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Final cutter guide
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Glue area - no print

Approved by FDA under NADA # 141-449 **1 Gallon**

safe-guard® AquaSol

(fenbendazole oral suspension)

Suspension Concentrate, Antiparasitic

200 mg of fenbendazole/mL
For oral administration via drinking water

DESCRIPTION: Safe-Guard® AquaSol is a suspension concentrate containing fenbendazole, an antiparasitic. Each mL of Safe-Guard® AquaSol contains 200 mg of fenbendazole.

INDICATIONS:
Chickens: Safe-Guard® AquaSol is indicated for the treatment and control of adult *Ascaridia galli* in broiler chickens and replacement chickens and for the treatment and control of adult *A. galli* and *Heterakis gallinarum* in breeding chickens and laying hens.

Swine: Safe-Guard® AquaSol is indicated for swine, except for nursing piglets, for the treatment and control of: **Lungworms:** Adult *Metastrongylus apri,* Adult *Metastrongylus pudendotectus:* **Gastrointestinal worms:** Adult and larvae (L3, L4 stages, liver, lung, intestinal forms) large roundworms *(Ascaris suum);* Adult nodular worms *(Oesophagostomum dentatum, O. quadrispinulatum);* Adult small stomach worms *(Hyostrongylus rubidus);* Adult and larvae (L2, L3, L4 stages - intestinal mucosal forms) whipworms *(Trichuris suis),* and **Kidney worms:** Adult and larvae *Stephanurus dentatus*

DOSAGE AND ADMINISTRATION: ***Chickens:*** Safe-Guard® AquaSol must be administered orally to chickens via the drinking water at a daily dose of 1 mg/kg BW (0.454 mg/lb) for 5 consecutive days. ***Swine:*** Safe-Guard® AquaSol must be administered orally to swine via the drinking water at a daily dose of 2.2 mg/kg BW (1mg/lb) given on 3 consecutive days.

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

RESIDUE WARNING: ***Chickens:*** No withdrawal period is required when used according to labeling. ***Swine:*** Swine intended for human consumption must not be slaughtered within 2 days from the last treatment.

STORAGE INFORMATION: Store at room temperature 30°C (86°F). Once opened, do not store the container above 25°C (77°F). Do not freeze. Use within 6 months after opening. Use the medicated water within 24 hours.
The container was opened (write the date here): _____

See attached Product Information Insert for complete directions and warnings before using.
For customer service, adverse effects reporting, and/or a copy of the SDS, call 1-800-211-3573.

Fenbendazole (active ingred.) made in China.
Formulated in France.
Net volume 1 Gallon

MERCK Animal Health
377122 R1

Base label - 110mm

production were used. Housing, management, and husbandry procedures were typical of commercial production practice. A complete feed, adequate to meet the nutritional needs of the study animals, was offered to the animals in self-feeders throughout the study. The feed did not contain antibiotics, anthelmintics, or any other medication.

Fifty-six days prior to treatment administration, all suitable study candidates were orally dosed with approximately 4000 embryonated *T. suis* eggs. A natural field isolate of *T. suis* collected in April 2010 from a sow located on a commercial farrow to wean operation located in the U.S. was used. Individual fecal samples were obtained from each candidate animal 46, 47, and 48 days after *T. suis* inoculation and analyzed for the presence of *T. suis* eggs. Animals with at least two fecal examinations positive for *T. suis* eggs were eligible for inclusion in the study.

In each study, 24 healthy pigs were randomized to two treatment groups (FBZ treated and non-medicated) by first blocking by weight in blocks of 4 pigs each and within each weight block, fecal egg count (FEC) in blocks of 2 pigs. The two pigs with the two lowest FEC counts within a weight block were randomized one per treatment group and the two pigs with the highest FEC counts within a weight block were randomized one per treatment group. The two animals assigned to the same treatment group within the same weight block were then assigned to the same pen. Six pens of 2 pigs each were used per treatment group.

