (*Haematopinus suis*) or mange mites (*Sarcoptes scabiei* var. *suis*) in or on pigs is between about 100 μg and about 300 μg per kg liveweight per day.

20

For the prevention or treatment of an infestation by worms, mites or lice, in or on sheep or cattle, a parasitically effective amount of ivermectin may be about 200 $\mu\text{g/kg}$ liveweight per day.

25

Typically, the aqueous formulation comprising the macrocyclic lactone is a dilute solution of the macrocyclic lactone.

30

The concentration of the macrocyclic lactone in the aqueous formulation is typically less than 10,000 $\mu\text{g/L}$. In some embodiments, the concentration is from 500 to 2,500 $\mu\text{g/L}$. In some embodiments, the concentration is less than 2,000 $\mu\text{g/L}$.

35

Typically, the animal is allowed to drink the aqueous

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formulation over an extended period by making the aqueous formulation accessible to the animal for drinking, and leaving the animal in the presence of the aqueous formulation for the extended period under conditions such
5 that the animal drinks the aqueous formulation.

Typically, the aqueous formulation comprising the macrocyclic lactone is the only source of water available to the animal throughout the extended period. However, in
10 some embodiments, other sources of water may be available to the animal at the same time as the aqueous formulation comprising the macrocyclic lactone or at different times during the period of treatment, for example, at different times of the day.

15 Typically the methods of the present invention are used to treat multiple animals simultaneously, eg a herd of pigs.

An advantage of the methods of the present invention is
20 that they can be used to treat or prevent an infestation by a parasite in or on an animal with less handling of the animal than treatment regimens that involve the administration of a drench or an injection. The administration of a drench or an injection to an animal
25 can be stressful for the animal, which may reduce weight gain by the animal. For larger animals such as pigs, injecting the animal can also be stressful and dangerous for the animal handler. Further, administration of the macrocyclic lactone via the animal's drinking water over
30 an extended period can be more effective in treating persistent parasites than treatment regimens involving the administration a single dose of the macrocyclic lactone.

An advantage of the methods of the present invention
35 compared to administering the macrocyclic lactone, or other parasitocidal agents, in an in-feed medication mixed with the animal's feed is that the methods of the present

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invention allow for more accurate dosing as sick animals may not eat as much as a healthy animal but typically continue to drink. Further, by administering the macrocyclic lactone in the drinking water over an extended
5 period, any short term fluctuations in water consumption by an animal will have little effect on the total dosage consumed by the animal over the extended period, minimising variations in the total dosage consumed by different animals in a herd of animals being treated by
10 the method of the present invention.

The administration of a macrocyclic lactone in the water drunk by an animal further allows for more rapid commencement and cessation of administration of the
15 macrocyclic lactone to a herd of animals than treatment using an in-feed medication, allowing the manager of the animals to respond quickly to changing circumstances. A macrocyclic lactone can typically be quickly included in the drinking water for a herd of animals, and the
20 inclusion of the macrocyclic lactone in the drinking water can also be quickly stopped. In contrast, when an in-feed medication is used to treat a herd of animals, it is typically not economically viable to cease treatment by removing any uneaten feed that has been mixed with the in-
25 feed medication and the feed mixed with the in-feed medication therefore typically remains available to the animals until all the feed has been consumed.

Typically the aqueous formulation comprising the
30 macrocyclic lactone is prepared shortly before the aqueous formulation is provided to the animal for drinking.

Typically the aqueous formulation comprising the macrocyclic lactone is prepared by mixing a formulation
35 comprising the macrocyclic lactone (referred to below as "the concentrated formulation") with water to form the aqueous formulation. The concentrated formulation may,

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for example, comprise one or more macrocyclic lactones, one or more solvents, one or more preservatives, one or more buffers and water. The concentrated formulation may also comprise other components such as flavours (e.g.

5 sucrose, lactose, artificial sweeteners such as saccharine, salt or yeasty extracts) or colouring agents (e.g. food grade dyes).

