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(71) Applicant: **VETOQUINOL S.A.** [FR/FR]; 70200 Magny-Vernois (FR).

(72) Inventors: **KANIKANTI, Venkata-Rangarao**; 10/154-D; 2nd Lane, Rajendra Nagar, Gudivada A.P. 521301 (IN). **HEEP, Iris**; Grüner Weg 7a, 50859 Köln (DE). **FELDHUES, Elisabeth**; Sauerbruchstr. 18, 51465 Bergisch Gladbach (DE). **SIEGEL, David**; Comeniusweg 6, 40764 Langenfeld (DE). **PETRY, Gabriele**; Maybachstr. 15, 47809 Krefeld (DE).

(74) Agent: **LAGNEAU, Nadège**; Novagraaf Technologies, 2, rue Sarah Bernhardt, CS 90017, 92665 Asnières-sur-Seine Cedex (FR).

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(54) Title: COMPOSITIONS COMPRISING TIGOLANER FOR CONTROLLING PARASITES

(57) Abstract: The present invention relates to a composition comprising tigolaner and, optionally endoparasiticidal agents, a method for its manufacture and its use as a medicament for controlling parasites.

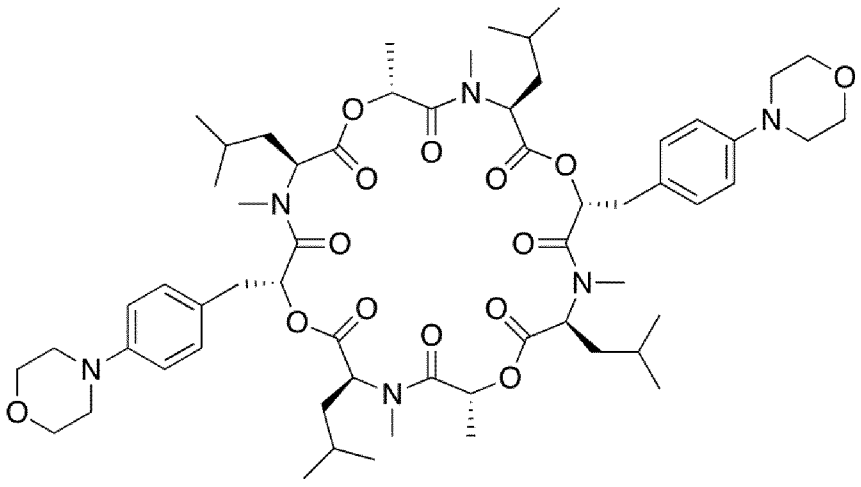
COMPOSITIONS COMPRISING TIGOLANER FOR CONTROLLING PARASITES

The present invention relates to a composition comprising tigolaner and, optionally endoparasiticidal agents, a method for its manufacture and its use as a medicament for controlling parasites.

Formulations for controlling ectoparasites in pets such as cats can be administered in so-called spot-on formulations. Spot-on treatment can be packaged in individual doses of liquid and is usually applied by pouring the liquid onto the back of the pet, for example between the shoulders. From there, the active agent is absorbed into the pet's system and/or distributed over the pet's skin and can act accordingly.

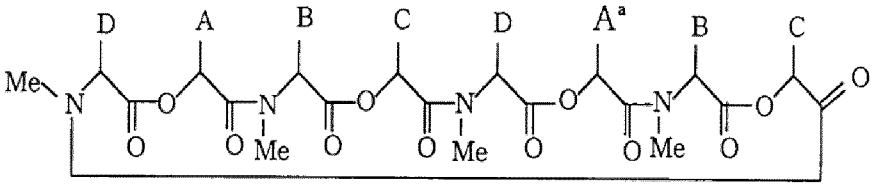
WO 2008/080542 A2 discloses a composition for controlling parasites on animals, comprising fipronil, flumethrin, an aliphatic cyclic carbonate and an aliphatic cyclic or acyclic polyether. WO 2005/105034 A1 is directed towards a composition of matter, comprising: a) 0.1-60% by weight of an active pyrethroid compound; b) 7.5-30.0% by weight of dinotefuran and/or dinotefuran analogues; c) 27.5-62.5% by weight of organic solvents from the class of the methylpyrrolidones, aliphatic alcohols and cyclic carbonates, aliphatic, cyclic or acyclic ethers and mixtures of these; d) 0-5% by weight of water; e) 0-0.5% by weight of phenolic antioxidants; and g) 0-0.5% by weight of organic acids.

Emodepside (cyclo[(*R*)-lactoyl-*N*-methyl-L-leucyl-(*R*)-3-(*p*-morpholinophenyl)lactoyl-*N*-methyl-L-leucyl-(*R*)-lactoyl-*N*-methyl-L-leucyl-(*R*)-3-(*p*-morpholinophenyl)lactoyl-*N*-methyl-L-leucyl) is an anthelmintic drug that is effective against a number of gastrointestinal nematodes. Its molecular structure which is depicted below can be described as a cyclic octadepsipeptides, a depsipeptide being a peptide in which one or more of its amide groups are replaced by the corresponding ester groups. On a technical scale emodepside may be obtained by derivatization of the naturally occurring substance PF1022A in which two hydrogen atoms are exchanged for morpholine rings.



