ECO
ANIMAL HEALTH

22 February 2006

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Princeton, NJ 08540
USA

Dockets Management Branch
HFA-305
5630 Fishers Lane, Room 1061
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CITIZEN PETITION
(ANADA SUITABILITY PETITION)

ECO Animal Health hereby submits this petition under Section 512(n)(3) of the Federal Food, Drug, and Cosmetic Act to seek permission from the Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, to file an Abbreviated New Animal Drug Application (ANADA) which differs in strength from the innovator product.

A. Action requested

ECO Animal Health seeks permission to file an ANADA for a generic equivalent of the innovator product Ivomec® (ivermectin) Injection for Cattle and Swine, 1% sterile solution, NADA 128-409, Merial Ltd., which differs from the innovator product in strength in that the generic product is provided as a 2% ivermectin solution for injection which is administered in one half the dose volume of the innovator product.

B. Statement of grounds

Under provisions of the Federal Food, Drug, and Cosmetic Act, Section 512(n)(3):

"If a person wants to submit an abbreviated application for a new animal drug-

(A) whose active ingredients, route of administration, dosage form, or strength differ from that of an approved new animal drug, or
(B) whose use with other animal drugs in animal feed differs from that of an approved new animal drug,

such person shall submit a petition to the Secretary seeking the permission to file such an application."

This ANADA Suitability Petition qualifies under the provisions of the Federal Food, Drug, and Cosmetic Act, Section 512 (n)(3)(A) in that permission is sought to change

only the strength (2% instead of 1%) and dose volume (one half that of the innovator product) while maintaining the same dose level of the approved new animal drug.

The proposed 2% ivermectin generic product is a true solution and contains the same active and inactive ingredients in the same concentration as the innovator product, except for the ivermectin active ingredient which is present at 2% instead of 1% and will be dosed at one half the volume of the innovator product.

A. Dosage Form: As indicated above, 2% ivermectin injection for cattle and swine is provided as a ready-to-use sterile solution for injection as is the innovator product.

B. Route of Administration: 2% ivermectin injection for cattle and swine is intended for subcutaneous injection as is the innovator product.

C. Recommended Dosages:

In cattle, the 2% ivermectin generic injection is formulated to provide the same recommended dose level of 200 mcg ivermectin/kilogram of body weight in cattle when given subcutaneously at the rate of 0.5 mL/110 lb (50 kg).

In swine, 2% ivermectin generic injection is formulated to deliver the recommended dose level of 300 mcg ivermectin/kilogram body weight when given subcutaneously in the neck at the rate of 0.5 mL/75 lb. (33 kg).

Thus the ivermectin generic product at 2% ivermectin strength and one-half the dose volume provides the same dose level as the 1% ivermectin innovator product.

The labeling for the 2% ivermectin generic solution will be identical to the pioneer Ivomec ® Injection for Cattle and Swine labeling with the exception of the substitution of ECO Animal Health's product name (to be determined), company name and address, and for the increased strength and decreased dose volume discussed above.

The indications for use will include the indications in the original NADA 128-409 and any approved supplements that are not subject to exclusivity at the time of ANADA approval.

A copy of the innovator package insert is attached as Appendix A as aid in this review.

C. Environmental impact

ECO Animal Health believes that this petition is subject to categorical exclusion under 21CFR25.24.

D. Economic impact

An economic impact analysis will be provided if requested after review of this petition.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

This submission includes an original and two additional copies.

ECO Animal Health develops and markets animal health products worldwide. In the United States, it is the animal health division of ECO LLC which holds the U. S. registrations. ECO LLC is located at 8209 Hollister Avenue, Las Vegas, NV 89131. The NCD Labeler Code is 066916. All correspondence and enquiries regarding animal health products should be directed to the Princeton, NJ address.

Please do not hesitate to contact me if you have any questions or require additional information.

Thank you.

Sincerely,

Nate Manco
Director, US Manufacturing Affairs
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Appendix A: Package Insert for Merial 1% Ivermectin Injection for Cattle and Swine

The package insert is provided on this page and the five following pages.

