1-P1176 JGS:CB.3596T.21

604759

PATENT APPLICATION FORM

COMMONWEALTH OF AUSTRALIA

Regulation 9

Patents Act 1952

We, BAYER AKTIENGESELLSCHAFT

of D-5090 Leverkusen, Bayerwerk, Germany

hereby apply for the grant of a Standard Patent for an invention entitl "Dermal Treatment of Worm Diseases in Cats with which Praziquantel".

For a Convention application - details of basic application-

Number	Country	Date of Application
P 36 34 755.8	Germany	11th October 1986

Our address for service is ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, 1 Alfred Street, Sydney, New South Wales, Australia 2000.

Dated this 7th day of October, 1987.

BAYER AKTIENGESELLSCHAFT
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.

J.G. SIELY F.I.P.A.A.

To:
Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

ASC 1

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 26.9.90

PATENT DECLARATION FORM (CONVENTION)
COMMONWEALTH OF AUSTRALIA
Patents Act 1952

Regulation 12 (2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

To be signed by the applicant(s) or in the case of a body corporate to be signed by a person authorised by the body corporate.

In support of the Convention application made for a patent for an invention entitled

(a) Insert title of invention.

(a) Dermal treatment of worm diseases in cats with praziquantel

(b) Insert full name(s) of declarant(s).

~~I/We~~ (b) Klaus Dänner and Günter Schumacher

(c) Insert address(es) of declarant(s).

of (c) c/o Bayer AG, D-5090 Leverkusen, Bayerwerk, Germany

do solemnly and sincerely declare as follows:—

~~1. I am/We are the applicant(s) for the patent~~

(OR, IN THE CASE OF AN APPLICATION BY A BODY CORPORATE.)

1. ~~I~~ am/We are authorised by BAYER AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/~~were~~ made in the following country or countries on the following date(s) namely:—

(d) Insert country in which basic application(s) was/were filed.
(e) Insert date of basic application(s).
(f) Insert full names of basic applicant(s).

in (d) Germany on (e) 11.10.1986
by (f)
in (d) on (e)
by (f) BAYER AKTIENGESELLSCHAFT, D-5090 Leverkusen, Germany
in (d) on (e)
by (f)

~~3. I am/We are the actual inventor(s) of the invention referred to in the basic application.~~

(OR, WHERE A PERSON OTHER THAN THE INVENTOR IS THE APPLICANT)

(g) Insert full name(s) of actual inventor(s)
(h) Insert address(es) of actual inventor(s).

3. (g) 1) Peter Andrews 2) Herbert Voege

of (h) 1) Gellertweg 2, D-5600 Wuppertal 1, Germany
2) Martin-Buber-Strasse 41, D-5090 Leverkusen 1, Germany

is/~~are~~ the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:

(i) Set out how applicant(s) derive(s) title from actual inventor(s) i.e., assignee of the invention from the actual inventor(s).

(i) The company are the Assignees of the said invention from the said inventors

4. The basic application(s) referred to in paragraph 2 of this Declaration was/~~were~~ the first application(s) made in a Convention country in respect of the invention the subject of the application.

Attestation or legalization not required.

Declared at Leverkusen this 7th day of July 198 7

BAYER AKTIENGESELLLSCHAFT

To:

The Commissioner of Patents

Signature of Declarant(s)
Klaus Dänner
Günter Schumacher
(secretaries)

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

A.S.C.—4

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-79534/87
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(54) Title
DERMAL APPLICATION OF PRAZIQUANTEL

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(56) Prior Art Documents
US 4001411

(57) Praziquantel, the common name for 2-(cyclohexylcarbonyl)-1,2,3,6,7,11-b-hexahydro-4 H-pyrazino[2,1-a-]-isoquinolin-4-one, is known.

CLAIM

1. Agents for the dermal treatment of worm diseases comprising praziquantel in admixture with N-methylpyrrolidone and/or isopropyl myristate and optionally at least one other solvent or auxiliary, wherein said praziquantel is present at a concentration of 0.1 -20% by weight.