Accordingly, in some embodiments, the method of the first
10 aspect of the present invention comprises mixing a formulation comprising:

one or more macrocyclic lactones;
one or more co-solvents;
one or more preservatives;
15 one or more buffers; and
water,

with water, providing the resultant aqueous formulation to the animal and allowing the animal to drink the aqueous formulation over an extended period.

20

The concentrated formulation may, for example, contain the constituents referred to in Table 1 in the amounts referred to in Table 1.

25 Table 1

Constituent	Amount
Macrocyclic lactone(s)	0.1 to 100 g/L
Co-solvent(s)	200 to 300 g/L
Preservative(s)	20 to 50 g/L
Buffer(s)	8 to 15 g/L
Water	q.s. to 1.0 g/L

The co-solvent or co-solvents solubilise the macrocyclic lactone in the formulation and assist in maintaining the
30 macrocyclic lactone in solution when the concentrated formulation is mixed with water. Suitable co-solvents

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include propylene glycol, a mixture of propylene glycol and Ecoteric T80/Tween 80, a mixture of propylene glycol and propyl alcohol, or a mixture of propylene glycol and glycol formal. Other suitable co-solvents include
5 vegetable oils, myglyol 840 and mineral oils. A mixture of different co-solvents may be used.

The preservative or preservatives act to preserve the macrocyclic lactone during storage of the concentrated
10 formulation and after the concentrated formulation has been mixed with water. Any preservative soluble in the concentrated formulation may be used. Suitable preservatives include benzyl alcohol, methyl paraben and propyl paraben.

15 The buffer or buffers maintain the pH of the concentrated formulation during storage of the concentrated formulation. The buffers are typically selected to maintain the pH of the concentrated formulation at about
20 5.5 to 7.5.

It has been found that formulations comprising:

- one or more macrocyclic lactones;
- one or more so-solvents;
- 25 one or more preservatives;
- one or more buffers; and
- water,

can be prepared comprising 0.1 to 100 g/L of the macrocyclic lactone(s). Advantageously, these
30 formulations comprise water as a solvent. Water is a relatively cheap solvent compared to the solvents used in some prior art formulations containing a macrocyclic lactone at a similar concentration. It has also been found that such formulations, containing water as a
35 solvent, can be prepared which are stable during storage for many months. Without wishing to be bound by theory, it is believed that the presence of the preservative(s)

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and the buffer(s) in the formulation stabilise the macrocyclic lactone in the formulation.

An example of a concentrated formulation is the
 5 formulation set out in Table 2. This concentrated formulation consists of the constituents referred to in Table 2 in the amounts referred to in Table 2. The concentrated formulation set out in Table 2 may be mixed
 10 with water to form an aqueous formulation comprising ivermectin for use in the treatment or prevention of an infestation by a parasite such as large round worm (*Ascaris suum*), small brown stomach worm (*Hyoststrongylus rubidus*), nodule worm (*Oesophagostomum spp*), stomach worm (*Ascarops strongylina*), intestinal thread worm
 15 (*Strongyloides ransomi*), kidney worms (*Stephanurus dentatus*), lung worms (*Metastrongylus spp*), lice (*Haematopinus suis*) or mange mites (*Sarcoptes scabiei* var. *suis*), in or on pigs in accordance with the method of the present invention.

20

Table 2

Constituent	CAS number	Constituent standard	Concentration	Purpose in formulation
Ivermectin	70288-86-7	TGAC Ph Eur 1999	10.81 g/L	Active
Propylene Glycol	57-55-6	USP	160.00 g/L	Co-solvent
Ecoteric T80/tween 80	9005-65-6	MS	100.00 g/L	Co-solvent
Benzyl Alcohol	100-51-6	BP	30.00 g/L	Preservative
Sodium Phosphate Monobasic Monohydrate	10049-21-5	MS	9.90 g/L	Buffer
Sodium Phosphate Dibasic anhydrous	10140-65-5	MS	1.10 g/L	Buffer
BHT Butylated hydroxy Toluene	128-37-0	MS	2.00 g/L	Buffer
R.O. Water	7732-18-5	MS	q.s to 1.0 L	Solvent

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The formulation set out in Table 2 is a micellar solution containing the ivermectin in solution.

