

Date of Approval: AUG 9 2004

FREEDOM OF INFORMATION SUMMARY

NADA 140-439

EQVALAN Liquid For Horses

(ivermectin)

This supplement amends the EQVALAN (ivermectin) Liquid For Horses labeling to add four species of internal parasites and to reflect a change in the Indications section which separates the listing of adult small strongyle species from their related fourth-stage larvae.

Sponsored by:

Merial Ltd.

2004-140-439

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1. GENERAL INFORMATION:

- a. File Number: NADA 140-439
- b. Sponsor: Merial Ltd.
3239 Satellite Blvd.
Building 500
Duluth, GA 30096-4640
- c. Established Name: Ivermectin
- d. Proprietary Name: EQVALAN Liquid For Horses
- e. Dosage Form: Liquid containing 1% ivermectin for administration by stomach tube or oral drench
- f. How Supplied: 100 mL plastic bottle. Each bottle contains sufficient ivermectin to treat ten 1100 lb (500 kg) horses.
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each mL contains 10 mg of ivermectin
- i. Route of Administration: Oral
- j. Species/Class: Equine
- k. Recommended Dosage: 91 mcg ivermectin per lb (200 mcg/kg)
- l. Pharmacological Category: Anthelmintic
- m. Indications: For treatment and control of the following parasites in horses: **Large strongyles** (adults)-*Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equinus*, *Triodontophorus* spp. including *T. brevicauda* and *T. serratus* and *Craterostomum acuticaudatum*; **Small Strongyles** (adults, including those resistant to some benzimidazole class compounds)- *Coronocyclus* spp. including *C. coronatus*, *C. labiatus*, and *C. labratus*, *Cyathostomum* spp. including *C. catinatum* and *C. pateratum*, *Cylicocyclus* spp. including *C. insigne*, *C. leptostomum*, *C. nassatus*, and *C. brevicapsulatus*,

Cylicodontophorus spp., *Cylicostephanus* spp. including *C. calicatus*, *C. goldi*, *C. longibursatus*, and *C. minutus*, and *Petrovinema poculatum*; **Small Strongyles**-fourth stage larvae; **Pinworms** (adults and fourth stage larvae)-*Oxyuris equi*; **Ascarids** (adults and third and fourth stage larvae)-*Parascaris equorum*; **Hairworms** (adults)-*Trichostrongylus axei*; **Large-mouth Stomach Worms** (adults)-*Habronema muscae*; **Bots** (oral and gastric stages)-*Gasterophilus* spp. including *G. intestinalis* and *G. nasalis*; **Lungworms** (adults and fourth stage larvae)-*Dictyocaulus arnfieldi*; **Intestinal Threadworms** (adults)-*Strongyloides westeri*; **Summer Sores** caused by *Habronema* and *Draschia* spp. cutaneous third stage larvae; Dermatitis caused by neck threadworm microfilariae, *Onchocerca* sp.

n. Effect of Supplement:

This supplement amends the EQVALAN (ivermectin) Oral Liquid For Horses labeling to add four species of internal parasites and to reflect a change in the Indications section which separates the listing of adult small strongyle species from their related fourth-stage larvae. Specifically, the supplement provides for the use of ivermectin oral liquid for the treatment and control of *Craterostomum acuticaudatum*, *Petrovinema poculatum*, and *Coronocyclus* spp. including *Coronocyclus coronatus* and *Coronocyclus labratus*. In addition, under the sub-heading Small Strongyles, the labeling has been revised to separate the listing of adult species from their related fourth-stage larvae.

2. EFFECTIVENESS:

This supplement revises the label Indications to add four species of internal parasites. Substantial evidence of effectiveness is based on an effectiveness study using ivermectin as a different approved dosage form, an oral paste, and on a demonstration of bioequivalence between the paste and the oral solution.

The bioequivalence of EQVALAN Liquid For Horses (NADA 140-439 original approval July 1, 1987) with EQVALAN Paste For Horses (NADA 134-314 original approval May 29, 1984) is contained in a Freedom of Information Summary for NADA 140-439. EQVALAN Liquid For Horses is expected to be effective for all of the parasites for which EQVALAN Paste For Horses is approved.