NADA 128-409, Approved by the FDA 8913412

ivomec®
(ivermectin)
Injection
for Cattle and Swine

1% Sterile Solution

A Parasiticide for the Treatment and Control of Internal and External Parasites of Cattle and Swine

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

INTRODUCTION

IVOMEC® (ivermectin) is an injectable parasiticide for cattle and swine. One low-volume dose effectively treats and controls the following internal and external parasites that may impair the health of cattle and swine: gastrointestinal roundworms (including inhibited *Ostertagia ostertagi* in cattle), lungworms, grubs, sucking lice, and mange mites of cattle; and gastrointestinal roundworms, lungworms, lice, and mange mites of swine. Discovered and developed by scientists from Merck Research Laboratories, ivermectin is a novel chemical entity. Its convenience, broad-spectrum efficacy, and safety margin make IVOMEC Injection a unique product for parasite control of cattle and swine.

PRODUCT DESCRIPTION

Ivermectin is derived from the avermectins, a family of potent, broad-spectrum antiparasitic agents isolated from fermentation of *Streptomyces avermitilis*.

IVOMEC Injection is a clear, ready-to-use, sterile solution containing 1% ivermectin, 40% glycerol formal, and propylene glycol, q.s. ad 100%. IVOMEC Injection is formulated to deliver the recommended dose level of 200 mcg ivermectin/kilogram of body weight in cattle when given subcutaneously at the rate of 1 mL/110 lb (50 kg). In Swine, IVOMEC Injection is formulated to deliver the recommended dose level of 300 mcg ivermectin/kilogram body weight when given subcutaneously in the neck at the rate of 1 mL per 75 lb (33 kg).

MODE OF ACTION

Ivermectin is 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).

The wide 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.

INDICATIONS

Cattle: IVOMEC Injection is indicated for the effective treatment and

Appendix A: Package Insert for Merial 1% Ivermectin Injection - Continued

and they do not readily cross the blood-brain barrier.

INDICATIONS

Cattle: IVOMEC Injection is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, grubs, sucking lice, and mange mites in cattle:

Gastrointestinal Roundworms (adults and fourth-stage larvae):
Ostertagia ostertagi (including inhibited *O. ostertagi*)
O. lyrata
Haemonchus placei
Trichostrongylus axei
T. colubriformis
Cooperia oncophora
C. punctata
C. pectinata
Oesophagostomum radiatum
Bunostomum phlebotomum
Nematodirus helvetianus (adults only)
N. spathiger (adults only)

Lungworms (adults and fourth-stage larvae):
Dictyocaulus viviparus

Cattle Grubs (parasitic stages):
Hypoderma bovis
H. lineatum

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mites (scabies):
Psoroptes ovis (syn. *P. communis* var. *bovis*)
Sarcoptes scabiei var. *bovis*

Persistent Activity

IVOMEC Injection has been proved to effectively control infections and to protect cattle from reinfection with *Dictyocaulus viviparus* for 28 days after treatment; *Ostertagia ostertagi* for 21 days after treatment; *Oesophagostomum radiatum*, *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

Swine: IVOMEC Injection is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, lice, and mange mites in swine:

Gastrointestinal Roundworms:
Large roundworm, *Ascaris suum*
(adults and fourth-stage larvae)
Red stomach worm, *Hyostrongylus rubidus*
(adults and fourth-stage larvae)
Nodular worm, *Oesophagostomum* spp.
(adults and fourth-stage larvae)
Threadworm, *Strongyloides ransomi* (adults)

Somatic Roundworm Larvae:
Threadworm, *Strongyloides ransomi* (somatic larvae)
Sows must be treated at least seven days before farrowing to prevent infection in piglets.