- 5 When the formulation set out in Table 2 is mixed with water to form an aqueous formulation comprising less than about 10,000 $\mu\text{g/L}$ of ivermectin, the ivermectin remains in solution in the aqueous formulation due to the low concentration of ivermectin in the aqueous formulation.

10

- In the methods of the present invention, the macrocyclic lactone is present in the aqueous formulation at a concentration sufficient to treat or prevent an infestation by a parasite in or on an animal (i.e. a concentration sufficient to provide a parasitically effective amount of the macrocyclic lactone) when the aqueous formulation is drunk by the animal over an extended period. The concentration required to provide a parasitically effective amount of the macrocyclic lactone will vary with the weight of the animal and the water consumption of the animal.

- The typical weight range, typical daily water consumption and suitable concentrations of ivermectin in the animal's drinking water to provide a dose of about 100 μg of ivermectin per kg liveweight per day for various classes of pigs are set out in Table 3.

Table 3

30

Class of pig	Typical weight range (kg)	Typical water consumption per day (L)	Concentration of Ivermectin in drinking water ($\mu\text{g/L}$)
Post Weaning Pigs	Up to 27	2 to 8	337 to 500

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Grower Pigs	27 to 46	8 to 12	337.5 to 383.3
Finishing Pigs	47 to 114	12 to 20	383.3 to 570
Non-pregnant gilts	150	12	1250
Pregnant Sows	220	12-25	1833 to 880
Lactating Sows	220	10-30	2200 to 733
Boars	250	20	1250

When the concentrated formulation set out in Table 2 is mixed with water to form an aqueous formulation comprising ivermectin for use in the treatment or prevention of an infestation by a parasite in or on pigs, the concentrated formulation is typically mixed with water in an amount to form an aqueous formulation containing a concentration of ivermectin sufficient to provide about 100 μg of ivermectin per kg liveweight per day when the aqueous formulation is drunk by the pigs.

The aqueous formulation is typically provided to the pigs for drinking for a period of from about 7 to 14 days, however, depending on the nature of the parasite being treated, this period can be extended. The concentration of ivermectin in the aqueous formulation is typically within the ranges set out in Table 3. Typically, the concentrated formulation is mixed with water to form the aqueous formulation shortly before the aqueous formulation is drunk by the pigs. Typically the aqueous formulation is drunk by the pigs within less than a day after the concentrated formulation is mixed with water to form the aqueous formulation. However, it has been surprisingly found that when the concentrated formulation set out in Table 2 is mixed with water to form a solution containing less than about 10,000 $\mu\text{g/L}$ of ivermectin, the ivermectin

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remains stable in the water for more than 28 days at room temperature (i.e. about 30°C).

An advantage of the methods of the present invention using
5 the concentrated formulation set out in Table 2 to form the aqueous formulation comprising the macrocyclic lactone is that when the concentrated formulation is mixed with water to form an aqueous formulation comprising ivermectin in an amount of less than about 10,000 µg/L, the
10 ivermectin is in solution in the water. As a result, when the aqueous formulation is consumed by a pig, the ivermectin is in a form that can be readily absorbed by the pig. In contrast, when feed mixed with an in-feed medication containing ivermectin is consumed by a pig the
15 ivermectin needs to be dissolved before it can be absorbed by the pig.