Based on the current data for EQVALAN Paste for Horses (supplemental approval to NADA 134-314 dated April 2, 2003), the following parasite species have been added to the label for EQVALAN Liquid For Horses: *Triodontophorus brevicauda* and *Triodontophorus serratus*, *Craterostomum acuticaudatum*, *Gasterophilus intestinalis* and *Gasterophilus nasalis*, *Coronocyclus coronatus*, *Coronocyclus labiatus*, and *Coronocyclus labratus*, *Cyathostomum catinatum* and *Cyathostomum pateratum*, *Cylicocyclus insigne*, *Cylicocyclus leptostomum*, *Cylicocyclus nassatus*, and *Cylicocyclus brevicapsulatus*, *Cylicostephanus calicatus*, *Cylicostephanus goldi*, *Cylicostephanus longibursatus*, and *Cylicostephanus minutus*, and *Petrovinema poculatum*.

3. TARGET ANIMAL SAFETY:

No new data was required for this supplement to NADA 140-439 (original approval July 1, 1987) and this supplement did not require review of the original target animal safety data for this product.

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Not for use in humans. Keep this and all drugs out of the reach of children." "Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes." "Do not use in horses intended for human consumption."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrates that EQVALAN Liquid For Horses is safe and effective for the labeled claim.

This drug is a prescription product. Administration of this product by stomach tube or oral drench requires the knowledge and experience of a veterinarian.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, parts of this supplemental approval for non-food producing animals qualify for three years of marketing exclusivity beginning August 9, 2004. The three years of marketing exclusivity applies only to the treatment and control of the following parasites: *Craterostomum acuticaudatum*, *Petrovinema poculatum*, and *Coronocyclus* spp. including *Coronocyclus coronatus* and *Coronocyclus labratus*.

In accordance with 21 CFR 514.106(b) (2), this is a Category II change which did not require reevaluation of other underlying safety or effectiveness data.

6. ATTACHMENTS:

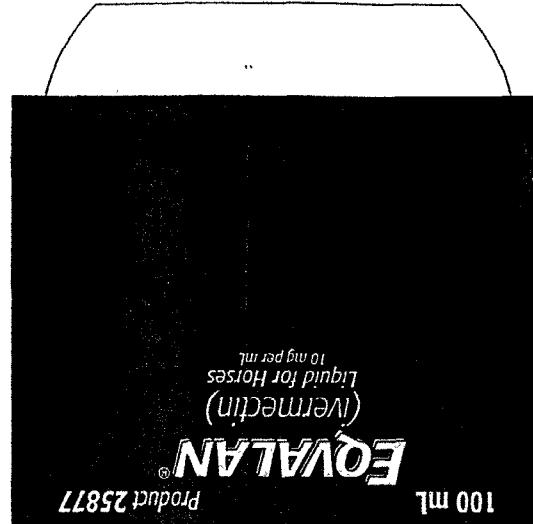
Facsimile labeling is attached as indicated below:

Carton

Package Insert

Bottle Label

1030-178100



INDICATIONS

EOVALAN® (ivermectin) Liquid provides effective treatment and control of the following parasites in horses. Large Strongyles (adults) - *Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equinus*, *Trichodontophorus* spp. including *T. brevicauda* and *T. serratus* and *Craterostomum acuticaudatum*; Small Strongyles (adults, including those resistant to some benzimidazole class compounds) - *Coronocylus* spp. including *C. coronatus*, *C. labiatus* and *C. labratus*, *Cyathostomum* spp. including *C. catinatum* and *C. pateratum*, *Cylicocyclus* spp. including *C. insigne*, *C. leptostomum*, *C. nassatus* and *C. brevicapsulatus*, *Cylicodontophorus* spp., *Cylcocephalus* spp. including *C. calicatus*, *C. goldi*, *C. longibursatus* and *C. minutus*, and *Petrovinema poculum*; Small Strongyles - Fourth-stage larvae; Pinworms (adults and fourth-stage larvae) - *Oxyuris equi*; Ascarids (adults and third- and fourth-stage larvae) - Parascaris equorum; Hairworms (adults) - *Trichostrongylus axei*; Large-mouth Stomach Worms (adults) - *Habronema muscae*; Bots (oral and gastric stages) - *Gasterophilus* spp. including *G. intestinalis* and *G. nasalis*; Lungworms (adults and fourth-stage larvae) - *Dictyocaulus arnfieldi*; Intestinal Threadworms (adults) - *Strongyloides westeri*; Summer sores caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae; Dermatitis caused by neck threadworm microfilariae, *Oncotocerca* sp.

