SPECIFICATION

Compositions for use in the treatment of mammals for controlling parasitic Diptera larvae

The present invention relates to compositions for use in the treatment of animals and productive livestock belonging to the class of Mammalia (mammals) for systemically controlling parasitic insect larvae of the order of Diptera which feed on tissue.

According to the present invention there are provided compositions comprising (a) 2-cyclopropylamino-4,6-diamino-s-triazine or an acid addition salt thereof which is non-toxic to mammals and (b) optionally a carrier and/or adjuvant for peroral administration to mammalian animals and livestock to systemically control tissue parasitic insects of the order Diptera.

The term addition salt is to be understood as meaning salts with pharmaceutically acceptable acids, for example with strong mineral acids, such as hydrochloric acid or sulfuric acid, or with organic acids, such as acetic acid, tartaric acid or citric acid.

The control of Diptera larvae, which live as parasites in the tissues of their host animals, is of extreme importance, especially in view of the considerable damage which can be caused by the parasites in livestock husbandry and most particularly in the husbandry of grazing animals.

The Diptera larvae can invade the tissues of their host animals in many different ways. Thus, after the Diptera females have laid their eggs, which they can do in or on various parts of the body of the host animals, the larvae hatched from the eggs can be ingested by the host animals by licking and they then bore into the pharynx, or the larvae can bore into the skin of the host animals. However, the eggs can also first be deposited on mosquitoes or flies. The larvae develop in the eggs and hatch as soon as the carrier insect seeks out a suitable host animal. In the case of the viviparous Diptera species the larvae can be deposited direct by the Diptera females into the nose or the eyes of the host animals.

After the larvae have invaded the host animals, they can migrate to those parts of the body which they prefer. The larvae can locate, for example, in or under the skin, in the gastro-intestinal tract or in the nasal cavities, the cavity of the pharynx or the frontal sinus of their hosts.

The various types of parasitism by Diptera larvae in animals are termed myiases.

Myiases can occur in numerous species of animals, for example in cattle, horses, donkeys, mules, reindeer, sheep, pigs, dogs and cats.

In the host animals, the infestation by parasitic Diptera larvae can, in addition to other adverse effects, result in a reduction in the milk yield, loss of wool, loss of weight or even in death. If the host animals are infested by skin parasites which cause swellings to form in the skin, the consequence can also be a depreciation in the value of the skins on account of perforation, because the swellings have a small orifice which is enlarged by the larvae before they leave the host for pupation.

As the larvae can infest very different, and in some cases very inaccessible, parts of the body of the host animals, their control is highly problematical.

Surprisingly, it has now been found that compositions of the invention are outstandingly suitable for the control of parasitic Diptera larvae. The compositions develop a systemic action which means that, on peroral application to the host animal, an action against the parasitic Diptera larvae also takes place in parts of the body which have not been treated. The use of the compositions of the invention thus enables parasitic Diptera larvae to be effectively controlled even in those parts of the body in which direct application is extremely difficult or virtually impossible.

The compositions of the invention are advantageously used in a concentration in the range of 1 to 20 mg/kg of body weight.

A particularly advantageous method of controlling the parasites consists in providing the animals to be treated with the active substance as a constituent of licking blocks or administering to them a formulation which effects release of the active substance in the rumen.

The use of licking blocks which contain the active substance proves particularly advantageous in the treatment of large herds living outdoors, where the individual treatment of the animals is laborious and time-consuming.

The advantage of a formulation which effects release of the active substance in the rumen is that the active substance is released slowly and thus develops its action over a prolonged period of time.

Furthermore, the application of the active substance by spraying a liquid formulation into the oesophagus of the animals to be treated, using a suitable applicator (drench gun), is also very advantageous.

The compositions of the invention have, in particular, a good action against myiasis-inducing larvae of insects of the order Diptera, which belong to the families Calliphoridae, Oestridae, Cuterebridae, Gasterophilidae, Sarcophagidae and Hypodermatididae, for example against larvae of Lucilia spec., Cochlyomyia hominivorax, Chrysomyia bezziana, Hypoderma lineata, Hypoderma bovis, Dermatobia hominis, Oedemagena tarandi, Gasterophilus spec., Oestrus ovis, Rhinoestrus purpureus, Wohlfahrtia vigil and Cuterebra spec.

The active ingredient can be prepared by methods which are known per se by, for example, a) reacting a 2-cyclopropylamino-4-amino-6-halogeno-s-triazine with ammonia or b) reacting a 2,4-diamino-6-halogeno-s-triazine with cyclopropylamine or c) reacting a 2-cyclopropylamino-4,6-dihalogeno-s-triazine with ammonia.

The replacement of the halogen atoms by ammonia takes place by dissolving the starting materials in inert solvents, for example acetone, acetone/water mixtures, methyl ethyl ketone, dioxan or dioxan/water mixtures, and reacting these mixtures under normal or, if desired, elevated pressure and at temperatures of 20 - 150°C and preferably 50 - 140°C with ammonia.

The starting materials are known.

