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(72) Inventeurs/Inventors:
BLAKELY, WILLIAM, GB;
CROMIE, LILLIAN, GB

(73) Propriétaire/Owner:
NORBROOK LABORATORIES LIMITED, GB

(74) Agent: OYEN WIGGS GREEN & MUTALA LLP

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(57) Abrégé/Abstract:
A topical formulation comprising as active ingredients, at least one effective agent derived from Streptomyces avermitilis, i.e. a macrocylic lactone e.g. an avermectin or chemically modified or synthetic derivative thereof, e.g. ivermectin, together with another anthelmintic of the sulphonamide type, e.g. clorsulon, in a carrier that facilitates topical administration and delivery of the active ingredients transdermal ly, e.g. a carrier that is useful for this purpose comprises alcoholic solvents, such as ethanol, and isopropanol, with optional excipients and formulation aids, which may comprise a polymeric species such as PVP or a poloxamer.

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(71) Applicant *(for all designated States except US)*: **NORBROOK LABORATORIES LIMITED** [GB/GB]; Station Works, Newry, County Down BT35 6JP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BLAKELY, William** [GB/GB]; 79 Chapel Road, Killeavy, Newry, County Down BT35 8JZ (GB). **CROMIE, Lillian** [GB/GB]; 65 Old Warrenpoint Road, Newry, County Down BT34 2PN (GB).

(74) Agents: **HAYES, Adrian, Chetwynd** et al.; Boult Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

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(54) Title: ANTHELMINTIC COMPOSITION

(57) Abstract: A topical formulation comprising as active ingredients, at least one effective agent derived from *Streptomyces avermitilis*, i.e. a macrocylic lactone e.g. an avermectin or chemically modified or synthetic derivative thereof, e.g. ivermectin, together with another anthelmintic of the sulphonamide type, e.g. clorsulon, in a carrier that facilitates topical administration and delivery of the active ingredients transdermal Iy, e.g. a carrier that is useful for this purpose comprises alcoholic solvents, such as ethanol, and isopropanol, with optional excipients and formulation aids, which may comprise a polymeric species such as PVP or a poloxamer.

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Anthelmintic Composition

Field of the Invention

This invention relates to a composition displaying efficacy against infections of *Fasciola hepatica*, *Ostertagia ostertagi* and *Cooperia oncophora* in susceptible ruminants, especially cattle.

Background of the Invention

Infections of *Fasciola hepatica*, Ostertagia *ostertagi* and *Cooperia oncophora* in livestock are problematic, and in particular first season grazing cattle can be susceptible in contaminated pastures. Injection solutions containing ivermectin and clorsulon are known in the industry for use in treating beef and non-lactating cattle.

Clorsulon is a compound belonging to the benzenesulphonamide (benzenesulfonamide -USA) family which is recommended for control of adult liver flukes (*Fasciola hepatica and Fasciola gigantica*) in cattle as suspensions for oral use or in injectable formulations for subcutaneous administrations. The oral recommended level is 7 mg/kg body weight (bw) and the subcutaneous level 2mg/kg bw. Currently, there is no known topical formulation, and this is likely to be due to foreseeable difficulties in achieving adequate penetration of the skin by clorsulon.

An objective of the invention is to provide a topical formulation which is effective against the aforesaid infections, preferably presented as a pour-on formulation. A further object of the invention is provide a composition comprising at least one effective agent derived from *Streptomyces avermitilis*, i.e. a macrocylic lactone or chemically modified or synthetic derivative thereof together with another anthelmintic of the sulphonamide type. Another

objective of the invention is to provide a composition suitable for the treatment of immature *Fasciola hepatica.*

With this objective in mind, a study was conducted to determine the feasibility of producing a topical formulation containing known agents already recognised in the field in other delivery forms, e.g. injections, as offering efficacy against infections of *Fasciola hepatica* (Adult), Ostertagia *ostertagi* (Adult) and *Cooperia oncophora* (Adult) in cattle.

The new formulation under consideration for the purposes of this study would include at least one anthelmintic compound of the disulphonamide type, e.g. clorsulon, a member of the benzenesulphonamide family (CAS.No. 60200-06-84; Amino-6-(trichloroethenyl)-1,3-benzene-disulfonamide), and an avermectin suitable for the treatment of immature *Fasciola hepatica* e.g. ivermectin, a mixture of semi-synthetic macrocyclic lactones (CAS.No. 70288-86-7; "22, 23-dihydro-C076B" a mixture of 80% ivermectin component B_{1a} (5-O-demethyl-22,23-dihydroavermectin A_{1a}) and 20% ivermectin component B_{1b} (5-O-demethyl-35-de(1-methylpropyl)-22, 23-dihydro-35-(1-methylethyl)avermectin A_{1a})).