(Emodepside)

WO 93/19053 A1 (EP 0 634 408 A1) discloses a compound of the general formula:



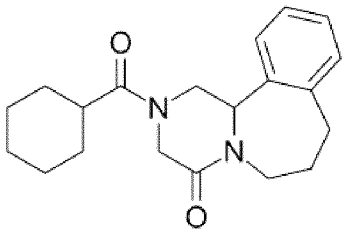
wherein A is benzyl group which has suitable substituent(s) or phenyl group which may have suitable substituent(s), A^a is benzyl group which may have suitable substituent(s) or phenyl group which may have suitable substituent(s), B and D are each lower alkyl, C is hydrogen or lower alkyl, and a pharmaceutically acceptable salt thereof.

EP 0 662 326 A2 concerns the use of praziquantel and epsiprantel for enhancing the endoparasiticidal activity of cyclic depsipeptides in endoparasiticidal compositions.

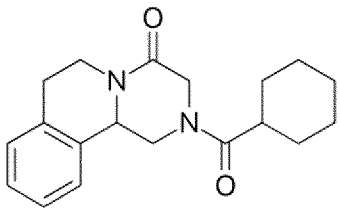
US 2003/125244 A1 relates to transdermally administrable compositions comprising cyclic depsipeptides, to their preparation and to their use for controlling endoparasites. In the compositions according this patent application the active compounds can also be present in a mixture with synergists or other compounds which are active against pathogenic endoparasites. Examples given for such active compounds are L-2,3,5,6-tetra-hydro-6-phenylimidazothiazol, benzimidazol carbamates, such as febantel, furthermore pyrantel, praziquantel and ivermectin.

US 2008/255037 A1 relates to compositions for external application which comprise emodepside and praziquantel or epsiprantel and 1,2-isopropylideneglycerol, to their preparation and to their use for controlling endoparasites.

Praziquantel and epsiprantel have the following structures:



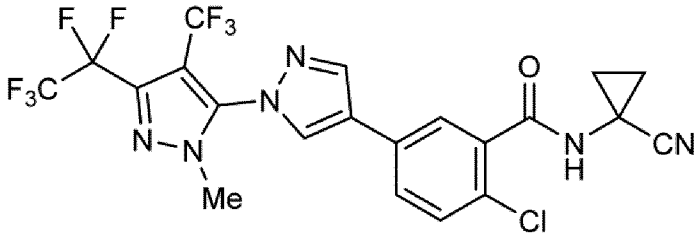
(Praziquantel)



(Epsiprantel)

Anthelmintic products for animals under the name Profender® are available on the market. These include the Profender® spot-on solution for cats which contains emodepside and praziquantel as active ingredients and butylhydroxyanisole, isopropylideneglycerol and lactic acid as excipients.

Tigolaner (WHO Drug Information, Vol. 31, No. 2, 2017, page 341) is an antiparasitic agent for veterinary use with the following structure:



Tigolaner is described in structure Ic-2, table 3 of WO 2014/122083 A1. By way of example, tigolaner is also mentioned in example 3 (page 39) of WO 2016/177619 A1. International patent applications relating to the synthesis of such compounds are, for example: WO 2014/012975 A1, WO 2015/078846 A1, WO 2015/078847 A1, WO 2015/150302 A1, WO 2015/181139 A1 and WO 2016/026789 A1.

Because of the wide variety of requirements to be met by modern pharmaceuticals, for example concerning level of activity (for example plasma concentration of the active compound), duration of action, spectrum of action, range of applications, toxicity, combination of active compounds, combination with formulation auxiliaries, and because of the possible occurrence of resistance, the development of novel pharmaceuticals cannot ever be regarded as complete, and there is a continuing great need for novel compositions which have advantages, at least in some aspects, over the known compositions.

To enable the pet owner to apply parasiticidally active compounds in a manner which is as simple as possible, it is furthermore desirable to provide an externally applicable composition, external application in the context of the present application generally meaning application to the skin or the coat of animals.

Such compositions need to meet additional criteria, e.g.:

- efficacy (particularly where an active compounds acts systemically)
- target animal safety, user safety
- well tolerated
- convenience

The present invention is directed towards a composition according to claim 1 and in a further embodiment to a composition according to claim 5 a method according to claim 14, a composition

for use as a medicament according to claim 15 and a composition for use in the treatment and/or prevention of parasite infections in animals according to claim 16. Advantageous embodiments are the subject of the dependent claims. They may be combined freely unless the context clearly indicates otherwise.

Accordingly one embodiment of the present invention is a composition comprising tigolaner and 1,2-isopropylideneglycerol. The composition may preferably comprise tigolaner in amounts of ≥ 1 weight-% to ≤ 15 weight-%; according to further preferred embodiments the composition may contain tigolaner in amounts of≥ 1 weight-% to ≤ 11 weight-% or ≥ 7 weight-% to ≤ 11 weight-% or ≥ 1 weight-% to ≤ 9.5 weight-% or ≥ 7 weight-% to ≤ 9.5 weight-%). The composition optionally further comprises praziquantel, preferably in concentrations ≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 6 weight-% to ≤ 9 weight-%). In compositions according to the invention that contain tigolaner and solketal but do not contain praziquantel, the amount of tigolaner is preferably < 10 weight-%, more preferably < 9.5 weight-%.