Non-medicated water consumption of the pigs in each treatment pen was measured prior to treatment administration to estimate the amount of water required for dosing on each day of the treatment period. The amount of FBZ Suspension administered in drinking water to the study pigs was calculated from pre-treatment body weights. Medicated water was prepared on each treatment day by diluting FBZ Suspension in drinking water to provide a daily dose of 2.2 mg FBZ/kg body weight to the FBZ treated group. The control group received non-medicated drinking water.

Only two pigs at the Minnesota (MN) site that were treated with FBZ had abnormal post-treatment observations ("loose stools"). These two pigs had exhibited abnormal fecal consistency prior to treatment with FBZ. There were no abnormal observations made at the California (CA) site on pigs after FBZ administration. There were no abnormal post-treatment observations attributed to administration of FBZ at either study site. The study animals were euthanized after either 8 or 9 days following the last FBZ administration for retrieval of the large intestinal tract. Adult *T.suis* worms attached to the tract and in the contents of the tract were counted.

Adequacy of infection was demonstrated at both study sites by having more than 6 non-medicated pigs (11 of the 12 non-medicated animals in MN and 9 of the 12 non-medicated animals in CA) with adult *T. suis* worm counts of 100 or more per animal.

There was a significant treatment effect in *T. suis* worm counts between medicated and non-medicated treatment groups at each study site (p=0.0006 in MN and p=0.0003 in CA). The percent reduction in *T. suis* worm counts in the FBZ medicated animals was greater than 90% (98.5% in MN and 98.6% in CA) compared to the non-medicated animals using transformed data (geometric means).

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Palatability: A pivotal palatability study was conducted to evaluate the palatability of 20% Fenbendazole Suspension in pigs through voluntary consumption of medicated water when offered for approximately 5 hours a day over 3 consecutive days at a dose of 2.2 mg fenbendazole/kg body weight (BW) per day (label dose). The average percent of medicated water consumed was 98.18%, thus the study demonstrated that 20% Fenbendazole Suspension has acceptable palatability.

ANIMAL SAFETY:
Chickens: Two margin of safety studies (growing broiler chickens and laying hens at peak egg production) and one reproductive safety study (broiler breeder chickens) were conducted. These studies supported the safety of Safe-Guard® AquaSol in broiler chickens, replacement chickens, laying hens and breeding chickens when administered in drinking water at 1 mg fenbendazole/kg body weight/day for 5 consecutive days.

The margin of safety in broiler chickens was conducted in 480 broiler chickens. Safe-Guard® AquaSol was administered orally as medicated drinking water to three groups of 120 chickens (60 male and 60 female in each group) at 1, 3, and 5 mg fenbendazole/kg body weight/day (1, 3, and 5 times the recommended label dose) for 15 consecutive days (3 times the recommended duration). Another group of 120 chickens (60 male and 60 female) was provided non-medicated drinking water and used as a control group. In all chickens, feed and water intake, body weights, clinical health, and mortality were recorded. Hematology and clinical chemistry parameters were evaluated in 24 chickens from each group. At the end of the treatment phase, gross necropsies were performed on 48 chickens from each group, and organs weights were evaluated. Histopathologic examinations were performed on 48 chickens each from the control and 5 mg fenbendazole/kg body weight groups. No clinically significant effects related to the administration of Safe Guard® AquaSol were observed for any of the parameters evaluated.

The margin of safety in laying hens was conducted in 144 laying hens. Safe-Guard® AquaSol was administered orally as medicated drinking water to three groups of 36 hens at 1, 3, and 5 times the recommended label dose (1, 3, and 5 mg fenbendazole/kg body weight/day) for 15 consecutive days (3 times the recommended duration). Another group of 36 hens was provided non-medicated drinking water and used as control group. In all hens, feed and water intake, body weights, clinical health, mortality, egg production, and egg quality parameters (including egg shell thickness and strength, egg weight, and Haugh unit) were evaluated. Hematology and clinical chemistry parameters were evaluated in 12 hens from each group. At the end of the treatment phase, gross necropsies were performed on 12 hens from each group, and organs weights were evaluated. Histopathologic examinations were performed on 12 hens each from the control and 5 mg fenbendazole/kg body weight groups. No clinically significant effects related to the administration of Safe-Guard® AquaSol were observed for any of the parameters evaluated.