This study followed an authorised protocol in accordance with recognised industry practice, at an accredited animal facility of Norbrook Laboratories Limited, Research Division, upon healthy male calves of European bovine stock.

During the study each animal was infected with 500 metacercariae of *Fasciola hepatica,* 10000 *Ostertagia ostertagi* larvae and 10000 *Cooperia oncophora* larvae. At 79 days following the administration of *Fasciola hepatica* and 32 days following administration of *Ostertagia ostertagi* and *Cooperia oncophora* the animals were treated with a pour-on formulation newly developed by Norbrook Laboratories Limited, comprising ivermectin and clorsulon. Approximately 3 weeks following treatment all animals were slaughtered and livers, abomasums and small intestines removed. These organs were processed to allow enumeration of helminths contained in each.

The calves used in the study were all healthy at selection and throughout the study period. The tested pour-on product was well tolerated in cattle and no adverse reactions to treatment were observed during the course of the study.

Enumeration of *Fasciola hepatica, Ostertagia ostertagi* and *Cooperia oncophora* burdens after slaughter and comparison to those of the untreated control group confirmed an efficacy of > 90% for each parasite and therefore it can be concluded that the tested pour-on product is

effective in the treatment of adult *Fasciola hepatica,* adult *Ostertagia ostertagi* and adult *Cooperia oncophora* infections in cattle.

The efficacy of the tested pour-on product, in this instance comprising ivermectin and clorsulon, against induced infections of adult *Fasciola hepatica,* adult *Ostertagia ostertagi* and adult *Cooperia oncophora* cattle following topical administration at a nominal dose rate of 500 μg ivermectin and 5mg clorsulon per kg bodyweight was recognised.

Summary of the Invention

Accordingly, the present invention provides a hitherto unavailable topical formulation comprising as active ingredients, at least one effective agent derived from *Streptomyces avermitilis*, i.e. a macrocylic lactone e.g. an avermectin or chemically modified or synthetic derivative thereof, e.g. ivermectin, together with another anthelmintic of the sulphonamide type, e.g. clorsulon, in a carrier that facilitates topical administration and delivery of the active ingredients transdermally. A carrier that is useful for this purpose comprises alcoholic solvents, such as ethanol, and isopropanol, with optional excipients and formulation aids, which may comprise a polymeric species such as PVP or a poloxamer. In preferred form, a pour-on formulation is provided containing clorsulon and ivermectin.

An embodiment of such a formulation of this invention is:

Ivermectin 0.5% (w/v)	Clorsulon 5.0% (w/v)
Ethanol 30% v/v	PEG200 10% v/v
Crodamol Cap 20% v/v	IPA (isopropanol) to 100% v/v
Brilliant Blue Dye 0.01%(w/v)	Denatonium Benzoate 0.001%(w/v)

The nominal dose rate thereof is 500 μg ivermectin and 5mg clorsulon per kg bodyweight.

A method of countering infection by immature *Fasciola hepatica* is enabled using such a formulation.

EXPERIMENTAL PROCEDURE

This study comprised a single group of four male calves, aged approximately 3 to 4 months old at the time of *Fasciola hepatica* administration. Faecal egg count examinations were carried out by an independent facility to determine that animals were helminth-free prior to infection with *Fasciola hepatica* metacercariae. The animals were acclimatized for 19 days prior to liver fluke administration.

Prior to treatment, (79 days pre treatment), all calves were initially infected with 500 metecercariae of *Fasciola hepatica* administered orally and subsequently, (32 days pre treatment) each calf was infected with 10000 larvae of *Ostertagia ostertagi* and 10000 larvae of *Cooperia oncophora* administered orally. The calves were weighed 3 days prior to administration of the subject pour-on product, to calculate the dose to be administered to each animal. The calves were slaughtered on the 18th day after treatment, with each animal's liver, abomasum and small intestine being removed and processed to allow helminth enumeration.

The pour-on product of the invention nominally contained 0.5% w/v ivermectin and 5.0% w/v clorsulon and had an assayed content of 0.498% w/v ivermectin and 4.94% w/v clorsulon. This provides a nominal dose rate of 500 µg ivermectin and 5mg clorsulon per kg bodyweight.

