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Title: VETERINARIAN COMPOSITION TO CONTROL HELMINTHES IN BOVINES, SWINES, CAPRINES, EQUINES, OVINES, CANINES AND FELINES

Abstract: This invention is related to the association of organics salts of levamisole and the nitraron of levamisole, more specifically the disophenato of levamisole and nitraron of levamisole with avermectines e milbemicines in veterinarian formulation in veterinary compounds and its in treatment for helminthiasis in mammals. "Pharmaceutical composition" according to the first claim, was characterized by the fact that the composition has avermectines described in the forth claim in association with disophenalato of levamisole in doze that could vary from 5 to 500 pg of active for kg by weight, rather between 50 to 350 pg of active for kg by alive weight, rather between 150 a 250 pg /kg.
"Veterinarian composition to control *Helminthes* in bovines, swines, caprines, equines, ovines, canines and felines."

The association of different classes of substances presenting antihelminthic actions aims to combat an increasing resistance of parasites to most of the drugs used. The resistance of parasites to different classes of antihelminthic drugs has been reported since early use of these drugs. The resistance for benzimidazoles is all over the world. Studies have been reported, mainly related to three main species of bovine’s parasites: *Ostertagia*, *Trichostrongylus*, *Cooperia*. Although parasites’ resistance to levamisole is well known, it is much more restrict than to benzimidazoles. Resistance and crossed resistance reports have been reported, mainly to *Cooperia* species.

The strategy to combat this resistance has been trying to avoid the indiscriminate use of antihelminthic drugs, to alternate drugs during treatment and to use potential number of parasites which survive the treatment. The association of active principles aiming a synergetic function among them is a well known strategy, mainly in the treatment of pathogenic agents with bacteria, protozoans, fungus, and parasites. A real synergism occurs when the association of two or more pharmaceutical actives is higher than all individual actions together.

The aim of this invention is to describe the use of organic salts of levamisole associated to avermectines and/or milbemicines in the combat to helminthiasis.

Levamisole (L-2,3,5,6-tetrahydro-6-phenil-imidazo-[2,1,b]thiazole), it is an antiparasitary widely used for intestinal control of nematodes and respiratory worms in some animals. Due to its basic characteristic, it forms salts with organic and inorganic acids, depending on pKₐ of this acid.

Antiparasitaries such as disophenol (2,6-dilodo-4-nitrofenol) and nitroxinil (xxx), which are used to control trematodes and some nematodes, produce a salt with levamisole under some conditions due to its acid characteristic of phenol group of these molecules. The description, obtainment, and use of nitroxinato of levamisole were described in the patent GB 2150024 A. Disophenol of levamisole and nitroxinato of levamisole from now will be referred only as levamisole organic salts, when suitable.

Avermectines, a compound which belongs to macrocyclic lactones, are powerful antiparasitary agents which are used to combat parasites in mammals. They are secondary metabolic produced by *Streptomyces avermitilis*, obtained through a fermenting process. Some avermectines are obtained in a semi synthetic composition as ivermectin, which is obtained through abamectine hydrogenization. A series of compounds denominated avermectines are abamectine, doramectine, eprinomectine, ivermectin and selamectine.
Milbemicine is similar to avermectines in their structure, because they have a 16 membered ring structures. However, it does not have a disaccharidic sub unit and there are constituent differences. Milbemicine used in the association are selected from the group which consists moxidectine, Milbemicine and Milbemicine oxima.

Considering these aspects, it is known that levamisole disophenolate, as well as levamisole nitrozinato, both combine the action of levamisole against nematodes, for example, Haemonchus contortus, Ostertagia spp., Trichostrongylus spp. (example: Trichostrongylus axei), Cooperia spp. (Cooperia oncophora), Nematodirus spp. (example: Oesaphagostomum venulosum), Strongyloides spp. (example: Strongyloides papillosus), Bunostomum spp. (ex: Bunostomum trigonocephalum), Chabertia spp. (ex: Chabertia ovina), Trichuris spp. (ex: Trichuris ovis) and Dictyocaulus spp. (ex: Dictyocaulus filaria and Dictyocaulus viviparous) with the action of disofenol or nitroxinil against trematodes, for example, Fasiiola hepatic and gigantic Fasciola, and some nematodes, for example, Haemonchus contortus, Bunostomum spp. Oesaphagostomum spp., Parafilaria bovicola. Considering that levamisole presents a low action against Ostertagia parasites and a good action against Cooperia class, and avermectines and Milbemicine has a good inverse action, which means low action against Cooperia and good action against Ostertagia, a combination of actions of levamisole disofenalete and levamisole nitrozinato with avermectines and milbemicines, aiming an wide spectrum formulation against parasites, besides a synergism of actions among actives. In such case, this association maybe indicated as a parasiticde in the treatment of nematodes, cestodes, and trematodes in bovines, swine, caprines, equines, ovines, canines and felines.