The reproductive safety in broiler breeding chickens was conducted in 220 broiler breeder chickens. Safe-Guard® AquaSol was administered orally as medicated drinking water to a group of 110 breeding chickens (10 male and 100 female) at 3 mg fenbendazole/kg body weight/day (3 times the recommended label dose) for 21 consecutive days (4 times the recommended duration). Another group of 110 breeding chickens (10 male and 100 female) were provided non-medicated drinking water and used as a control group. The parameters evaluated in the study included feed and water intake, body weights, clinical health, egg production and weight, fertility, hatchability, and 14-day old chick viability. Necropsy of unhatched eggs was performed to record the percentage of dead embryos and dead and culled hatchlings. At the end of the treatment phase, 30 breeding chickens (10 male and 20 female) from each group were necropsied; and gross pathology and weights of testes and female reproductive tracts were evaluated. Histopathologic evaluations were performed on the gross lesions collected during the necropsy. No clinically significant effects related to the administration of Safe-Guard® AquaSol were observed for any of the parameters evaluated.

Swine: Animal safety was established using a combination of swine pharmacokinetic, physiologic, and pharmacologic data that provided a basis for bridging the safety data of Safe-Guard® Type A medicated article (NADA 131-675) to Safe-Guard® AquaSol oral suspension in swine.

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HOW SUPPLIED: 1 Liter and 1 Gallon (3,785 mL) HDPE plastic containers

For Patent Information: http://www.merck.com/product/patent/home.html.

Use Only as Directed

Fenbendazole (active ingred.) made in China. Formulated in France.

	Distributed by: Intervet Inc. 2 Giralda Farms Madison, NJ 07940

Approved by FDA under NADA # 141-449

Revision Date: 02/21

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Madison, NJ 07940
All rights reserved.
Fenbendazole (active ingred.) made in China.
Formulated in France.
Net volume 1 Gallon

MERCK Animal Health
377122 R1

Front cover - 100mm

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Approved by FDA under NADA # 141-449

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GENERAL MIXING DIRECTIONS:
Chickens:
Dose calculation:
The daily dose of 1 mg fenbendazole per kg BW (0.454 mg/lb) is equivalent to 0.005 mL Safe-Guard® AquaSol per kg BW (0.00227 mL/lb). The required daily volume of product is calculated from the total estimated body weight [kg] of the entire group of chickens to be treated. Please use the following formula:

Total estimated body weight [kg] of the chickens to be treated x 0.005 mL
= mL Safe-Guard® AquaSol/day

Examples:

Total body weight of birds to be treated	Volume of Safe-Guard® AquaSol per day	Volume of Safe-Guard® AquaSol (for 5 days)
5,000 kg (11,000 lb)	25 mL	5 x 25 mL = 125 mL
10,000 kg (22,000 lb)	50 mL	5 x 50 mL = 250 mL
80,000 kg (176,000 lb)	400 mL	5 x 400 mL = 2,000 mL
320,000 kg (704,000 lb)	1,600 mL	5 x 1,600 mL = 8,000 mL

Follow the instructions in the order described below to prepare the medicated water. The medicated water must be prepared daily prior to each administration.