The pour-on product was administered by topical administration along the midline of the back on a narrow strip between the withers and the tail head on an area that was 24 inches long for each animal. This corresponds to the proposed route of administration for the pour-on product. All doses were administered to each animal on a single occasion using 20ml syringes which have an accuracy of 0.5ml. The doses administered to each animal are detailed in Table 1.

Liver Fluke Count: Liver fluke were counted by emptying the contents if the labelled container into a flat-bottomed glass dish. A dark surface beneath the dish assisted in identifying small or immature flukes. A total count was recorded. Counting was carried out by an independent external service provider and was conducted blind with reference to group.

Nematode Counts: The contents of each labelled jar were examined separately. Small quantities were poured into ruled Petri dishes with parallel lines marked 1 cm apart on their underside, and the worms were counted using a dissecting stereomicroscope. Since iodine had been added during processing of the samples to colour the nematodes, a solution of sodium thiosulphate was used to decolourise the background if necessary. The count for each jar was recorded separately, and multiplied by 100 (the original dilution factor). The series of 2 counts were averaged to give the final count. Nematodes were identified by picking out male worms into an embryo dish containing lactophenol and transferring onto microscope slides with a drop of lactophenol added and coverslips placed in top. The worms were identified using standard parasitological textbooks. Counting was carried out by an independent facility and was conducted blind with reference to group.

Analysis

After slaughter, the counts of *Fasciola hepatica, Ostertagia ostertagi* and *Cooperia oncophora* from each animal were enumerated and summarised using the mean, geometric mean, minimum, maximum and sample size. Since this study did not contain a control group, the control group results from a parallel study which utilised the same levels of infection with the infections at the same stage at slaughter (adult *Fasciola hepatica* and adult nematodes), were used to calculate efficacy as detailed below (See Tables 3a – 5b for all results).

$$\% \text{ efficacy} = \frac{\text{Geometric Mean of Controls} - \text{Geometric Mean Treated}}{\text{Geometric Mean of Controls}} \times 100$$

Group geometric means counts were compared by two sample t-test after logarithmic transformation to normalise the data. If the data did not follow the normal distribution then a non-parametric test was applied to compare the groups, names the Mann-Whitney test for unmatched pairs. No covariants were used in the data analysis.

RESULTS:

Faecal egg counts.

All faecal samples taken prior to treatment were found to be free of helminth eggs. Three of the four faecal samples taken 29 days after *Ostertagia ostertagi* and *Cooperia oncophora* infection, were found to contain strongyle-type eggs (See Table 2).

Fasciola hepatica counts after slaughter:

Summary of *Fasciola hepatica* counts.

	Treated	Control
Mean	7.75	198.63
Maximum	19	264
Minimum	1	84
Geometric mean	5.16	189.38
Number	4	8

The overall mean establishment percentage of flukes in the untreated control group was 39.7%, this is slightly above the expected range (approximately 30-35% based on similar studies of this type) for the number of metacercariae administered (500 each) and age of cattle. The level of infection achieved is well above the minimal mean of 20 flukes per animal (as detailed in VICH GL 12 Efficacy of Anthelmintics: Specific Recommendations for Bovines) required to deem the infection adequate.

At the time of treatment, the *Fasciola hepatica* were within the 8 to 12 week range (as detailed in the VICH GL 12 Efficacy of Anthelmintics: Specific Requirements for Bovines) required to be classified as an adult.

The efficacy of flukicide treatment was 97.3% (See Table 6 for Summary of Efficacy Calculations). The statistical differences between the number of flukes recovered from treated test animals and untreated control animals were highly significant (p=0.0117) by the non-parametric Mann Whitney (Wilcoxon Rank-Sum) Test on log-transformed data, as the assumptions of normality were not satisfied. See Table 3 for individual *Fasciola hepatica* counts.

Ostertagia ostertagi counts after slaughter:

Summary of *Ostertagia ostertagi* counts.

	Treated	Control
Mean	0	1937.50
Maximum	0	2950
Minimum	0	550
Geometric mean	0	1646.48
Number	4	8

The mean establishment percentage of *Ostertagia ostertagi* in the untreated control group was 19.4%, within the range expected (based on experience of similar studies) from the number of larvae administered (10000 each) and age of cattle. The level of infection achieved is well above the minimal mean of 100 nematodes per animal (as detailed in VICH GL 12 Efficacy of Anthelmintics: Specific Recommendations for Bovines) required to deem the infection adequate.

