Date of Approval: July 6, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-318

VIRBAMEC
(ivermectin)

Pour-on for Cattle

Parasiticide

The effect of the supplement is the addition of a new 10 L package size; and revised labeling that includes updated speciation of *Cooperia*, Environmental Safety information, Mode of Action information, Residue information, and Indications section.

Sponsored by:

Virbac AH, Inc.

1. GENERAL INFORMATION:

a. ANADA Number:	ANADA 200-318
b. Sponsor:	Virbac AH, Inc. 3200 Meacham Blvd. Ft. Worth, TX 76137 Drug Labeler Code: 051311
c. Established Name:	Ivermectin
d. Proprietary Name:	VIRBAMEC Pour-on for Cattle
e. Dosage Form:	Pour-On
f. How Supplied:	8.5 fl. oz/250 mL and 33.8 fl oz/1 L bottle with a measure-pour system, a 84.5 fl oz/2.5 L or a 169 fl oz/5 L bottle and a 338 fl oz/10 L bottle intended for use with appropriate automatic dosing equipment.
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Each mL of solution contains 5 mg of ivermectin
i. Route of Administration:	Topical
j. Species/Class:	Cattle
k. Recommended Dosage:	500 mcg/kg (1 mL for each 22 lb. of bodyweight)
l. Pharmacological Category:	Parasiticide
m. Indications:	VIRBAMEC Pour-On applied at the recommended dose level of 500 mcg/kg is indicated for the effective treatment and control of these parasites.

Gastrointestinal Roundworms
Ostertagia ostertagi (adults and L4)
(including inhibited stage)
Haemonchus placei (adults and L4)
Trichostrongylus axei (adults and L4)
T. colubriformis (adults and L4)
Cooperia oncophora (adults and L4)
Cooperia punctata (adults and L4)
Cooperia surnabada (adults and L4)
Strongyloides papillosus (adults)
Oesophagostomum radiatum (adults and L4)
Trichuris spp. (adults)

Lungworms
Dictyocaulus viviparus (adults and L4)

Cattle Grubs (parasitic stages)
Hypoderma bovis
H. lineatum

Mites
Sarcoptes scabiei var. *bovis*

Lice
Linognathus vituli
Haematopinus eurysternus
Damalinia bovis
Solenopotes capillatus

Horn Flies
Haematobia irritans

Persistent Activity:
VIRBAMEC Pour-On has been proved to effectively control infections and protect cattle from re-infection with *Ostertagia ostertagi*, *Oesophagostomum radiatum*, *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata* and *Cooperia oncophora* for 14 days after treatment.

n. Pioneer Product: IVOMEC Pour-on; ivermectin; NADA 140-841; Merial Ltd.

o. Effect of Supplement: The effect of the supplement is the addition of a new 10 L package size; and revised labeling that includes updated (a) speciation of *Cooperia*, (b) Environmental Safety information, (c) Mode of Action information, (d) Residue Information, and (e) Indications section.

2. TARGET ANIMAL SAFETY AND EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily, the ANADA sponsor shows the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement of an *in vivo* bioequivalence study (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guidance, revised October 9, 2002).

Based on the formulation characteristics of the generic product, Virbac AH, Inc. was granted a waiver from the requirement of an *in vivo* bioequivalence study for the generic product VIRBAMEC (ivermectin) Pour-on for Cattle. The generic product is administered as a pour-on, contains the same active ingredient in the same concentration and dosage form as the pioneer product, and contains no inactive ingredients that may significantly affect the absorption of the active ingredient. The pioneer product IVOMEC (ivermectin) Pour-on for Cattle, the subject of Merial Ltd., NADA 140-841, was approved on December 4, 1990.

These supplements include the revision of the **Indications** section of the labeling including the first sentence of that label section which now reads:

VIRBAMEC Pour-On applied at the recommended dose level of 500 mcg/kg is indicated for the effective treatment and control of these parasites.

A comprehensive list of all the parasites for which treatment is approved follows in the indications section. One parasite, formerly listed simply as *Cooperia* spp., is now listed as three individual species of *Cooperia*: *Cooperia oncophora, Cooperia punctata, Cooperia surnabada*.

The **Mode of Action** section of the labeling has also been updated to reflect current scientific understanding for the way in which ivermectin acts on the various parasites for which it is approved for treatment. The revised label reads:

Mode of Action:

Ivermectin is a member of the macrocylic 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 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 in this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gabaminobutyric acid (GABA). The margin of safety for compounds of this class is attributable to the fact that mammals do not have the glutamate-gated chloride channels, the macrocylic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood brain barrier.

3. HUMAN SAFETY:

- **Tolerances for Residues:**
  The tolerance established for the pioneer product applies to the generic product. A tolerance of 100 parts per billion (ppb) and 10 ppb is established for 22, 23-dihydroavermectin B_1a (marker residue) residues in the liver and muscle, respectively, of cattle under 21 CFR 556.344. The Acceptable Daily Intake (ADI) for total residues of ivermectin is 1 microgram per kilogram of body weight per day.

- **Withdrawal Times:**
  Because a waiver of the *in vivo* bioequivalence study was granted, the withdrawal times are those previously assigned to the pioneer product.

  The withdrawal period of 48 days has been established for VIRBAMEC (ivermectin) Pour-On in cattle (21 CFR 524.1193).

- **Regulatory Method for Residues:**
  The analytical methods for the determination of ivermectin in tissues are HPLC methods with fluorescence detection. These methods are found on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

The **Residue Information** section of the labeling was updated as follows:

The compressed arrow **WARNING** section of the labeling has been replaced with the **Residue Information** section and revised as shown below:

Residue Information

Cattle must not be treated within 48 days of slaughter for human consumption. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

The **Environmental Safety** section of the labeling was updated by adding the second paragraph to the section below:

Environmental Safety

Studies indicate that when ivermectin comes in contact with the soil, it readily and tightly binds to the soil and becomes inactive over time. Free ivermectin may adversely affect fish or certain water borne organisms on which they feed. Do not permit cattle to enter lakes, streams or ponds for at least 6 hours after treatment. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

As with other avermectins, ivermectin is excreted in the dung of treated animals and can inhibit the reproduction and growth of pest and beneficial insects that use dung as a source of food and for reproduction. The magnitude and duration of such effects are species and life-cycle specific. When used according to label directions, the product is not expected to have an adverse impact on populations of dung-dependent insects.

4. AGENCY CONCLUSIONS:

These supplemental ANADAs submitted under section 512(b)(2) of the Federal, Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that VIRBAMEC Pour-on for Cattle, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as follows:

<u>Generic Labeling for ANADA 200-318:</u>
Package Insert
Container Labels and Carton Labels:
- 8.5 fl oz (250 mL)
- 33.8 fl oz (1 L)
- 84.5 fl oz (2.5 L)
- 169 fl oz (5 L)
- 338 fl oz (10 L)

Pioneer Labeling for NADA 140-841:
Package Insert
250 mL Container: Container Labels, Label Outsert, and Carton Labels
1 L Container: Container Labels, Label Outsert, and Carton Labels
2.5 L Container: Container Labels and Carton Labels
5 L Container: Container Labels
20 L Container: Container Labels and Label Outsert