Swine:
Dose calculation:
The daily dose is 2.2mg fenbendazole per kg BW which is equivalent to 0.011mL Safe-Guard® AquaSol. The required daily volume of product is calculated from the total estimated body weight [kg] of the entire group of pigs to be treated. Please use the following formula:

Total estimated body weight [kg] of the pigs to be treated x 0.011mL
= mL Safe-Guard® AquaSol/day

Examples:

Total body weight of pigs to be treated	Volume of Safe-Guard® AquaSol per day	Volume of Safe-Guard® AquaSol (for 3 days)
10,000kg (22,000 lb)	110 mL	3 x 110mL = 330 mL
80,000kg (176,000 lb)	880 mL	3 x 880mL = 2640 mL
320,000 kg (704,000 lb)	3520 mL	3 x 3520mL = 10,560 mL

Follow the instructions in the order described below to prepare the medicated water. The medicated water must be prepared daily prior to each administration.

<u>Prepare a 1 to 1 dilution (pre-dilution) of Safe-Guard® AquaSol in water:</u>
1) Calculate the volume of Safe-Guard® AquaSol to be administered daily.
2) Select a measuring device capable of accurately measuring a volume of at least twice the calculated Safe-Guard® AquaSol daily volume.
[Note: If the total volume of the 1 to 1 dilution needed exceeds the volume of the largest available measuring device, divide the total volume into two or more smaller batches of 1 to 1 dilution, prepared following the steps below. Safe-Guard® AquaSol should always be measured by adding it to a measuring device that already contains an equivalent volume of water.]
3) Pour a volume of water equal to the calculated volume of product needed into the measuring device.
4) Shake the product well before mixing.
5) Fill up the measuring device containing the water with the calculated volume of the product to obtain the 1 to 1 dilution.
[Note: If more than the required amount of the product is accidently poured into the measuring device, discard the entire contents and repeat the process from Step 3 above.]
6) Add the 1 to 1 dilution of Safe-Guard® AquaSol in water to the water supply system as described below. Be careful to avoid any accidental spill or loss of 1 to 1 dilution which may inadvertently result in less than the required dose of fenbendazole.
7) Rinse the container used to prepare the 1 to 1 dilution of Safe-Guard® AquaSol with additional water, and add the rinse water to the medicated water tank or the stock suspension tank of the dosing pump.

<u>For use with a medication tank:</u>
Add the entire 1 to 1 dilution of Safe-Guard® AquaSol in water to the medication tank containing the volume of drinking water usually consumed by the animals in 3 to 24 hours. Stir the medicated water in the medication tank until the medicated water is visibly homogeneous. The medicated water should appear hazy. No further stirring during administration is necessary.

<u>For use with a dosing pump:</u>
Add the entire 1 to 1 dilution of Safe-Guard® AquaSol in water to the water in the stock suspension tank of the dosing pump. The volume of water in the stock suspension container has to be calculated taking as a basis the present injection rate of the dosing pump and the volume of drinking water usually consumed by the animals over a period of 3 to 24 hours. Stir until the content in the stock suspension tank is visibly homogeneous. The medicated water should appear hazy.

At concentrations of up to 5 mL/L stock suspension (1 g fenbendazole/L) no stirring is required. At concentrations from 5 mL up to 75 mL of product /L stock suspension (1,000 mg to 15,000 mg fenbendazole/L) and within up to 8 hours during the treatment administration period no stirring of the stock suspension is required. If the administration period exceeds 8 hours, but being no longer than 24 hours, the stock suspension container needs to be equipped with a stirring device.

During treatment, all animals must have sole and unrestricted access to the medicated water. After complete consumption of the medicated water, the animals should have access to non-medicated drinking water *ad libitum*. Ensure that the total amount of medicated water offered is consumed.

USER SAFETY WARNINGS: Not for use in humans. Keep out of reach of children. Protective gloves should be used and care should be taken when handling the product to avoid skin and eye exposure and accidental ingestion. Accidental exposure may result in skin and eye irritation. Accidental ingestion may cause gastrointestinal disturbances and hypersensitivity reactions in humans. For customer service, adverse effects reporting, and/or a copy of the SDS, call 1-800-211-3573. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

RESIDUE WARNING: ***Chickens:*** No withdrawal period is required when used according to labeling. ***Swine:*** Swine intended for human consumption must not be slaughtered within 2 days from the last treatment.