Treatment of test animals occurred on 32 days after administration of *Ostertagia ostertagi* larvae to all animals. Consequently, at the time of treatment the *Ostertagia ostertagi* were within the 28 to 32 day range (as detailed in VICH GL 12 Efficacy of Anthelmintics: Specific Recommendations for Bovines) required to be classified as adult.

The efficacy of treatment was 100.0% (See Table 6 for Summary for Efficacy Calculations). The statistical differences between the numbers of nematodes recovered from treated test animals and untreated control group animals were highly significant (p=0.0107) by the non-parametric Mann Whitney (Wilcoxon Rank-Sum) Test on log-transformed data, as the

assumptions of normality were not satisfied. See Table 4 for individual *Ostertagia ostertagi* counts.

Cooperia oncophora counts after slaughter:

Summary of *Cooperia oncophora* counts.

	Treated	Control
Mean	100.00	5662.50
Maximum	350	7950
Minimum	0	3750
Geometric mean	10.57	5485.59
Number	4	8

The establishment percentage from the untreated control group was 56.6%, within the range expected (based on experience of similar studies) from the number of larvae administered (10000 each) and age of cattle. The level of infection achieved is well above the minimal mean of 100 nematodes per animal (as detailed in VICH GL 12 Efficacy of Anthelmintics: Specific Recommendations for Bovines) required to deem the infection adequate.

At the time the *Cooperia oncophora* were within the 28 to 32 day range (as detailed in VICH GL 12 Efficacy of Anthelmintics: Specific Recommendations for Bovines) required to be classified as adult.

The efficacy of treatment was 99.8% (See Table 6 for Summary of Efficacy Calculations). The statistical differences between the numbers of nematodes recovered from treated test animals were highly significant (p=0.0244) by the parametric t test on log-transformed data, as the assumptions of normality were satisfied. See Table 5 for individual *Cooperia oncophora* counts.

From the results it has been demonstrated that administration of the pour-on product of this invention resulted in efficacy of 97.3% against *Fasciola hepatica* aged 11 weeks post-infection, and therefore meets the >90% efficacy requirement of VICH GL 12 (Efficacy of Anthelmintics: Specific Recommendations for Bovines). Data analysis has shown that the effect of treatment produced highly statistically significant differences in the fluke burden. The study also showed that the subject Ivermectin/Clorsulon Pour-On of the invention had an efficacy of 100.0% against adult *Ostertagia ostertagi* and 99.8% against adult *Cooperia ancophora*, again meeting the >90% efficacy requirement of VICH GL 12. Data analysis has

shown that the effect of treatment produced highly statistically significant differences in the nematode burden.

The pour-on product was well tolerated in cattle at application and no localised or systematic adverse reactions to treatment were recorded at any stage following treatment.

It can be concluded that the ivermectin/clorsulon pour-on product of this invention, administered topically at a dose rate of 500 µg ivermectin and 5mg clorsulon per kg bodyweight is clinically effective in the treatment of adult *Fasciola hepatica*, adult *Ostertagia ostertagi* and adult *Cooperia oncophora* in cattle. For each parasite efficacy was over 90% and there was a statistically significant difference($P<0.05$) between the counts in treated and untreated animals. With this particular formulation blood plasma levels of clorsulon between 1.20 ug and 2.4ug per ml were observed in treated animals with Tmaxs of 54 +/- 22.9.

Table 1. Animal and Dosage Details.

Animal Identity	Breed	Sex	Age[1] (months)	Weight[2] (kg)	Dose Administered (ml)
DY 1109-2	Fr	M	4.0	201.0	20.0
DY 1819-7	Fr	M	3.5	154.0	15.5
DY 1820-1	Ayr	M	4.0	141.0	14.0
DY 2474-2	Fr	M	4.0	187.5	19.0

1 – Approximate age at selection.

2 – Animals weighed 3 days prior to administration of pour-on product.

Ayr = Ayrshire;

Fr = Friesian;

M = Male

Table 2. Faecal Egg Counts (3 days prior to treatment)

Animal Identity	Strongyle Faecal Egg Count (epg)
DY 1109-2	0
DY 1819-7	900
DY 1820-1	700
DY 2474-2	800

epg = eggs per gram.