Associations of avermectines and levamisole have already been described before in patent WO 00061068 and in patent application WO 2004/009080 A1. The greatest discovery in the study is the use of salts of levamisole, which besides levamisole action they present fascioliscide action, when associated with avermectines. Other associations with fascioliscide compounds were proposed in patent WO 95/05812 and GB 2386067A, both describe the association of avermectines and milbemicines with closantel.

INVENTION AIM

This invention aims a veterinarian pharmaceutical formula which presents fascioliscide action and a potent action against nematodes, cestodes, trematodes. Other aim of the invention is to describe a new veterinarian pharmaceutical product presenting the association of organic salts of levamisole with avermectines and milbemicines. This invention also aims to describe the association of disophenalato of levamisole with avermectines and milbemicines for antiparasitary agent.
INVENTION DESCRIPTION

This invention presents new veterinarian products from the association of avermectines and milbemicines with other antiparasitary agents, such as organic salts of levamisole.

Levamisole organic salts used in this invention are of levamisole nitrozinato and levamisole disophenalato.

Avermectines and milbemicines used in this invention are abamectine, ivermectin, doramectine, eprinomectine, selamectine, moxidectine, milbemicine and milbemicine oxima.

The used dosage will depend on the helminthes' nature, the animal which will be treated and administration route. Nitrozinato of levamisole can range from 1 to 50 mg of nitrozinato of levamisole per weigh/kilo, rather from 5 to 15 mg of nitrozinato of levamisole per body weight, considering that dosage of 7,2 mg/kg of weight brings satisfactory results in the control of parasites. Disophenalato of levamisole can range from 1 to 50 mg of levamisole nitrozinato per kilo of body weigh, considering that a dosage of 8,9 mg/kg of weight generally brings satisfactory results in the control of parasites. Avermectines and milbemicines' dosages range from 5 a 500 Ug of the active per kilo of weight, rather from 50 to 350 ug of the active per kilo of body weight, but a dosage of 200ug/kilo of weight generally has satisfactory results in the control of parasites.

The pharmaceutical formulations, according to this invention, can be used to administrate the associations of levamisole organic salts with milbemicines and/or avermectines in order to kill internal parasites, such as, nematodes, cestodes, trematodes and fasciola, parasites in animals such as bovines, swines, caprines, felines, canines, equines; according to the dosages and purposes presented in this study specifically for these associations.

The administration could be parentheral, which means, intravenous, subcutaneous or intra muscular administration; oral administration as a solution or suspension, in pills, bolus, capsules or as food supplement; can be administrated by derm through transdermic formulations type "pour on". The administration is done with a unique and effective dose, and administration route is rather parentheral.

The associations are rather done among levamisole organic salt and avermectines or milbemicine. For example, the association of levamisole nitrozinato with abamectine in a parentheral veterinarian formulation. These can be free associations with the use of one or more levamisole organic salts and one or more avermectines or milbemicines, or the mix of them.

It is important to understand that the invention is not limited
to details and steps here described. It is possible to be done or performed in different ways and clarifying that the terminology used aims the description and not the limitation of it.
Claims

1. "VETERINARIAN COMPOSITION TO CONTROL HELMINTHES IN BOVINES, SWINS, CAPRINES, EQUINES, OVINES, CANINES AND FELINES", characterized for the comprehension of association of levamisole organic salts with avermectines and/or milbemicines.

2. "COMPOSITION", according to claim 1, characterized by levamisole organic salt to comprehend levamisole disophenalato

3a) "COMPOSITION", according to claim 1, characterized by levamisole organic salt to comprehend levamisole nitroxinato

4. "COMPOSITION", according to claim 1, characterized by the fact that avermectines and milbemicines are abamectine, ivermectin, doramectine, eprinomectine, selamectine, moxidectine, milbemicine and milbemicine oxima.

5. "PHARMACEUTICAL COMPOSITION", according to claim 1, characterized by the fact that the composition has disophenalato of levamisole in the association with avermectines and/or milbemicines in dosages ranging from 1 to 50 mg of disophenalato of levamisole per kg of weight, rather from 5 to 15 mg of disophenalato of levamisole per body weight.

6. "PHARMACEUTICAL COMPOSITION", according to 1a claim, characterized by that fact that the composition has nitroxinato of levamisole in the association with avermectines and/or milbemicines in dosages ranging from 1 to 50 mg of nitroxinato of levamisole per kilo of weight, rather ranging from 5 to 15 mg of disophenalato of levamisole per kilo of body weight.

7. "PHARMACEUTICAL COMPOSITION", according to 1a claim, characterized by that fact that the composition has avermectines described in claim 4 in association with disophenalato of levamisole and nitroxinato of levamisole in dosages ranging from 5 to 500 µg of active per kilo of weight, rather ranging from 5 to 350 µg of active per kilo of weight, rather ranging from 150 to 250 µg/kg.