DOSAGE AND ADMINISTRATION

EOVALAN Liquid for Horses is formulated for administration by stomach tube (nasogastric intubation) or as an oral drench. The recommended dose is 91 mcg of ivermectin per lb (200 mcg/kg) of body weight. Each mL contains sufficient ivermectin to treat 110 lb (50 kg) of body weight; 10 mL will treat an 1100 lb (500 kg) horse.

See package insert for complete indications and use directions.

Each mL contains 10 mg ivermectin, 0.2 mL propylene glycol, 80 mg polysorbate 80, 9 mg sodium phosphate monobasic monohydrate, 1.3 mg sodium phosphate dibasic anhydrous, 1 mg butylated hydroxytoluene, 0.1 mg disodium edetate, 3% benzyl alcohol and purified water q.s. ad 100%.

Lot No & Exp Date ▼

No Varnish Area
1.5" x 1"

Marketed by
Merial Limited
Duluth, GA 30096-4640
Rev 06-04

1030-1781-00

NADA 140-439, Approved by the FDA

FOR VETERINARY USE ONLY

EQVALAN®
(ivermectin)

Liquid for
10 mL



Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

100 mL



WARNING: Not for use in humans. Keep this and all drugs out of the reach of children. Do not use in horses intended for human consumption. Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

PRECAUTIONS: EOVALAN® (ivermectin) Liquid has been formulated specifically for use in horses only. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

Environmental Safety: Ivermectin and excreted ivermectin residues may adversely affect aquatic organisms. Do not contaminate ground or surface water. Dispose of drug container in an approved landfill or by incineration.

ANIMAL SAFETY: EOVALAN Liquid may be used in horses of all ages, including mares at any stage of pregnancy. Stallions may be treated without adversely affecting their fertility.

STORAGE INFORMATION: Store in a tightly closed container at room temperature. Protect EOVALAN Liquid (undiluted or diluted) from light.

Large Strongyles, Small Strongyles, Hairworms, Pinworms, Roundworms (ascaris), Intestinal Threadworms, Large-mouth Stomach Worms, Bots, Lungworms, Summer Sores and Cutaneous Onchocerciasis.

RECOMMENDED DOSE: 91 mcg of ivermectin per lb (200 mcg/kg) of body weight. Each mL contains sufficient ivermectin to treat 110 lb (50 kg) of body weight; 10 mL will treat an 1100 lb (500 kg) horse.

See package insert for complete indications and use directions.

Rev 06-04
1022-1779-00

Lot No & Exp Date ▼

1-5/8" x 1/2"
No Varnish Area

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For VETERINARY USE ONLY

EQVALAN® *(ivermectin)*

Liquid for Horses
10 mg per mL

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Product 25877
100 mL



WARNING: Not for use in humans. Keep this and all drugs out of the reach of children. Do not use in horses intended for human consumption. Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes.

PRECAUTIONS: EQVALAN® (ivermectin) Liquid has been formulated specifically for use in horses only. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

STORAGE INFORMATION: Store in a tightly closed container at room temperature. Protect EQVALAN Liquid (undiluted or diluted) from light.

U.S. Pat. 4,99,569

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<p>infections of neck threadworm microfilariae, <i>Onchocerca</i> sp. These reactions are most likely the result of microfilariae dying in large numbers. Symptomatic treatment may be advisable.</p> <p>Healing of summer sores involving extensive tissue changes may require other therapy in conjunction with EQVALAN Liquid. Reinfestation, and measures for its prevention, should also be considered.</p> <p>Owners should be advised to consult their veterinarian if these conditions do not improve.</p> <p>CLINICAL PHARMACOLOGY</p> <p>Mode of Action: Ivermectin is</p>	<p>a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).</p> <p>The margin of safety is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.</p> <p>ANIMAL SAFETY</p> <p>EQVALAN Liquid may be used in horses of all ages, including mares at any stage of pregnancy. Stallions may be treated without adversely affecting their fertility.</p> <p>STORAGE INFORMATION</p> <p>Store in a tightly closed</p>	<p>container at room temperature. Protect EQVALAN Liquid (undiluted or diluted) from light.</p> <p>HOW SUPPLIED</p> <p>EQVALAN Liquid for Horses (Product 25877) is available in a 100 mL plastic bottle. Each bottle contains sufficient ivermectin to treat 10–500 kg (1100 lb) horses. Contents may be poured into a graduated cylinder for dose measurement. Alternatively, a clean syringe may be inserted directly into the bottle to draw off the appropriate dose.</p>	<p>Product 25877</p> <p>Merial Limited, a company limited by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex CM19 5TG, England, and domesticated in Delaware, USA as Merial LLC.</p> <p>EQVALAN is a registered trademark of Merial Limited. Copyright © 2004, Merial Limited All Rights Reserved.</p> <p>Marketed by Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640</p>	<p>NADA 140-339, Approved by the FDA</p> <p>FOR VETERINARY USE ONLY</p> <p>EQVALAN® <i>(ivermectin)</i> Liquid for Horses 10 mg per ml</p>  <p>Rev 05-04</p> <p>1050178000</p> <p><small>Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian</small></p> <p><small>MERIAL</small></p>
13	14	15	16	17