Table 3a. ***Fasciola hepatica*** **Counts (Treated).**

Animal Identity	*Fasciola hepatica* Count
DY 1109-2	8
DY 1819-7	1
DY 1820-1	3
DY 2474-2	9
Mean	7.75
Geometric Mean	5.16
Minimum	1
Maximum	19
Sample Size	4

Table 3b. ***Fasciola hepatica*** **Counts (Control).**

Animal Identity	*Fasciola hepatica* Count
DY 351-1	214
DY 1097-3	165
DY 1167-7	84
DY 1184-3	257
DY 1498-7	196
DY 1499-1	264
DY 1500-2	203
DY 1577-7	206
Mean	198.63
Geometric Mean	189.38
Minimum	84
Maximum	264
Sample Size	8

Table 4a. ***Ostertagia ostertagi*** **Counts (Treated).**

Animal Identity	*Ostertagia ostertagi* Count
DY 1109-2	0
DY 1819-7	0
DY 1820-1	0
DY 2474-2	0
Mean	0
Geometric Mean	0
Minimum	0
Maximum	0
Sample Size	4

Table 4b. ***Ostertagia ostertagi*** **Counts (Control).**

Animal Identity	*Ostertagia ostertagi* Count
DY 351-1	2950
DY 1097-3	550
DY 1167-7	2650
DY 1184-3	2550
DY 1498-7	1800
DY 1499-1	650
DY 1500-2	2900
DY 1577-7	1450
Mean	1937.50
Geometric Mean	1646.48
Minimum	550
Maximum	2950
Sample Size	8

Table 5. ***Cooperia oncophora*** **Counts (Treated).**

Animal Identity	Count
DY 1109-2	0
DY 1819-7	350
DY 1820-1	50
DY 2474-2	0
Mean	100.00
Geometric Mean	10.57
Minimum	0
Maximum	350
Sample Size	4

Table 5. ***Cooperia oncophora*** **Counts (Control).**

Animal Identity	*Fasciola hepatica* Count
DY 351-1	4800
DY 1097-3	7950
DY 1167-7	7900
DY 1184-3	5550
DY 1498-7	6050
DY 1499-1	4800
DY 1500-2	3750
DY 1577-7	4500
Mean	5662.50
Geometric Mean	5485.59
Minimum	3750
Maximum	7950
Sample Size	8

Table 6. Summary of Efficacy Calculations.

Helminth	Treated Geometric Mean	Control Group Geometric Mean	Percentage Efficacy
Fasciola hepatica	5.16	189.38	97.3
Ostertagia ostertagi	0	1646.48	100.0
Cooperia oncophora	10.57	5485.59	99.8

Claims:

1. A topical anthelmintic formulation comprising, as active ingredients, a therapeutically effective amount of at least one avermectin, with a therapeutically effective amount of clorsulon, in a carrier adapted for topical administration and delivery of the active ingredients transdermally, wherein the carrier comprises alcoholic solvents comprising ethanol and isopropanol, and wherein the alcoholic solvents comprise at least 30% (v/v) of ethanol together with isopropanol quantity sufficient to 100%.

2. A topical anthelmintic formulation according to claim 1, wherein said carrier further comprises excipients and formulation aids.

3. A topical anthelmintic formulation according to claim 1 or claim 2, wherein the formulation is presented as a pour-on.

4. A topical anthelmintic formulation according to any one of claims 1 to 3, wherein the formulation comprises ivermectin.

5. A topical anthelmintic formulation according to any one of claims 1 to 4, having an efficacy such that, when applied to the skin of an animal infected by *F. hepatica*, at least 90% of the mature *F. hepatica* are killed.

6. A topical anthelmintic formulation according to any one of claims 1 to 4, wherein the therapeutically effective amount for cattle of clorsulon is at least 5% (w/v) .

7. A topical anthelmintic formulation according to any one of claims 1 to 6, wherein the carrier comprises a polymeric species.

8. A topical anthelmintic formulation according to claim 4 for use on cattle, wherein

the dosage rate is controlled to provide about 500 μg ivermectin and 5 mg/kg of clorsulon.

9. A topical anthelmintic formulation for use on cattle, presented as a pour-on and consisting of:

Ivermectin 0.5% (w/v)	Clorsulon 5.0% (w/v)
Ethanol 30% v/v	PEG200 10% v/v
Crodamal Cap 20% v/v	IPA (isopropanol) to 100% v/v
Brilliant Blue Dye 0.01% (w/v)	Denatonium Benzoate 0.001 % (w/v)