Lungworms:
Metastrongylus spp. (adults)

Lice:
Haematopinus suis

Mange Mites:
Sarcoptes scabiei var. *suis*

DOSAGE

Cattle: IVOMEC Injection should be given only by subcutaneous

Appendix A: Package Insert for Merial 1% Ivermectin Injection - Continued

Mange Mites:
Sarcoptes scabiei var. *suis*

DOSAGE

Cattle: IVOMEC Injection should be given only by subcutaneous injection under the loose skin in front of or behind the shoulder at the recommended dose level of 200 mcg of ivermectin per kilogram of body weight. Each mL of IVOMEC contains 10 mg of ivermectin, sufficient to treat 110 lb (50 kg) of body weight (maximum 10 mL per injection site).

Body Weight (lb)	Dose Volume (mL)
220	2
330	3
440	4
550	5
660	6
770	7
880	8
990	9
1100	10

Swine: IVOMEC Injection should be given only by subcutaneous injection in the neck of swine at the recommended dose level of 300 mcg of ivermectin per kilogram (2.2 lb) of body weight. Each mL of IVOMEC contains 10 mg of ivermectin, sufficient to treat 75 lb of body weight.

	Body Weight (lb)	Dose Volume (mL)
Growing Pigs	19	1/4
	38	1/2
	75	1
	150	2
Breeding Animals (Sows, Gilts, and Boars)	225	3
	300	4
	375	5
	450	6

ADMINISTRATION

Cattle: IVOMEC Injection is to be given subcutaneously only, to reduce risk of potentially fatal clostridial infection of the injection site. Animals should be appropriately restrained to achieve the proper route of administration. Use of a 16-gauge, 1/2 to 3/4" needle is suggested. Inject under the loose skin in front of or behind the shoulder (see illustration).

Appendix A: Package Insert for Merial 1% Ivermectin Injection - Continued

When using the 200, 500 or 1000 mL pack size, use only automatic syringe equipment.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infections.

No special handling or protective clothing is necessary.

Swine: IVOMEC® (ivermectin) Injection is to be given subcutaneously in the neck. Animals should be appropriately restrained to achieve the proper route of administration. Use of a 16- or 18-gauge needle is suggested for sows and boars, while an 18- or 20-gauge needle may be appropriate for young animals. Inject under the skin, immediately behind the ear (see illustration).

When using the 200 mL, 500 mL or 1000 mL pack size, use only automatic syringe equipment. As with any injection, sterile equipment should be used. The injection site should be cleaned and disinfected with alcohol before injection. The rubber stopper should also be disinfected with alcohol to prevent contamination of the contents. Mild and transient pain reactions may be seen in some swine following subcutaneous administration.

Recommended Treatment Program

Swine: At the time of initiating any parasite control program, it is important to treat all breeding animals in the herd. After the initial treatment, use IVOMEC Injection regularly as follows:

BREEDING ANIMALS

Sows: Treat prior to farrowing, preferably 7–14 days before, to minimize infection of piglets.

Gilts: Treat 7–14 days prior to breeding.

Treat 7–14 days prior to farrowing.

Boars: Frequency and need for treatments are dependent upon exposure.

Treat at least two times a year.

FEEDER PIGS

(Weaners/Growers/Finishers)

All weaner/feeder pigs should be treated before placement in clean quarters.

Pigs exposed to contaminated soil or pasture may need retreatment if reinfection occurs.

NOTE:

(1) IVOMEC Injection has a persistent drug level sufficient to control mite infestations throughout the egg to adult life cycle. However, since the ivermectin effect is not immediate, care must be taken to prevent reinfestation from exposure to untreated animals or contaminated facilities. Generally, pigs should not be moved to clean quarters or exposed to uninfested pigs for approximately one week after treatment. Sows should be treated at least one week before farrowing to minimize transfer of mites to newborn baby pigs.

(2) Louse eggs are unaffected by IVOMEC Injection and may require up to three weeks to hatch. Louse infestations developing from hatching eggs may require retreatment.

(3) Consult a veterinarian for aid in the diagnosis and control of internal and external parasites of swine.