According to a further embodiment, the present invention comprises a composition comprising praziquantel, emodepside and a solvent component further comprises tigolaner. These substances have the structures already defined in the preceding section. The composition according to this embodiment expands the endoparasiticidal action of praziquantel and emodepside with the ectoparasiticidal action of tigolaner. In particular, cestodes, trematodes, nematodes, acantocephales fleas and ticks can be controlled.

Unless otherwise specified, the solvent component preferably contains solvents suitable for a transdermal application of the active pharmaceutical ingredients such as DMSO, NMP, 2-pyrrolidone, dimethylacetamide (DMAc), glycerine formal (also referred to as glycerol formal), tetraglycol, triethylphosphate, propylene carbonate or 1,2-isopropylideneglycerol (also known as solketal).

By controlling the pathogenic endoparasites, it is intended to reduce disease, mortality and decreasing performance (for example in the production of meat, milk, wool, hides, eggs, honey, etc), so that more economical and simpler animal keeping is possible by using the active compounds. The pathogenic endoparasites include cestodes, trematodes, nematodes and acantocephales:

Praziquantel controls especially the following endoparasites:

from the order of the Pseudophyllidea, for example: Diphyllobothrium spp., Spirometra spp., Schistocephalus spp., Ligula spp., Bothridium spp., Diphlogonoporus spp.

from the order of the Cyclophyllidea, for example: Mesocestoides spp., Anoplocephala spp.,

Paranoplocephala spp., Moniezia spp., Thysanosomsa spp., Thysaniezia spp., Avitellina spp., Stilesia spp., Cittotaenia spp., Andyra spp., Bertiella spp., Taenia spp., Echinococcus spp., Hydatigera spp., Davainea spp., Raillietina spp., Hymenolepis spp., Echinolepis spp., Echinocotyle spp., Diorchis spp., Dipylidium spp., Joyeuxiella spp., Diplopylidium spp.

from the subclass of the Monogenea, for example: Gyrodactylus spp., Dactylogyrus spp., Polystoma spp.

from the subclass of the Digenea, for example: Diplostomum spp., Posthodiplostomum spp., Schistosoma spp., Trichobilharzia spp., Ornithobilharzia spp., Austrobilharzia spp., Gigantobilharzia spp., Leucochloridium spp., Brachylaima spp., Echinostoma spp., Echinoparyphium spp., Echinochasmus spp., Hypoderaeum spp., Fasciola spp., Fasciolides spp., Fasciolopsis spp., Cyclocoelum spp., Typhlocoelum spp., Paramphistomum spp., Calicophoron spp., Cotylophoron spp., Gigantocotyle spp., Fischoederius spp., Gastrothylacus spp., Notocotylus spp., Catatropis spp., Plagiorchis spp., Prosthogonimus spp., Dicrocoelium spp., Eurytrema spp., Troglotrema spp., Paragonimus spp., Collyriclum spp., Nanophyetus spp., Opisthorchis spp., Clonorchis spp. Metorchis spp., Heterophyes spp., Metagonimus spp.

Emodepside controls especially the following endoparasites:

from the order of the Enoplida, for example: Trichuris spp., Capillaria spp., Trichomosoides spp., Trichinella spp.

from the order of the Rhabditia, for example: Micronema spp., Strongyloides spp., Aelurostrongylus spp., Troglostrongylus brevior

from the order of the Strongylida, for example: Stronylus spp., Triodontophorus spp., Oesophagodontus spp., Trichonema spp., Gyalocephalus spp., Cylindropharynx spp., Poteriostomum spp., Cyclococercus spp., Cylicostephanus spp., Oesophagostomum spp., Chabertia spp., Stephanurus spp., Ancylostoma spp., Uncinaria spp., Bunostomum spp.

Globocephalus spp., Syngamus spp., Cyathostoma spp., Metastrongylus spp., Dictyocaulus spp., Muellerius spp., Protostrongylus spp., Neostrongylus spp., Cystocaulus spp., Pneumostrongylus spp., Spicocaulus spp., Elaphostrongylus spp. Parelaphostrongylus spp., Crenosoma spp., Paracrenosoma spp., Angiostrongylus spp., Aelurostrongylus spp., Filaroides spp., Parafilaroides spp., Trichostrongylus spp., Haemonchus spp., Ostertagia spp., Marshallagia spp., Cooperia spp., Nematodirus spp., Hyostrongylus spp., Obeliscoides spp., Amidostomum spp., Ollulanus spp.

from the order of the Oxyurida, for example: Oxyuris spp., Enterobius spp., Passalurus spp., Syphacia spp., Aspiculuris spp., Heterakis spp.

from the order of the Ascaridia, for example: Ascaris spp., Toxascaris spp., Toxocara spp., Parascaris spp., Anisakis spp., Ascaridia spp.

from the order of the Spirurida, for example: Gnathostoma spp., Physaloptera spp., Thelazia spp., Gongylonema spp., Habronema spp., Parabronema spp., Draschia spp., Dracunculus spp.

from the order of the Filariida, for example: Stephanofilaria spp., Parafilaria spp., Setaria spp., Loa spp., Dirofilaria spp., Litomosoides spp., Brugia spp., Wuchereria spp., Onchocerca spp.

from the order of the Gigantorhynchida, for example: Filicollis spp., Moniliformis spp., Macracanthorhynchus spp., Prosthenorchis spp.