OTHER WARNINGS: Parasite resistance may develop to any dewormer. All dewormers require accurate dosing for best results. Following the use of any dewormer, effectiveness of treatment should be monitored. A decrease of effectiveness over time may indicate the development of resistance to the dewormer administered. The parasite management plan should be adjusted accordingly based on regular monitoring.

EFFECTIVENESS:
Chickens: Six pivotal dose confirmation studies and five field effectiveness studies were conducted to evaluate the effectiveness of Safe-Guard® AquaSol oral suspension against adult *A. galli* in broiler chickens and replacement chickens and against *A. galli* and *H. gallinarum* in breeding chickens and laying hens. Safe-Guard® AquaSol was administered orally in drinking water at 1 mg fenbendazole/kg body weight/day for 5 consecutive days. The chickens were necropsied 7 to 8 days after the last treatment, and adult worms in the intestines and ceca of the chickens in the control and treated groups were counted to determine percent efficacy.

Three dose confirmation studies were conducted in European Union (EU), using 105 Rhode Island Red breed hens (2 years old) for each study. In all three studies, the efficacy against *A. galli* (97.9%, 97.3%, and 93.9%) and *H. gallinarum* (99.8%, 96.9%, and 97.3%) was greater than 90%. A fourth dose confirmation study was conducted in the United States (US) using 264 Rhode Island Red breed hens (12 months old). In the study, the efficacy against adult *A. galli* and *H. gallinarum* was 98.7% and 99.2%, respectively. A fifth dose confirmation study was conducted in the US using 176 Cobb breed broiler chickens (4 to 5 weeks old). In the study, the efficacy against adult *A. galli* was 99.4%. A sixth dose confirmation study was conducted in the US using 176 Ross breed broiler chickens (4 to 5 weeks old). In the study, the efficacy against adult *A. galli* was 100%.

A field effectiveness study was conducted in the EU in a flock of 13,244 Hy-Line layer breed replacement chickens (13 weeks old). Fifteen chickens were necropsied before treatment initiation, and 15 chickens were necropsied seven days after treatment for worm counts. The efficacy against adult *A. galli* was 90.2%. A second field effectiveness study was conducted in the US using 550 Ross breed broiler chickens (4 to 5 weeks old). The efficacy against adult *A. galli* was 100%. A third field effectiveness study was conducted in the US using 550 White Leghorn replacement chickens (14 weeks old). The efficacy against adult *A. galli* and *H. gallinarum* was 100% and 88.9%, respectively. A fourth field effectiveness study was conducted in the US using 550 Cobb breed breeder hens (63 weeks old). The efficacy against adult *A. galli* and *H. gallinarum* was 97.6% and 95.3%, respectively. A fifth effectiveness study was conducted in the US using 550 Cobb breed broiler chickens (4 to 5 weeks old). The efficacy against adult *A. galli* was 100%.

The pivotal dose confirmation studies and field effectiveness studies demonstrated substantial evidence of effectiveness of Safe-Guard® AquaSol at the dose of 1 mg fenbendazole/kg body weight/day for 5 consecutive days against adult *A. galli* in broiler chickens and replacement chickens and against adult *A. galli* and *H. gallinarum* in breeding chickens and laying hens.

Swine: A multi-site, masked, negative-controlled dose confirmation field study was conducted to provide substantial evidence of the effectiveness of Fenbendazole (FBZ) Suspension (20% w/v) administered orally in drinking water to pigs for three consecutive days to provide a dose of 2.2 mg FBZ/kg body weight daily against the dose-limiting worm *Trichuris suis (T. suis*). A common protocol was implemented in two different geographical locations and with two different investigators.

Weaned, growing-finishing pigs of approximately 6 weeks of age were used in the study. Each study site selected pigs from one source herd verified to be free of *T. suis* infection. Barrow and gilt breeds representative of U.S. commercial

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Page 3 - 90mm

Page 4 - 90mm

Page 5 - 90mm