The aqueous formulation comprising the macrocyclic lactone is provided to the animal(s) for drinking over an extended
20 period of time. If the aqueous formulation comprising the macrocyclic lactone is the only source of water available to the animal(s), providing the aqueous formulation to the animal(s) over an extended period advantageously minimises the effects of any fluctuations in day to day water
25 consumption (for example due to changes in temperature) on the total dose of the macrocyclic lactone consumed by the animal(s) over the treatment period compared to shorter treatment periods. However, in some embodiments, the aqueous formulation may be provided to the animal(s) in a
30 manner that results in the animal(s) consuming a pre-determined amount of the macrocyclic lactone per day, irrespective of any fluctuation in water consumption from day to day. This may be achieved by determining the minimum volume of water that will be consumed by the
35 animal(s) in a day, preparing an aqueous formulation having a concentration of the macrocyclic lactone such that when that volume of the aqueous formulation is drunk

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by the animal(s) they will have consumed the predetermined amount of the macrocyclic lactone, supplying the aqueous formulation to the animal(s) until that volume of the aqueous formulation has been consumed, and then supplying
5 water not containing the macrocyclic lactone for the remainder of the day. For example, the aqueous formulation comprising the macrocyclic lactone may be supplied to the animal(s) using a large gravity feed medication tank which will be drunk until empty, and then
10 non-medicated water supply would commence for the remainder of the day. This method may advantageously reduce the overall cost of the treatment program by ensuring that the animals are not over-dosed with the macrocyclic lactone.

15 In some embodiments of the methods of the present invention, the aqueous formulation comprising the macrocyclic lactone is prepared by mixing a concentrated solution of the macrocyclic lactone with water using a
20 proportionating pump, such as those sold under the trade mark DOSATRON (manufactured by DOSATRON INTERNATIONAL, RUE PASCAL, B.P. 6, 33370 TRESSES, BORDEAUX, FRANCE). Such pumps are currently used for medicating drinking water with products such as vitamins, electrolytes, and
25 nutritional supplements. These pumps are installed in the water supply line, and operate without electricity, using water pressure as the power source. The water pressure activates the injector, which takes up a percentage of the concentrated solution of the product to be mixed with the
30 water from a stock solution container. Inside the injector, the concentrate is mixed with the water, and the water pressure forces the solution downstream. The amount of concentrate is directly proportional to the volume of water entering the injector, regardless of variations in
35 flow or pressure which may occur.

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EXAMPLES

Example 1 - Comparison of the method of the present invention and an in-feed control program

5

Trials were carried out to compare the efficacy of administering ivermectin in the drinking water of pigs over an extended period with an in-feed treatment regimen in inhibiting intestinal parasitism due to *Ascaris suum* in
10 pigs.

Two separate sites were used in the trials, each site having several rows of pig sheds, allowing side by side treatment groups. Five sheds were used for each treatment
15 group in the trial, each shed holding approximately 400 pigs from 8 weeks old until slaughter age at 22 weeks old. At each site, two treatment groups were established; the "Ivermectin treatment group" (treatment group (A)) and the "Morantel in-feed treatment group" (treatment group (B)).

20

Treatment group (A) was administered ivermectin in the pigs' drinking water at a dosage of 100 µg/kg liveweight/day for 7 days ending 7 days prior to
slaughter. The pigs had free access to the medicated
25 drinking water and free access to feed throughout this 7 day period. At other times during the trial, the pigs had free access to unmedicated drinking water and free access to food.

30 Treatment group (B) was treated with the commercial product sold under the name "Wormtec" by Morantel in admixture with the pigs' feed. The product was mixed with the pigs' feed in accordance with the directions on the label for the product. The label states that the product
35 contains 30 g morantel citrate per kg. The product was mixed with the feed at 1 kg per tonne of finished feed. The pigs had free access to the medicated feed until all

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this feed had been consumed (all the medicated feed was consumed before 7 days before slaughter). Prior to commencement of the administration of the medicated feed and after all the medicated feed had been consumed, the
 5 pigs had free access to unmedicated feed. Throughout the trial, the pigs had free access to drinking water.