4. Agents according to any one of claims 1 to 3, whenever applied dermally to cats.

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AUSTRALIA

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COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

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Complete Specification Lodged:
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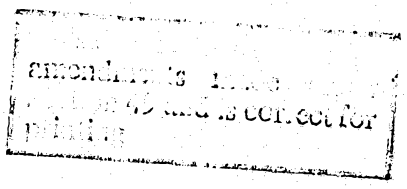

Priority:
Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant:	BAYER AKTIENGESELLSCHAFT
Address of Applicant:	D-5090 Leverkusen, Bayerwerk, Germany
Actual Inventor:	Peter ANDREWS & Herbert VOEGE
Address for Service:	ARTHUR S. CAVE & CO. Patent & Trade Mark Attorneys Goldfields House 1 Alfred Street SYDNEY N.S.W. 2000 AUSTRALIA

Complete Specification for the invention entitled ~~"IMPROVEMENTS~~ "Dermal Treatment of Worm Diseases in Cats with Praziquantel". cement is a full description of this invention including the best method of performing it known to me:-

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The present invention relates to the dermal use of praziquantel for combating worm diseases in cats and agents suitable for this application.

It is known that praziquantel can be used for combating worm diseases in animals, for example dogs and cats (U.S. Patent 4,113,867; P. Andrews et al. Medicinal Research Rev. Vol. 3(2) 147 - 200 (1983)). Treatment of dogs and cats is by oral or parenteral administration of the active compound in doses of about 5 mg/kg of body weight. Oral treatment, in which the active compound is administered directly into the habitat of the parasite, is preferred. A very good activity in low doses can therefore be expected with this type of administration.

A significantly poorer activity must be expected if the active compound is administered dermally. This is also generally known (Herlich et al. Veterinary Med. 56, pages 219 - 221 (1961); Hotson et al. Australian Vet. J. 39; pages 108 - 115 (1963)). Investigations with praziquantel on rats show that higher active compound doses are required both with dermal and with subcutaneous administration of praziquantel than with oral administration (H. Thomas et al. Z. Parasitenkd. 52; 117 - 127 (1977).

In investigations against Schistosoma mansoni in mice, it was found that on oral administration of the active compound only one tenth of the amount administered dermally was required to achieve the same action (R. Gönnert et al. Z. Parasitenkd. 52; pages 129-150 (1977)).

It was likewise found in investigations against Taenia hydatigena in dogs that the dermal use form gave only unsatisfactory results. A dose of 1 mg/kg is recommended for oral use. The dermal use of a solution of the active compounds in isopropanol at a dose of 5 mg/kg

showed an action in only one out of 2 dogs (H. Thomas et al. Research Vet. Sci. 24; pages 20-25 (1978)).

It was therefore to be expected that on dermal use of praziquantel higher doses (about 10 times higher) are required than with oral use.

However, in addition to activity, dermal agents must also fulfil certain expectations of the user. Even after application, the coat of the animal should not look wet or feel damp. In addition, the amount of solvent to be used must be kept as low as possible in order to avoid harmful effects of the solvent on the animal. It has scarcely been possible to find solvents which are harmless to cats and which dissolve the amount of praziquantel required for activity. This was one reason why there are as yet no agents which contain praziquantel and can be used dermally on cats.

It has now been found that praziquantel can be used for dermal combating of worm diseases in cats in application amounts of 0.1-5mg per kg of body weight.

Agents for dermal combating of worm diseases in cats have been found which contain praziquantel in concentrations of 0.1-20 percent by weight in admixture with N-methylpyrrolidone and/or isopropyl myristate and optionally at least one other solvent or auxiliary. It has been found that these agents must be administered to cats in amounts of 0.01-0.5 ml/kg of cat live weight for combating worm diseases.

It was surprising that worm diseases in cats can be combated successfully with this treatment. Surprisingly, in contrast to the statements from the prior art, the amount of

praziquantel which is also required for oral use is sufficient for dermal treatment of cats. In spite of the requirement of using small amounts of solvents, sufficient amounts of active compound can thus be applied to the cats.

The advantage of dermal use is obvious. The animal does not have to be held before the treatment, as is necessary in the case of administration as an injection. It also does not have to be treated with medicated food, where there is the risk of refusal of food. Simple application of drops of the formulation to the animal, for example between the shoulder blades, in order to avoid the animal licking the agent off its coat, is sufficient.