Pests targeted by tigolaner include:

from the order of the Anoplura, for example, Haematopinus spp., Linognathus spp., Solenopotes spp., Pediculus spp., Pthirus spp.;

from the order of the Mallophaga, for example, Trimenopon spp., Menopon spp., Eomena¬canthus spp., Menacanthus spp., Trichodectes spp., Felicola spp., Damalinea spp., Bovicola spp.;

from the order of the Diptera, suborder Brachycera, for example, Chrysops spp., Tabanus spp., Musca spp., Hydrotaea spp., Muscina spp., Haematobosca spp., Haematobia spp., Stomoxys spp., Fan¬nia spp., Glossina spp., Lucilia spp., Calliphora spp., Auchmeromyia spp., Cordylobia spp., Cochliomyia spp., Chrysomyia spp., Sarcophaga spp., Wohlfartia spp., Gasterophilus spp., Oesteromyia spp., Oedemagena spp., Hypo¬derma spp., Oestrus spp., Rhinoestrus spp., Melophagus spp., Hippobosca spp.;

from the order of the Diptera, suborder Nematocera, for example, Culex spp., Aedes spp., Anopheles spp., Culicoides spp., Phlebotomus spp., Simulium spp..

from the order of the Siphonaptera, for example, Ctenocephalides spp., Echidnophaga spp., Ceratophyllus spp., Pulex spp..

from the order of the Metastigmata, for example, Hyalomma spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Haemaphysalis spp., Dermacentor spp., Ixodes spp., Argas spp., Ornithodorus spp., Otobius spp.;

from the order of the Mesostigmata, for example, Dermanyssus spp., Ornithonyssus spp., Pneumonyssus spp..

from the order of the Prostigmata, for example, Cheyletiella spp., Psorergates spp., Myobia spp.,

Demodex spp., Neotrombicula spp.;

from the order of the Astigmata, for example, Acarus spp., Myocoptes spp., Psoroptes spp., Chorioptes spp., Otodectes spp., Sarcoptes spp., Notoedres spp., Knemidocoptes spp., Neoknemidocoptes spp., Cytodites spp., Laminosioptes spp..

Particular emphasis may be given to the action against fleas (Siphonaptera, for example, Ctenocephalides spp., Echidnophaga spp., Ceratophyllus spp., Pulex spp.), ticks (Hyalomma spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Haemaphysalis spp., Dermacentor spp., Ixodes spp., Argas spp., Ornithodorus spp., Otobius spp.) and the Diptera mentioned above (Chrysops spp., Tabanus spp., Musca spp., Hydrotaea spp., Muscina spp., Haematobosca spp., Haematobia spp., Stomoxys spp., Fannia spp., Glossina spp., Lucilia spp., Calliphora spp., Auchmeromyia spp., Cordylobia spp., Cochliomyia spp., Chrysomyia spp., Sarcophaga spp., Wohlfartia spp., Gasterophilus spp., Oesteromyia spp., Oedemagena spp., Hypoderma spp., Oestrus spp., Rhinoestrus spp., Melophagus spp., Hippobosca spp.).

In one embodiment of the composition the solvent component comprises 1,2-isopropylideneglycerol and the water content of the composition is at most 5% by weight, preferably at most 3 % by weight, more preferably at most 2 % by weight, even more preferably at most 1.5 % by weight, in particular at most 1 % by weight.

In another embodiment of the composition the solvent component comprises only 1,2-isopropylideneglycerol. The solubility of tigolaner in solketal alone has been determined to be in the range of ca 9.5 – 9.9 % w/w. Surprisingly it has been found that it could be increased to at more than 10.5% w/w in solketal in the presence of praziquantel, in particular of 7.5 to 8.5% w/w of praziquantel.

In another embodiment the composition comprises:

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 6 weight-% to ≤ 9 weight-%) praziquantel;

≥ 1 weight-% to ≤ 10 weight-% (preferably ≥ 1.2 weight-% to ≤ 3 weight-%) emodepside;

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 7 weight-% to ≤ 11 weight-%) tigolaner;

wherein the weight-percentages are based on the total weight of the composition.

Preferably the composition comprises:

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 6 weight-% to ≤ 9 weight-%) praziquantel;

≥ 1 weight-% to ≤ 10 weight-% (preferably ≥ 1.2 weight-% to ≤ 3 weight-%) emodepside;

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 7 weight-% to ≤ 11 weight-%) tigolaner

≥ 0 weight-% to ≤ 5 weight-% (preferably ≥ 1 weight-% to ≤ 3 weight-%) of other components excluding solvents;

wherein the weight-percentages are based on the total weight of the composition and the balance to 100 weight% is constituted by 1,2-isopropylideneglycerol as the solvent component.

In another embodiment the composition further comprises an anti-oxidant. These anti-oxidants can in particular protect praziquantel and/or emodepside against oxidation.