Special Minor Use

Reindeer: For the treatment and control of warbles (*Oedemagena tarandi*) in reindeer, inject 200 micrograms ivermectin per kilogram of

Appendix A: Package Insert for Merial 1% Ivermectin Injection - Continued

(3) Consult a veterinarian for aid in the diagnosis and control of internal and external parasites of swine.

Special Minor Use

Reindeer: For the treatment and control of warbles (*Oedemagena tarandi*) in reindeer, inject 200 micrograms ivermectin per kilogram of body weight, subcutaneously. Follow use directions for cattle as described under **ADMINISTRATION**.

American Bison: For the treatment and control of grubs (*Hypoderma bovis*) in American bison, inject 200 micrograms ivermectin per kilogram of body weight, subcutaneously. Follow use directions for cattle as described under **ADMINISTRATION**.

RESIDUE INFORMATION: Do not treat reindeer or American bison within 8 weeks (56 days) of slaughter.

WARNING

Not for use in humans.

Keep this and all drugs out of the reach of children.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Merial at 1-888-637-4251.

RESIDUE INFORMATION: Do not treat cattle within 35 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age.

Do not treat swine within 18 days of slaughter.

PRECAUTIONS

Transitory discomfort has been observed in some cattle following subcutaneous administration. A low incidence of soft tissue swelling at the injection site has been observed. These reactions have disappeared without treatment. For cattle, divide doses greater than 10 mL between two injection sites to reduce occasional discomfort or site reaction.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infections.

Observe cattle for injection site reactions. Reactions may be due to clostridial infection and should be aggressively treated with appropriate antibiotics. If injection site infections are suspected, consult your veterinarian.

This product is not for intravenous or intramuscular use.

Protect product from light.

IVOMEC Injection for Cattle and Swine has been developed specifically for use in cattle, swine, reindeer, and American bison only. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

When to Treat Cattle with Grubs

IVOMEC effectively controls all stages of cattle grubs. However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble fly) season. Destruction of *Hypoderma* larvae (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions including the possibility of fatalities. Killing *Hypoderma lineatum* when it is in the tissue surrounding the esophagus (gullet) may cause salivation and bloat; killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. These reactions are not specific to treatment with IVOMEC, but can occur with any successful treatment of grubs. Cattle should be treated either before or after these stages of grub development. Consult your veterinarian concerning the proper time for treatment.

Cattle treated with IVOMEC after the end of the heel fly season may be retreated with IVOMEC during the winter for internal parasites, mange mites, or sucking lice without danger of grub-related reactions. A planned parasite control program is recommended.

Environmental Safety

Studies indicate that when ivermectin comes in contact with the soil, it

Appendix A: Package Insert for Merial 1% Ivermectin Injection - Continued

A planned parasite control program is recommended.

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 and certain water-borne organisms on which they feed. Do not permit water runoff from feedlots or production sites to enter lakes, streams, or ponds. 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.

HOW SUPPLIED

IVOMEC Injection for Cattle and Swine is available in five ready-to-use pack sizes:

The 50 mL pack is a multiple-dose, rubber-capped bottle. Each bottle contains sufficient solution to treat 10 head of 550 lb (250 kg) cattle or 100 head of 38 lb (17.3 kg) swine.

The 200 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 40 head of 550 lb (250 kg) cattle or 400 head of 38 lb (17.3 kg) swine.

The 500 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 100 head of 550 lb (250 kg) cattle or 1000 head of 38 lb (17.3 kg) swine.

The 2x 500 mL includes two 500 mL packs with sufficient solution to treat 200 head of 550 lb (250 kg) cattle or 2000 head of 38 lb (17.3 kg) swine.

The 1000 mL is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 200 head of 550 lb (250 kg) cattle or 2000 head of 38 lb (17.3 kg) swine.

(Merial Limited: Registered in England and Wales [Reg. No. 3332751] with registered offices at 27 Knightsbridge, London, SW1X 7QT, England and domesticated in Delaware, USA as Merial LLC).

Merial Limited
Iselin, NJ, U.S.A.

U.S. Pat. 4,199,569 & 4,853,372

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