As a result of the small amount of active compound which is used, N-methylpyrrolidone and/or isopropyl myristate or mixtures of N-methylpyrrolidone and/or isopropyl myristate and/or at least one other solvent, in which sufficient amounts of active compound are dissolved and which neither irritate the skin of the animal nor harm the animal if it licks the agent off its coat, can be selected.

Praziquantel, the common name for 2-(cyclohexylcarbonyl)-1,2,3,6,7,11-b-hexahydro-4 H-pyrazino[2,1-a-]-isoquinolin-4-one, is known.

As already mentioned, praziquantel is used in the process according to the invention in application amounts of 0.1-5 mg, preferably 1-5 mg and particularly preferably about 1 mg per kg of body weight.

The agents according to the invention contain 0.1-20, preferably 1-5 and particularly preferably about 1 percent by

weight of praziquantel, in admixture with N-methylpyrrolidone and/or isopropyl myristate and, if appropriate, at least one other solvent and/or auxiliary.

The agents according to the invention are employed in amounts of 0.01-0.5 ml, preferably 0.1-0.5 ml and particularly preferably about 0.1 ml per kg of live weight of the cats.

The agents according to the invention are sprayed on, applied dropwise, dripped on or misted on to limited areas of the coat of the cat. Areas on the animal from which the agent cannot be licked off without difficulty are preferably treated.

The agents according to the invention are prepared by dissolving, suspending or emulsifying the active compound in N-methylpyrrolidone and/or isopropyl myristate or mixtures of N-methylpyrrolidone and/or isopropyl myristate and/or at least one other solvent which are tolerated by the skin. If appropriate, other auxiliaries, such as dyestuffs, absorption-promoting substances, antioxidants, light stabilizers of adhesives, are added.

Solvents which are particularly suitable for use in admixture with N-methylpyrrolidone and/or isopropyl myristate in the preparation of the agents according to the invention are:

Alkanols, such as ethyl alcohol, isopropyl alcohol, n-butyl alcohol and amyl alcohol.

Glycols, such as propylene glycol, glycerol, 1,3-butylene glycol, polyethylene glycols and polypropylene glycols.

Aromatic alcohols, such as benzyl alcohol, phenylethanol and phenoxyethanol.

Trihydric alcohols, such as glycerol.

Carboxylic acid esters, such as, for example, ethyl acetate, benzyl benzoate, butyl acetate and ethyl lactate.

Aromatic and/or aliphatic hydrocarbons.

Oils, such as, for example, cottonseed oil, groundnut oil, maize core oil, olive oil, caster oil, sesame oil and synthetic analogues of these oils.

Water.

Ketones, such as, for example, acetone and methyl ethyl ketone.

Ethers, such as alkylene glycol alkyl ethers, dipropylene glycol monomethyl ether and diethylene glycol monobutyl ether.

Furthermore dimethylformamide, dimethylacetamide and 2-dimethyl-4-oxymethylene-1,3-dioxolane.

The agents according to the invention can also contain emulsifiers and wetting agents, such as, for example, anionic surfactants, such as, for example, Na lauryl sulphate, fatty alcohol ether-sulphates and the monoethanolamine salt of mono/dialkyl polyglycol ether-orthophosphoric acid esters; cationic surfactants, such as, for example, cetyltrimethylammonium chloride;

ampholytic surfactants, such as, for example, di-Na N-lauryl-β-iminodipropionate and lecithin; non-ionic surfactants, such as, for example, polyoxyethylated castor oil, polyoxyethylated sorbitan monoleate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate and alkylphenol polyglycol ethers.

The agents according to the invention can also contain absorption-promoting substances, such as, for example, dimethylsulphoxide. They can furthermore contain spreading oils. The spreading oils include, inter alia: silicone oils of varying viscosity, fatty acid esters, such as ethyl stearate, di-n-butyl adipate, hexyl laurate, dipropylene glycol pelargonate, esters of a branched fatty acid of medium chain length with saturated C_6 - C_{18} fatty alcohols, ~~isopropyl myristate~~, isopropyl palmitate, caprylic/capric acid esters of saturated fatty alcohols of C_{12}-C_{18} chain length, isopropyl stearate, oleyl oleate, decyl oleate, ethyl oleate, ethyl lactate, dibutyl phthalate, diisopropyl adipate, triglycerides, such as caprylic/capric acid triglyceride, triglyceride mixtures with vegetable fatty acids of C_8-C_{12} chain length or other specially selected natural fatty acids, partial glyceride mixtures of saturated or unsaturated fatty acids which optionally also contain hydroxyl groups, mono- and diglycerides of C_8/C_{10} fatty acids and others.