Example 1 (Preparation of active ingredient)

a) *2-Cyclopropylamino-4,6-diamino-s-triazine*

A mixture of 100 g of 2-cyclopropylamino-4-amino-6-chloro-s-triazine, 51 g of ammonia and 500 ml of dioxan is heated to 140°C in an autoclave for 24 hours. After cooling, the dioxan is removed by filtering with suction in vacuo and the crystalline residue is washed with water and dried. The crude product is recrystallised from methanol; melting point 219-222°C.

b) *2-Cyclopropylamino-4,6-diamino-s-triazine, salt with 2 mols of hydrochloric acid*

25 g of 2-cyclopropylamino-4,6-diamino-s-triazine are dissolved in 2,000 ml of hot absolute ethanol. This solution is cooled to 15°C and cooled further with ice and hydrogen chloride gas is then introduced until the solution is saturated, whereupon white crystals precipitate. These crystals are collected by filtration and the crude salt is washed copiously with ether; melting point 195°C (decomposition).

The compositions of the invention can be used as pure active substance or together with suitable carriers and/or adjuvants. Suitable carriers and adjuvants can be solid or liquid and are the substances conventionally employed in the art of formulation, for example natural or regenerated substances, solvents and/or dispersants.

Depending on the use, the active substance can be administered in the form of solutions, emulsions, wettable powders, suspensions, granules, pellets, bolusses, tablets or capsules. The active substance or compositions containing these can, however, also be added to the feed or drink or can be contained in a premix. The active substance can, for example, be combined with adjuncts such as kaolin, lime, aluminium oxide, ground mussel shells, bolus alba, aerosil, starch or lactose, talc, bentonite, sodium chloride, calcium phosphate, cottonseed meal or liquids which are inert to the active substances, such as oils and other solvents and diluents harmless to the animals to be treated ("Aerosil" is a registered Trade Mark).

The active substance can also be administered, to the animals to be treated, as a constituent of licking blocks.

The use of a formulation which effects release of the active substance or of a non-toxic acid addition salt thereof in the rumen is particularly suitable for slow release of the active substance.

In the following Examples illustrating the present invention, parts and percentages shown therein are by weight.

Formulation Examples 2 to 7

The active substance or its non-toxic acid addition salts can be processed to the following formulations.

Granules: (Example 2)

5 parts of active substance are dissolved in a solvent such as methylene chloride and the solution is mixed with 2 parts of polyethylene glycol ("carbowax"). 91.5 parts of calcium carbonate are impregnated with the mixture and 1.5 parts of precipitated silica are mixed in and the solvent is then evaporated ("Carbowax is a registered Trade Mark")

Wettable powder: (Example 3)

50 parts of active substance are mixed with 5 parts of a dispersant, for example sodium ligninsulfonate, 5 parts of a wetting agent, for example dibutylnaphthalenesulfonic acid, 10 parts of silica and 30 parts of kaolin and the mixture is finely ground.

Emulsifiable concentrate: (Example 4)

20 parts of active substance are mixed with 20 parts of emulsifier, for example a mixture of alkylaryl polyglycol ether with alkylarylsulfonates, and 60 parts of solvent, until the solution is completely homogeneous. With water, this concentrate gives an emulsion of any desired concentration.

Premix: (Feed additive) (Example 5)

5 parts of active substance and 5 parts of secondary calcium phosphate, or kaolin, aerosil or carbonated lime, are mixed homogeneously with 90 parts of a feed, for example feed concentrate.

Solutions (for dilution with drinking water) (Example 6)

a) 15% active substance in "Solketal®" (2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane)
b) 10% active substance in "Carbitol®" (diethylene glycol monoethyl ether)
c) 10% active substance in polyethylene glycol 300
d) 5% active substance in glycerol

Soluble powder (Example 7)

25 parts of active substance
1 part of Tensopol (SP-USP (sodium lauryl-sulfate USP)
3 parts of colloidal silica K 320
71 parts of urea

The constituents are mixed and the mixture is ground finely in a suitable mill.

Other biocidal active substances or agents, which are inert to the active substances and tolerated by the animals to be treated, or mineral salts or vitamins can be admixed to the compositions described.

Test

Peroral use in sheep and cattle

The active substance is administered perorally in an amount of 5 mg/kg of body weight in a suitable formulation to sheep and cattle, using a drench gun. The animals treated are artificially infested with larvae of *Lucilia sericata*. The larvicidal action is assessed after 72 hours.

In this test, the active compound shows a pronounced larvicidal action.

CLAIMS

1. Composition comprising (a) 2-cyclopropylamino-4,6-diamino-s-triazine or an acid addition salt thereof which is non-toxic to mammals and (b) optionally a carrier and/or adjuvant for peroral administration to mammalian animals and livestock to systemically control tissue parasitic insects of the order Diptera.
2. Composition according to claim 1 wherein said composition is in a form which allows its release in the rumen.
3. Composition according to claim 1 wherein said composition is formulated as a licking block.
4. Composition according to claim 1 wherein said composition is in a form capable of being sprayed into the oesophagus of the animal to be treated.
5. A composition according to claim 1 substantially as described with reference to and of Examples 2 to 7.

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