In another embodiment the anti-oxidant is butyl hydroxyanisole (BHA) and/or butyl hydroxytoluene (BHT). Preferably the present compositions contain BHT. According to another preferred embodiment the present compositions contain BHA and BHT.

In another embodiment the composition further comprises an acid. These acids are preferably carboxylic acids. They can act as a stabilizer.

In another embodiment the acid is lactic acid.

In another embodiment the composition comprises:

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 6 weight-% to ≤ 9 weight-%) praziquantel;

≥ 1 weight-% to ≤ 10 weight-% (preferably ≥ 1.2 weight-% to ≤ 3 weight-%) emodepside;

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 7 weight-% to ≤ 11 weight-%) tigolaner;

≥ 0.01 weight-% to ≤ 1 weight-% (preferably ≥ 0.1 weight-% to ≤ 0.5 weight-%) butyl hydroxyanisole (BHA) and/or butyl hydroxytoluene (BHT);

≥ 1 weight-% to ≤ 5 weight-% (preferably ≥ 1.5 weight-% to ≤ 2.5 weight-%) lactic acid;

wherein the weight-percentages are based on the total weight of the composition.

Preferably the composition comprises:

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 6 weight-% to ≤ 9 weight-%) praziquantel;

≥ 1 weight-% to ≤ 10 weight-% (preferably ≥ 1.2 weight-% to ≤ 3 weight-%) emodepside;

≥ 1 weight-% to ≤ 15 weight-% (preferably ≥ 7 weight-% to ≤ 11 weight-%) tigolaner;

≥ 0.01 weight-% to ≤ 1 weight-% (preferably ≥ 0.1 weight-% to ≤ 0.5 weight-%) butyl hydroxyanisole (BHA) and/or butyl hydroxytoluene (BHT);

≥ 1 weight-% to ≤ 5 weight-% (preferably ≥ 1.5 weight-% to ≤ 2.5 weight-%) lactic acid;

wherein the weight-percentages are based on the total weight of the composition and the balance to 100 weight% is constituted by 1,2-isopropylideneglycerol as the solvent component.

The presence of lactic acid slightly lowers the solubility of tigolaner in 1,2-isopropylideneglycerol. It is therefore preferred to use low concentrations of lactic acid in compositions that contain tigolaner and 1,2-isopropylideneglycerol, namely

≥ 1 weight-% to ≤ 3 weight-% (preferably ≥ 1 weight-% to ≤ 2.5 weight-%) lactic acid.

The invention is also directed towards a method for producing a composition according to the invention, comprising the step of dissolving the active ingredient or active ingredients as well as optional further ingredients in a solvent component. According to one embodiment this method comprsises the step of dissolving praziquantel, emodepside and tigolaner in a solvent component.

The compositions are prepared by mixing appropriate amounts of the components in suitable vessels; preferably, the components are mixed until a clear solution is formed.

According to one embodiment, in compositions containing emodepside and tigolaner, emodepside can be added before tigolaner to facilitate the dissolution of tigolaner.

According to a further embodiment, in compositions containing praziquantel, emodepside and tigolaner, praziquantel and emodepside can be added before tigolaner to facilitate the dissolution of tigolaner.

To speed up dissolution kinetics, the mixture can be warmed and/ or shear force can be applied.

The preparation of the present compositions can be conducted under inert gas, preferably dry inert gas, for example by blanketing with Nitrogen or Argon. “Dry” inert gas preferably means that the gas contains less than 100 ppm (per volume) water.

In general, it has been found to be advantageous to meter compositions according to the invention such that per application from about 1 to about 100 mg of the active compound in question are administered per kg of body weight. Preferred in the case of emodepside are from 1 to 20 mg, in particular from 1 to 10 mg, of active compound per kg of body weight; in the case of praziquantel

from 5 to 50 mg, in particular from 5 to 20 mg, of active compound per kg of body weight; and in the case of tigolaner 5 to 30 mg, in particular 10 to 20 mg per kg of body weight.

A further aspect of the invention is a composition according to the invention for use as a medicament.

Without being bound to any theory it is believed that Tigolaner mainly acts systemically, i.e. it penetrates through the skin and enters the blood circulation. Since Emodepside and praziquantel act against endoparasites it is believed that they also act systemically.

Application can take place both prophylactically and therapeutically.

Preferably, the compositions according to the invention are suitable for spot-on, pour-on or spray application, where the spray application may be carried out, for example, using a pump spray or an aerosol spray (pressurized spray). For specific indications, the formulations may also be used after dilution with water as a dip; in this case, the formulation should contain emulsifying additives.

The preferred application forms are pump spray, pour-on and spot-on. The spot-on application is very particularly preferred.

The invention also encompasses a composition according to the invention for use in the treatment and/or prevention of parasite infections in animals.

Animals are preferably mammals such as for example cats, dogs or ferrets.

In one embodiment the animals are cats.

In another embodiment the parasites are endoparasites and ectoparasites.