Measurements were conducted for treatment groups (A) and (B) of the total mortality within an entering population
 10 of grower pigs until slaughter, average daily weight gains in the grower-to-finisher period, numbers of intestines infected with adult worms at slaughter and number of livers affected with "milk spots". An evaluation of the occurrence of intestinal parasitism and other conditions
 15 was made on the basis of typical macroscopic findings at autopsy and at slaughter of all trial pigs.

As the results set out in Table 4 below show, of the 1,920 pigs in treatment group (A), none had detectable ascarid
 20 infection in their small intestines. Of the 1,980 pigs in treatment group (B), 583 (30.7%) had detectable ascarid infections in their small intestines. The numbers of livers affected with noticeable "milk spots" was 46 to 51% in each group. The growth rates and mortality rates among
 25 pigs in each group were similar.

Table 4

	(A)	(B)
Numbers of pigs entering sheds	1,920 (5 sheds)	1,980 (5 sheds)
Numbers of pigs leaving sheds (% mortality)	1,885 (1.8 %)	1,938 (2.1 %)
Number of intestines examined at slaughter	1,850	1,900

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Number of intestines with detectable worm infestation	0	583 (30.7%)
Numbers of livers examined	1,850	1,900
Numbers of livers affected with milk spots	855 (46.2%)	971 (51.1%)
Treatment cost per pig	AUS \$0.34	AUS \$0.35
Average daily weight gain	0.69 kg/day	0.66 kg/day

These results demonstrate that administering ivermectin to the pigs via their water supply was more effective in inhibiting ascarid development in the later intestinal stages of development than the commercially available in-feed treatment.

Example 2 - Comparison of the method of the present invention with control, in-feed and injection treatment regimens

Forty eight young (2-9 months of age) pigs were selected on the basis of confirmed positive individual strongyle faecal egg counts.

The trial pigs were relocated to individual pens and introduced to a fully fed ration and water in individual drinkers. Pens were raised with metal mesh floors and were vigorously cleaned at least once daily (using a high pressure water hose) to prevent any further infections occurring post relocation. Individual daily water consumption and feed intake were monitored from day -7 to day 0 to confirm normal water intake and feed intake and to assist with dose calculations. Individual faecal

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samples were collected between day -3 and -1 (inclusive), and individual strongyle faecal egg counts performed (along with a single bulk coproculture for larval differentiation). On day -1 or 0, trial pigs were ranked
5 (from highest to lowest) on individual strongyle faecal egg counts, sequentially blocked (into fours) and randomly allocated from within each block to four treatment groups, each of twelve pigs. Allocation was such that each group had a similar group mean strongyle faecal egg count and
10 range of egg counts within the group.

All pigs were weighed on day 0 (using electronic stock scales which were validated before and after use).

15 Trial pigs in Group 2 were treated with the test formulation (the formulation set out on Table 2) for seven days in their drinking water to provide a dosage of ivermectin of 100 µg/kg liveweight/day. Medication was mixed up and supplied once daily. Water plus medication
20 was supplied in individual drinkers and individual daily water intake assessment (Group 2 only) continued from day 0 to 6 inclusive, to determine actual administered dose rates.

25 Pigs in Group 3 commenced treatment with a registered ivermectin-based in feed medication (Ivomec Premix for Pigs®), at 100 µg/kg in feed. Medication was mixed up according to label directions in the pigs' feed and supplied once daily from day 0 to day 6 inclusive.
30 Medicated feed was supplied in individual feeders and individual daily feed intake (Group 3 only) continued from day 0 to day 6 inclusive, to determine actual administered dose rates.

35 Pigs in Group 4 were treated once on day 0 (via subcutaneous injection) with Ivomec Antiparasitic

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Injection for Pigs® according to day 0 bodyweight, at the label dose rate (300 µg/kg).

Pigs in Group 1 were retained untreated as negative
5 controls.

The treatment details are summarised in Table 5.