105 s spp. including: <i>is brevicauda</i> <i>is serratus</i> <i>acuticaudatum</i> as (adults, resistant to azole class)	<i>Cylcostephanus goldi</i> <i>Cylcostephanus longilobatus</i> <i>Cylcostephanus minutus</i> <i>Petrovinema poculum</i> Small Strongyles: Fourth-stage larvae Pinworms (adults and fourth- stage larvae) - <i>Oxyuris equi</i> Roundworms or ascarids (adults and third- and fourth- stage larvae) - <i>Parascaris</i> <i>equorum</i> Hairworms (adults) - <i>Trichostrongylus axei</i> Large-mouth Stomach worms (adults) - <i>Habronema muscae</i> Bots (oral and gastric stages) - <i>Gasterophilus</i> spp. including <i>G.</i> <i>intestinallis</i> and <i>G. nasalis</i> Lungworms (adults and fourth- stage larvae) - <i>Dictyocaulus</i> <i>armento</i> Intestinal threadworms (adults) - <i>Strongyloides westeri</i>	Summer sores caused by <i>Habronema</i> and <i>Draschia</i> spp. cutaneous third-stage larvae; dermatitis caused by neck threadworm microfilariae, <i>Oncocerca</i> sp. DOSAGE EQVALAN Liquid for Horses is formulated for administration by stomach tube (nasogastric intubation) or as an oral drench. The recommended dose is 91 mcg of ivermectin per lb (200 mcg/kg) of body weight. Each mL contains sufficient ivermectin to treat 110 lb (50 kg) of body weight. 10 mL will treat an 1100 lb (500 kg) horse.	6	syringe inserted into the bottle to measure the appropriate dose, or pour the EQVALAN Liquid into a graduated cylinder for dose measurement. Use a clean syringe if accessing the bottle to avoid contaminating the remaining product. Special consideration should be given to the effects or potential for injury from handling, restraint, and placement of the stomach tube during administration of EQVALAN Liquid. EQVALAN Liquid should be administered by drench if the risks associated with tubing are of concern. Due to the potential consequences of improper	7	administration, EQVALAN Liquid is intended for use by a veterinarian only and is not recommended for dispensing. EQVALAN Liquid in 1 to 20 and 1 to 40 dilutions with tap water has been shown to be stable for 72 hours under the conditions recommended for the product (i.e., at room temperature, in a tightly closed container, protected from light). The diluted product does not promote the growth of common organisms. However, prolonged storage of the diluted product cannot be recommended, as the effects of possible contaminations and interactions with untested	8	materials are unknown. Administration by stomach tube (gravity or positive flow): The recommended dose can be used undiluted or diluted up to 40 times with clean tepid water. Use tepid water to flush any drug remaining in the tube into the horse's stomach. Administration by drench: For administration of EQVALAN Liquid by drench, an undiluted dose is recommended. Clear the horse's mouth of any food material, elevate the horse's head, and using a syringe, deposit the appropriate dose in the back of the mouth. In order to avoid unnecessary	9	coughing or the potential for material to enter the trachea and lungs, do not use excessive pressure (squirting), do not use a large (diluted) dose volume, and do not deposit the dose in the laryngeal area. Increased dose rejection may occur if the dose is deposited in the buccal space. Keep horse's head elevated and observe the horse to insure the dose is retained.
4	5								PARASITE CONTROL PROGRAM All horses should be included in a regular parasite control program with particular attention being paid to mares, foals and yearlings. Foals	