In another embodiment the parasites are selected from the group consisting of:

Endoparasites selected from: *Toxocara cati, Toxascaris leonina, Ancylostoma tubaeforme, Uncinaria stenocephala, Dipylidium caninum, Taenia taeniaeformis, Echinococcus multiocularis, Aelurostrongylus abstrusus,* and *Troglostrongylus spp.;*

Ectoparasites selected from: *Ctenocephalides spp., Echidnophaga spp., Cteratophyllus spp., Pulex spp., Hyalomma spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Haemaphysalis spp., Dermacentor spp., Ixodes spp., Argas spp., Ornithodorus spp., Otobius spp., Otodectes cynotis, Notoedres cati,*

and combinations thereof.

Tigolaner shows long-term efficacy. The present compositions may therefore be applied to the host

animal in intervals of 4 weeks or more, preferably 8 weeks or more, more preferably 10 weeks or more, in particular 12 weeks or more.

Examples

The present invention will be further described in the following examples without wishing to be limited by them. Solketal is 1,2-isopropylideneglycerol. All examples shown include Solketal that already contains 0.3 % BHA for general stability of the solvent.

Examples were prepared by mixing the ingredients using a stirrer. In compositions containing praziquantel and tigolaner, praziquantel was added first to facilitate the dissolution of tigolaner. In compositions containing emodepside and tigolaner, a preferred option is that emodepside is added first to facilitate the dissolution of Tigolaner. In compositions containing praziquantel, emodepside and tigolaner, the preferred option is that praziquantel and emodepside are added first to facilitate the dissolution of Tigolaner. All examples are homogeneous solutions.

Example 1:

Ingredient	% w/w
Tigolaner	9.7
Solketal	to 100.0

Example 2:

Ingredient	% w/w
Tigolaner	10.7
Praziquantel	7.4
Solketal	to 100.0

Example 3:

Ingredient	% w/w
Tigolaner	11.0
Praziquantel	7.4
Emodepside	1.7
Solketal	to 100.0

Example 4:

Ingredient	% w/w

Tigolaner	8.9
Praziquantel	7.4
Emodepside	1.85
Milchsäure	2.0
BHT	0.1
Solketal	to 100.0

Example 5:

Ingredient	% w/w
Tigolaner	8.9
Praziquantel	7.4
Emodepside	1.85
Milchsäure	2.0
BHT	0.2
Solketal	to 100.0

Example 6:

Ingredient	% w/w
Tigolaner	8.9
Praziquantel	7.4
Emodepside	1.85
Milchsäure	2.0
BHT	0.4
Solketal	to 100.0

Example 7:

Ingredient	% w/w
Tigolaner	9
Solketal	to 100.0

Example 8:

Ingredient	% w/w
Tigolaner	9.5
Solketal	to 100.0

Example 9:

Ingredient	% w/w
Tigolaner	9
BHT	0.1
Solketal	to 100.0

Example 10:

Ingredient	% w/w
Tigolaner	9.5
BHT	0.1
Solketal	to 100.0

Example 11:

Ingredient	% w/w
Tigolaner	9
BHT	0.2
Solketal	to 100.0

Example 12:

Ingredient	% w/w
Tigolaner	9.5
BHT	0.2
Solketal	to 100.0

Example 13:

Ingredient	% w/w
Tigolaner	9
BHT	0.4
Solketal	to 100.0

Example 14:

Ingredient	% w/w
Tigolaner	9.5
BHT	0.4
Solketal	to 100.0

Example 15:

Ingredient	% w/w
Tigolaner	9
Praziquantel	7.94
Emodepside	1.984
BHT	0.4
Solketal	to 100.0

Example 16:

Ingredient	% w/w
Tigolaner	9
Praziquantel	7.94
Emodepside	1.984
BHT	0.2
Lactic acid	2.0
Solketal	to 100.0

Example 17:

Ingredient	% w/w
Tigolaner	9
Praziquantel	7.54
Emodepside	1.885
BHT	0.2
Lactic acid	2.0
Solketal	to 100.0

Example 118:

Ingredient	% w/w
Tigolaner	9
Praziquantel	7.54
Emodepside	1.885
BHT	0.4
Lactic acid	2.0
Solketal	to 100.0

Example 19:

Ingredient	% w/w
Tigolaner	9
Praziquantel	7.54
Emodepside	1.885
BHT	0.1
Lactic acid	2.0
Solketal	to 100.0

Example 20:

Ingredient	% w/w
Tigolaner	8.909
Praziquantel	7.409

Emodepside	1.864
BHT	0.4
Lactic acid	2.0
Solketal	to 100.0

Example 21:

Ingredient	% w/w
Tigolaner	9.1
Praziquantel	7.94
Emodepside	1.98
BHT	0.4
Lactic acid	2.0
Solketal	to 100.0

Example 22:

Ingredient	% w/w
Tigolaner	9.1
Praziquantel	7.94
Emodepside	1.98
BHT	0.2
Lactic acid	2.0
Solketal	to 100.0

Example 23:

Ingredient	% w/w
Tigolaner	9.1
Praziquantel	7.94
Emodepside	1.98
BHT	0.1
Lactic acid	2.0
Solketal	to 100.0

Example 24:

Ingredient	% w/w
Tigolaner	8.909
Praziquantel	7.409
Emodepside	1.864
BHT	0.2
Lactic acid	2.0
Solketal	to 100.0

Example 25:

Ingredient	% w/w
Tigolaner	8.909
Praziquantel	7.409
Emodepside	1.864
BHT	0.1
Lactic acid	2.0
Solketal	to 100.0