Individual faecal samples were collected from all trial
10 pigs on day 10 (4 days after the conclusion of water medication) and on day 17 (10 days after the conclusion of water and in-feed medication) and individual strongyle faecal egg counts and group bulk coprocultures for larval differentiation performed. The average number of eggs
15 from *Strongylus* species, *Trichostrongylus* species, *Ascaris* species, and *Metastrongylus* species in the faecal samples collected on day 17 for each treatment group are set out in Table 6.

20 Table 5

Group	Treatment	Dose rate (mg/kg)	Method of administration	No. of animals
1	Negative Controls	---	---	12
2	Test Formulation	100 µg/kg	Orally, via drinking water once daily, days 0 to 6 inclusive	12
3	Ivomec Premix for Pigs (6g/kg Ivermectin)	100 µg/kg	Orally, via feed once daily, days 0 to 6 inclusive	12
4	Ivomec Antiparasitic Injection for Pigs (10g/L Ivermectin)	300 µg/kg	Subcutaneous injection	12

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Table 6

Treatment	Av. Strong.	Av. Tric.	Av. Ascaris	Av. Meta.
Negative Control	0	7	2893	280
Test formulation	0	0	0	0
Ivomec Premix	0	0	0	0
Ivomec Injection	0	0	210	7

Example 3 - Stability of ivermectin formulation

5

A formulation having the components set out in Table 6 below was prepared for stability testing.

Table 6

10

Material Name	Concentrate
Ivermectin 92.87% w/w conc.	10.77 g/L
Ecoteric T80 / Tween 80	100.00g/L
Propylene Glycol USP	160.00 g/L
Benzyl Alcohol BP	30.00 g/L
Sodium Phosphate Anhydrous Monohydrate	9.90 g/L
Sodium Phosphate Diabasic Anhydrous	1.10 g/L
Butylated Hydroxy Toluene	2.00 g/L
R.O. Water	7183.22 g/L
TOTAL	1031.99 g/L

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Samples were packed in 100 mL white, HDPE containers and placed for stability testing for 24 months in an oven set at a temperature of 30°C, and at warehouse conditions.

- 5 The HPLC validated analytical method no. PHARM1 was used for Ivermectin active ingredient content testing and CIPAC methods for examination of physical parameters.

The results for samples stored over 3, 6, 12 and 24 months
10 are shown in Table 7. These results demonstrate that the ivermectin in the formulation described above is stable for a considerable period of time.

Table 7

Parameter	Starting Results	3 months at 30°C/ 3 months at stores	6 months at 30°C/ 6 months at stores	12 months at 30°C/ 12 months at stores	24 months at 30°C/ 24 months at stores
Appearance	Clear colourless liquid	Clear colourless liquid	Clear colourless liquid	Clear colourless liquid	Clear colourless liquid
S.G. @ 20°C	1.033	1.033/1.033	1.033/1.033	1.033/1.033	1.033/1.033
Ivermectin A.I. [g/L]	10.03	10.41/10.41	10.40/10.25	10.27/10.47	10.41/10.29
pH (direct)	6.08	6.04/6.0	6.13/6.14	6.09/6.10	6.09/6.12

- 15 In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense,
20 i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

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CLAIMS:

1. A method of treating or preventing an infestation by a parasite in or on an animal, the method comprising providing an aqueous formulation comprising a macrocyclic lactone to the animal and allowing the animal to drink the aqueous formulation for an extended period.
2. The method as claimed in claim 1, wherein the extended period is greater than about 6 days.
3. The method as claimed in claim 1 or claim 2, wherein the extended period is from about 7 to about 100 days.
4. The method as claimed in any one of claims 1 to 3, wherein the extended period is from about 7 to about 14 days.
5. The method as claimed in any one of claims 1 to 4, wherein the aqueous formulation comprises the macrocyclic lactone at a concentration such that the animal consumes about 50 to about 300 μ g of the macrocyclic lactone per kg liveweight of the animal per day.
6. The method as claimed in any one of claims 1 to 5, wherein the parasite is a worm, lice or mite.
7. The method as claimed in any one of claims 1 to 6, wherein the macrocyclic lactone is ivermectin.
8. The method as claimed in any one of claims 1 to 7, wherein the animal is a pig or chicken.
9. The method as claimed in any one of claims 1 to 8,

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wherein the animal is a pig and the parasite is selected from one or more of gastrointestinal roundworms, kidney worms, lungworms, lice and mange mites.