Fatty alcohols, such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol and oleyl alcohol.

Fatty acids, such as, for example, oleic acid.

Other auxiliaries which may be mentioned are: adhesion promoters, for example carboxymethylcellulose, methylcellulose and other cellulose and starch derivatives, polyacrylates, alginates, gelatine, gum arabic, polyvinylpyrrolidone, polyvinyl alcohol, copolymers of methyl vinyl ether and maleic anhydride, polyethylene glycols, paraffins, oils, waxes and colloidal silicic

acid; dyestuffs which are permitted for use on animals; antioxidants, such as, for example, sulphites or metabisulphites, such as potassium metabisulphite, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole and tocopherol; and light stabilizers, for example from the benzophenone or novantisolic acid class.

The agents according to the invention can be used against all the parasitic tapeworms in cats. These include

- Hydatigera taeniaeformis
- Dipylidium canium
- Joyeuxiella pasquali
- Echinococcus multilocularis

They are particularly preferably used against Hydatigera taeniaeformis.

Examples of the agents according to the invention which may be mentioned are the agents with the following compositions:

~~Example 1~~

Praziquantel	20 g
Benzyl alcohol	to 100 ml

Example 2

Praziquantel	20 g
Isopropyl myristate	5 g
Benzyl alcohol	to 100 ml

Example 3

Praziquantel	10 g
Ethyl lactate	to 100 ml

Example 4

Praziquantel	10 g
Isopropyl myristate	5 g
~~Ethyl lactate~~	~~to 100 ml~~

Example 5

Praziquantel	10 g
Isopropyl myristate	5 g
N-Methylpyrrolidone	to 100 ml

~~Example 6~~

Praziquantel	10 g
Dimethylsulphoxide (DMSO)	20 g
Benzyl alcohol	to 100 ml

Example 7

Praziquantel	10 g
Benzyl alcohol	to 100 ml

Example 8

Praziquantel	20 g
Benzyl alcohol	43.9 g
Benzyl benzoate	43.9 g

Example 9

Praziquantel	1 g
Isopropyl myristate	5 g
~~Benzyl alcohol~~	~~97.04 g~~

Example ~~10~~ 2

Praziquantel	1 g
Isopropyl myristate	5 g
N-Methylpyrrolidone	96.19 g

Example ~~11~~ 3

Praziquantel	1 g
DMSO	30 g
N-Methylpyrrolidone	73.97 g

Example A

In vivo tapeworm test

Taenia taeniaeformis - cats

Cats infected experimentally with Taenia taeniaeformis are treated once 6 weeks after the infection by applying to the skin between the neck and the shoulder blades the agent in an amount such that the stated dose of active compound is achieved. The number of tapeworms excreted in the faeces deposited 0-48 hours after treatment is determined. 6 weeks after the first treatment, a treatment which is known to be fully effective is administered and the faeces are then examined to investigate whether tapeworms have survived the first treatment. If no tapeworms have considered the first treatment, the first treatment was fully effective. The agent and the dose of active compound, in mg/kg of cat live weight, required for full activity are shown in the following table.

Agent according to Example	Fully effective dose of active compound in mg/kg
2	1
5	1
8	1
11	1

The claims defining the invention are as follows:

1. Agents for the dermal treatment of worm diseases comprising praziquantel in admixture with N-methylpyrrolidone and/or isopropyl myristate and optionally at least one other solvent or auxiliary, wherein said praziquantel is present at a concentration of 0.1 -20% by weight.

2. Agents according to claim 1, wherein said praziquantel is present at a concentration of 1-5% by weight.

3. Agents according to any one of claims 1 to 2 wherein said N-methylpyrrolidone is present at a concentration of about 96.19% by weight.

4. Agents according to any one of claims 1 to 3, whenever applied dermally to cats.

5. Agents for the dermal treatment of worm diseases, substantially as herein described with reference to any one of Examples 1 to 3.

DATED this 10th day of September, 1990.

BAYER AKTIENGESELLSCHAFT
By Its Patent Attorneys
ARTHUR S. CAVE & CO.