Biological Examples

A. Summary of in-vitro test results for Tigolaner as disclosed in WO2014/122083:

Test methods and results have already been described in WO2014/122083. Results disclosed therein for Tigolaner (Ex. Ic-2 in WO2014/122083) for parasites relevant in the veterinary field are summarized below:

Amblyomma hebraeum: 100 % efficacy at 100 ppm

Boophilus microplus – Dip test: 100 % efficacy at 100 ppm

Boophilus microplus – injection test: 100 % efficacy at 20 µg/tick

Ctenocephalides felis – oral test: 100 % efficacy at 100 ppm

Ctenocephalides felis – contact test: 100 % efficacy at 1 µg/cm^2

Lucilia cuprina: 100 % efficacy at 100 ppm

Musca domestica: 100 % efficacy at 100 ppm

Rhipicephalus sanguineus – contact test: 100 % efficacy at 1 µg/cm^2

Ixodes ricinus – contact test: 100 % efficacy at 1 µg/cm^2

Amblyomma hebraeum – contact test: 100 % efficacy at 1 µg/cm^2

B. Summary of in-vivo test results for Tigolaner in rats as disclosed in WO2014/122083:

Test methods and results have already been described in WO2014/122083. Results for Tigolaner (Ex. Ic-2 in WO2014/122083) for parasites relevant in the veterinary field are summarized below:

Dermacentor variabilis - systemic in vivo activity against American dog tick nymphs on rats: Efficacy of >90% against tick nymphs on day 2 at an application rate of 10 mg/kg.

Ctenocephalides felis - systemic in vivo activity against fleas on rats: efficacy of >95 % on day 2 and of >90 % on day 9 at an application rate of 10 mg/kg.

C. In-vivo study endoparasites: Efficacy of a spot-on formulation against patent *Toxocara cati* and *Dipylidium caninum* infections in experimentally infected cats.

Before treatment 16 cats were experimentally infected each with *T. cati* (larvated eggs) and a feline strain of *D. caninum* (using infected *C. felis* fleas – oral and topical infestations).

On Day -1, 14 cats with patent infections of both *T. cati* and *D. caninum* were included in the study. Cats were allocated to 2 groups consisting of 7 cats each.

The spot-on Investigational Veterinary Product (IVP) was a composition according to the present invention containing 10% tigolaner, 7.94 % praziquantel and 1.98 % emodepside (w/v) in a solution on solketal basis. The IVP was administered to the cats in the IVP group (group 2) on Day 0 at a dose rate of 3.2 mg emodepside plus 12.7 mg praziquantel and 16 mg tigolaner/kg BW (BW = body weight), corresponding to 0.16 mL of the spot-on formulation/kg BW. Cats in group 1 served as the negative control group. On Day 10 the cats were subjected to euthanasia and gastrointestinal helminths were recovered during necropsy. Worms were identified and counted. Efficacy calculations were based on the number of worms recovered at necropsy in the IVP group, compared to the negative control group. The following formula was used:

$$\text{Efficacy (\%)} = 100 \times (Mc - Mt)/Mc,$$

where

Mc = Geometric mean number of worms/scoleces in the negative control group (group 1)

Mt = Geometric mean number of worms/scoleces in the IVP group (group 2)

All cats in the control group contained *T. cati* worms, whilst 5 cats contained *D. caninum* scoleces. An efficacy of 100% was obtained in IVP group against both *T. cati* and *D. caninum*.

No Adverse Events (AEs) occurred.

D. In-vivo study ectoparasites: Efficacy of a spot-on formulation against experimental ticks and flea infestations in cats.

On SD –4 twelve cats were included in the study. On SD –1, cats were experimentally infested with *Ixodes ricinus* ticks, which were counted without removal on SD 0 (for group allocation) and were removed and counted on SD 2 (treatment efficacy). On SD 0, six cats were treated with the IVP applied once as a spot-on at a dosage of 14 mg tigolaner + 3 mg emodepside + 12 mg praziquantel per kg bodyweight. Six cats served as untreated controls.

The IVP contained 10 % (m/V) Tigolaner, 8.58 % (m/V) Praziquantel and 2.14 % (m/V) emodepside in a solution on solketal basis.

Cats were experimentally infested with ticks and fleas fortnightly. Efficacy of the IVP was determined by comparison of tick and flea counts of the treatment group versus the control group. General health was observed daily.

Table 1: Study design

Group	No. of cats	Treatment and dosage	Day of treatment	Days of infestations and counts	
				I. ricinus ticks*	*C. felis* fleas**
1	6	IVP [14 mg Tigolaner + 3 mg emodepside + 12 mg praziquantel]	0	Infestations: SDs –1, 16, 29, 43, 57, 72, 85 Counts (48h): SDs 0, 2, 18, 31, 45, 59, 74, 87	Infestations: SDs 1,15, 42, 56, 71, 78 Counts: SDs 2, 16, 29, 43, 57, 72, 85
2	6	n/a	n/a		

*Each cat was infested with 20 female and 20 male *Ixodes ricinus* ticks. ** Each cat was infested with 100 *C. felis*

Table 2: Efficacy against fleas and ticks based on arithmetic means

Efficacy against fleas	SD 2	SD 16	SD 29	SD 43	SD 57	SD 72	SD 85
	100.00	99.09	100.00	100.00	100.00	100.00	99.59
Efficacy against ticks	SD 2	SD 18	SD 31	SD 45	SD 59	SD 74	SD 87
	100.00	100.00	100.00	97.60	100.00	100.00	100.00

Efficacy (≥99%) against fleas could be claimed on all study days up to SD 85.