- 5 10. The method as claimed in any one of claims 1 to 9,
wherein a formulation comprising:
one or more macrocyclic lactones;
one or more co-solvents;
one or more preservatives;
10 one or more buffers; and
water,
is added to a source of water available to the animal
for drinking to produce the aqueous formulation.
11. The method as claimed in any one of claims 1 to 10,
15 wherein the macrocyclic lactone is in solution in the
aqueous formulation.
12. The method as claimed in any one of claims 1 to 11,
wherein the aqueous formulation comprises the
macrocyclic lactone in an amount of from about 250 to
20 about 10,000 $\mu\text{g/L}$.
13. A method of treating or preventing an infestation by
a parasite in or on an animal, the method comprising
administering a macrocyclic lactone in an amount of
from about 50 to about 300 μg per kg liveweight of
25 the animal per day to the animal in the animal's
drinking water for an extended period.
14. The method as claimed in claim 13, wherein the
extended period is from about 7 to about 100 days.
15. The method as claimed in claim 13 or 14, wherein the
30 extended period is from about 7 to about 14 days.

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16. The method as claimed in any one of claims 13 to 15, wherein the animal is a pig or chicken.
17. A formulation comprising:
one or more macrocyclic lactones;
5 one or more co-solvents;
one or more preservatives;
one or more buffers; and
water,
when added to a source of water available to an
10 animal for drinking.
18. A formulation comprising:
one or more macrocyclic lactones;
one or more co-solvents;
one or more preservatives;
15 one or more buffers; and
water,
when added to a source of water available to an
animal for drinking to form the aqueous formulation
used in the method of any one of claims 1 to 12.
- 20 19. The formulation as claimed in claim 17 or 18, wherein the macrocyclic lactone is ivermectin.
20. The formulation as claimed in any one of claims 17 to 19, wherein, when added to a source of water
available to an animal for drinking, the resultant
25 formulation comprises the one or more macrocyclic
lactones in an amount of from about 250 to about
10,000 $\mu\text{g/L}$.
21. The formulation as claimed in any one of claims 17 to 20, wherein the co-solvents are propylene glycol and
30 ecoteric T80/tween 80.

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22. The formulation as claimed in any one of claims 17 to 21, wherein the preservative is benzyl alcohol.
23. The formulation as claimed in any one of claims 17 to 22, wherein the one or more buffers are sodium
5 phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous and butylated hydroxy toluene.
24. The formulation as claimed in any one of claims 17 to 23, wherein the one or more macrocyclic lactones are in solution.
- 10 25. The formulation as claimed in any one of claims 17 to 24, further comprising flavours or colouring agents.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/001685

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 31/7048 (2006.01) A61K 9/08 (2006.01) A61P 33/10 (2006.01)

A23K 1/17 (2006.01) A61P 33/00 (2006.01) A61P 33/14 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

Medline WPAT chemical abstracts (drinking water, water source, water supply, ivermectin, milbemycin, abamectin, macrocyclic lactone, doramectin, emamectin, moxidectin, avermectin, eprinomectin, selamectin, lepipmectin)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6627613 B2 (Strobel, M.A.) 30 September 2003 (see the entire patent, in particular column 5 lines 28-32 and 59-62, column 6 lines 10-13. 35-43, examples 1 and 3 and claims 5 and 19)	1-16
X	US 6780885 B1 (Campbell <i>et al.</i>) 24 August 2004 (see the entire patent, in particular column 3 lines 34-66, column 5 line 47 to column 6 line 24 and the claims)	1-16
A	US 4622313 A (Wyvrat, M. J. Jr.) 11 November 1986 (see the entire patent, in particular column 8 lines 51-52)	1-25

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"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	

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/001685

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6174866 B1 (SMOTER, R.) 16 January 2001 (see the entire patent, in particular column 3 lines 3-8)	1-25
X	EP 240274 A2 (Merck & Co. Ltd.) 7 October 1987 (see the entire document, in particular page 6 line 26 to page 7 line 17 and claim 9)	1-9, 11-16
X	US 4205081 A (Sakamoto <i>et al.</i>) 27 May 1980 (see the entire document, in particular column 2 lines 33-57)	1-4, 6, 8, 12
A	US 4333925 A (Buhs <i>et al.</i>) 8 June 1982 (see the entire patent, in particular column 4 line 63 to column 5 line 43 and column 6 lines 37-68)	1-25
X	WO 2000/050009 A1 (Idexx Laboratories, Inc.) 31 August 2000 (see the entire document, in particular page 3 lines 2-24, page 4 lines 20-29 and page 7 lines 5-17)	1-9
X	WO 2001/051028 A2 (Blue Ridge Pharmaceuticals, Inc.) 19 July 2001 (see the entire document, in particular pages 1 and 8 and example 1)	1-16
X	KOOPMAN, J. P., et al., [Effects of ivermectin on psoroptic ear mange in rabbits] Effect van ivermectine op Psoroptes-oorschurft bij konijnen, Tijdschr. Diergeneeskde., deel 114, afl. 15/16, 1989, pages 825-828. (see the entire document, in particular see the English abstract)	1, 6-7, 12
X	ORTIZ, J et al., Effects of different methods of administration of ivermectin on its efficacy against shedding of gastrointestinal nematode eggs by gazelles, The Veterinary Record, 2001, Vol. 149, No. 1, pages 12-15. (see the entire document, in particular page 14 column 2 lines 39-46)	1, 6-7, 12
A	Schillhorn van Veen, T. W. et al., Anthelmintic activity of ivermectin in pigs naturally infected with Ascaris and Trichuris, Am J Vet Res, 1983, Vol. 44 No. 9, pages 1732- 1733. (see the entire document, in particular page 1732 column 3)	1-25
X	Papini, R. and Marconcini, A., Treatment with Ivermectin in drinking water against Myobia musculi and Myocoptes musculinus mange in naturally infected laboratory mice, Angew. Parasitology (1991), Vol. 32, No. 1, pages 11-13. (see the entire document, in particular "Materials & Methods")	1, 6-7, 12
X	CONOLE, J., et al., Some Observations on the Pharmacological Properties of Ivermectin during Treatment of a Mite Infestation in Mice, Contemporary topic in laboratory animal science/American Association for Laboratory Animal Science (2003), Vol. 42, No. 4, pages 42-45. (see page 43 column 1)	1-4, 6-7
X	PubMed abstract ID 10403444 (and Davis, J. A., et al., Behavioral effects of ivermectin in mice, Laboratory animal science (1999), Vol. 49, No. 3, pages 288-296). (see the entire abstract)	1-4, 6-7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/001685

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PubMed abstract ID 2153865 (and Diggs, H. E., <i>et al.</i> , Effect of chronic ivermectin treatment on GABA receptor function in ethanol withdrawal-seizure prone and resistant mice, Laboratory animal science (1990), Vo. 40, No. 1, pages 68-71) (see the entire abstract)	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2006/001685

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
US	6627613	US	2003040494		
US	6780885	AU	30898/01	WO	0151028
US	4622313	ZA	8605737		
US	6174866				
EP	0240274	AU	71000/87	JP	62265223
				ZA	8702392
US	4205081	JP	54105235	NL	7900556
US	4333925	AU	83299/82	DK	208382
		ES	8303528	GR	75502
		NZ	200497	PT	74846
				EP	0065403
				JP	57206695
				ZA	8203196
WO	0050009	AU	36061/00		
WO	0151028	AU	30898/01	US	6780885
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.					
END OF ANNEX					