Therapeutic efficacy (≥90%) against ticks could be claimed on SD 2 and preventive efficacy against ticks could be claimed up to SD 87.

The IVP was very well tolerated in cats upon single topical treatment. There were no adverse events related to IVP-treatment during this study

Patent claims

1. A composition comprising tigolaner and 1,2-isopropylideneglycerol.

2. Composition according to claim 1 comprising ≥ 1 weight-% to ≤ 15 weight-% tigolaner

3. Composition according to claim 1 or 2, further comprising praziquantel.

4. Composition according to claim 3, comprising ≥ 1 weight-% to ≤ 15 weight-% praziquantel.

5. A composition comprising praziquantel, emodepside and a solvent component, characterized in that the composition further comprises tigolaner.

6. The composition according to claim 5, wherein the solvent component comprises 1,2-isopropylideneglycerol and wherein the water content of the composition is at most 5% by weight, preferably at most 3 % by weight, more preferably at most 2 % by weight.

7. The composition according to one of the preceding claims, wherein the solvent component comprises only 1,2-isopropylideneglycerol.

8. The composition according to one of claims 5 to 7, comprising:

   ≥ 1 weight-% to ≤ 15 weight-% praziquantel;

   ≥ 1 weight-% to ≤ 10 weight-% emodepside;

   ≥ 1 weight-% to ≤ 15 weight-% tigolaner;

   wherein the weight-percentages are based on the total weight of the composition and add up to ≤ 100 weight-%.

9. The composition according to one of the preceding claims, further comprising an anti-oxidant.

10. The composition according to claim 9, wherein the anti-oxidant is butyl hydroxyanisole (BHA) and/or butyl hydroxytoluene (BHT).

11. The composition according to one of the preceding claims, further comprising an acid.

12. The composition according to claim 11, wherein the acid is lactic acid.

13. The composition according to one of claims 9 to 12, comprising:

    ≥ 1 weight-% to ≤ 15 weight-% praziquantel;

≥ 1 weight-% to ≤ 10 weight-% emodepside;

≥ 1 weight-% to ≤ 15 weight-% tigolaner;

≥ 0.01 weight-% to ≤ 1 weight-% butyl hydroxyanisole (BHA) and/or butyl hydroxytoluene (BHT);

≥ 1 weight-% to ≤ 5 weight-% lactic acid;

wherein the weight-percentages are based on the total weight of the composition and add up to ≤ 100 weight-%.

14. A method for producing a composition according to claim 5, comprising the step of dissolving praziquantel, emodepside and tigolaner in a solvent component.

15. A composition according to one of claims 1 to 13 for use as a medicament.

16. A composition according to one of claims 1 to 13 for use in the treatment and/or prevention of parasite infections in animals.

17. The composition for use according to claim 16, wherein the animals are cats.

18. The composition for use according to claim 16 or 17, wherein the parasites are endoparasites and ectoparasites.

19. The composition for use according to one of claims 16 to 18, wherein the parasites are selected from the group consisting of:

Endoparasites selected from: *Toxocara cati, Toxascaris leonina, Ancylostoma tubaeforme, Uncinaria stenocephala, Dipylidium caninum, Taenia taeniaeformis, Echinococcus multiocularis, Aelurostrongylus abstrusus,* and *Troglostrongylus spp.;*

Ectoparasites selected from: *Ctenocephalides spp., Echidnophaga spp., Cteratophyllus spp., Pulex spp., Hyalomma spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Haemaphysalis spp., Dermacentor spp., Ixodes spp., Argas spp., Ornithodorus spp., Otobius spp., Otodectes cynotis, Notoedres cati,*

and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/072640

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/08 A61K31/166 A61K47/10 A61P33/02 A61P33/14
A61K31/4155 A61K31/4985 A61K31/5377
ADD.
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)
A61K A61P

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)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/048381 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 14 March 2019 (2019-03-14)	1,2,7, 9-11, 15-19
Y	claims 1, 5, 9, 10, 13 page 19, lines 15-17, 22 -----	3-6,8, 12-14
Y	US 2008/255037 A1 (KANIKANTI VENTAKA-RANGARAO [DE] ET AL) 16 October 2008 (2008-10-16) claims 1-11 paragraphs [0043], [0044] example 1 -----	3-6,8, 12-14

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2020	22/10/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Vázquez Lantes, M

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2020/072640

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19

A composition comprising tigolaner.

1.1. claims: 1-4(completely); 7-13, 15-19(partially)

A composition comprising tigolaner and 1,2-isopropylideneglycerol.

1.2. claims: 5, 6, 14(completely); 7-13, 15-19(partially)

A composition comprising praziquantel, emodepside and a solvent component, characterized that the composition further comprises tigolaner.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/072640

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