Date of Approval: August 13, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-833

IVOMEC Plus Injection for Cattle

ivermectin and clorsulon injection

To decrease the withdrawal period from 49 days to 21 days.

Sponsored by:

Merial Ltd.

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I. GENERAL INFORMATION

A. File Number

NADA 140-833

B. Sponsor

Merial Ltd.
3239 Satellite Blvd., Bldg. 500
Duluth, GA 30096-4640

Drug Labeler Code: 050604

C. Proprietary Name

IVOMEC Plus Injection for Cattle

D. Established Name

Ivermectin and clorsulon injection

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Sterile Injectable Solution

G. Amount of Active Ingredient

10 mg (1%) ivermectin and 100 mg (10%) clorsulon/mL

H. How Supplied

50 mL rubber capped bottle, and 200, 500, and 1000 mL soft collapsible packs for use with automatic syringes

I. Dispensing Status

OTC

J. Dosage Regimen

1 mL for each 50 kg (110 lb) of body weight or 200 µg ivermectin and 2 mg clorsulon per kg

K. Route of Administration

Subcutaneous injection

L. Species/Class

Cattle

M. Indication

For the treatment and control of internal parasites, including adult liver flukes, and external parasites. There was no change in the approved indications.

N. Effect of Supplement

This supplement provides for a decrease in the withdrawal period from 49 days to 21 days and revision of the drug product established name to match the USP monograph title ivermectin and clorsulon injection.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of 140-833 dated September 17, 1990, and supplemental approvals dated February 24, 1997; April 1, 1999; and April 21, 2004; contain dosage characterization information for cattle at a dose of 1 mL per 50 kg of body weight.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 140-833 dated September 17, 1990, and supplemental approvals dated February 24, 1997; April 1, 1999; and April 21, 2004; contain summaries of studies that demonstrate effectiveness of the drug for cattle at a dose of 1 mL per 50 kg of body weight.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 140-833 dated September 17, 1990, contains a summary of target animal safety studies for cattle at a dose of 1 mL per 50 kg of body weight.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

Ivermectin and clorsulon are not known to have antimicrobial properties, and have not been shown to impact antimicrobial resistance among bacterial populations. Therefore, at this time, the agency does not think that the proposed use of these drugs will impact antimicrobial resistance among bacteria of public health concern in or on treated cattle.

B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of ivermectin and clorsulon are not known to have antimicrobial properties; additionally, residues and metabolites of ivermectin and clorsulon have not been shown to impact bacterial populations. Therefore, at this time, the agency does not think that residues and metabolites present from the proposed use of these drugs in or on the edible food products from treated cattle

will impact the intestinal flora of human consumers and there is no need to establish a microbiological acceptable daily intake.

C. Toxicology

Clorsulon: CVM did not require any toxicology studies for the supplemental approval of clorsulon in this combination product. Safety of this drug in the combination product has been established by data in NADA 136-742 (FOI Summary dated January 29, 1985).

Ivermectin

1. Summary of Toxicology Studies

Toxicology studies of ivermectin are included in the FOI summaries for the original approval of NADA 128-409, dated February 13, 1984, and a supplemental approval of NADA 128-409, dated September 13, 1995. An additional toxicology study, provided for this NADA, is summarized below:

a. Human Clinical Tolerance Study

This clinical study entitled, "Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects", was published in the Journal of Clinical Pharmacology in October 2002; 42(10):1122-33.

i. Study Title: A double-blind, randomized, placebo-controlled, and multiple-rising dose study to investigate the safety, tolerability, and pharmacokinetics of multiple doses of ivermectin (MK-0933) in healthy male and female human subjects.

ii. Study Report No.: MK-0933 Protocol 066

iii. Study Report date: October 11, 2001

iv. Performing Laboratory (in Life): Clinical Pharmacology Associates, 2060 NW 22nd Avenue, Miami, FL, USA

v. Clinical Investigator: Kenneth C. Lasseter, MD, Clinical Pharmacology Associates, Miami, FL, USA

vi. Study Objective: To investigate the neurological effects and general toxicity of ivermectin, with specific emphasis on the mydriatic effects in a human clinical tolerance study.

vii. Experimental Design and Methods: Sixty-four healthy, non-smoking human subjects, aged 21 to 45 years and weighing 50 to 90 kg, with a minimum visual acuity of 20/30 (corrected) in at least one eye and evaluable pupillometry measurement were sequentially assigned to one of four treatment panels. Subjects were randomized and stratified by gender within each panel to receive either ivermectin or placebo at 30 or 60 mg (three times a week) and 90 or 120 mg (single dose). The

30 mg panel also received a single dose with food after a 1-week washout.

Doses were administered sequentially, to establish safety at a lower dose before proceeding to a higher dose. Approved 3 mg ivermectin tablets and matching placebo tablets were orally administered once *per* day, up to three times in one week, using 0, 30, and 60 mg ivermectin *per* person (10 to 40 tablets *per* dose) and a single dose 90 or 120 mg. Safety endpoints measured included pupillometry, neurological examinations, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, hematology, blood chemistry and urinalysis.

viii. Study Results: All oral doses of ivermectin were well tolerated. No drug related adverse effects were reported or detected in the study based on pupillometry, neurological examinations, vital signs, 12-lead ECGs, physical examinations, urinalysis, or blood parameters.

ix. Conclusion: Because oral single doses up to 120 mg ivermectin *per* person showed no observable toxicity, the no-observed effect level (NOEL) for acute oral toxicity of ivermectin was determined to be 1.5 mg/kg bodyweight (1.5 mg/kg bw) calculated based on the median body weight (77.9 kg).

2. Determination of Toxicological No-Observed Effect Level (NOEL) for chronic exposure and Toxicological NOEL for acute exposure

The findings from human studies are consistent with the findings from laboratory animal studies, demonstrating neurotoxic effects as the most relevant endpoint of toxicological concern for ivermectin. Therefore, the mouse teratology study, which was used previously to establish the NOEL in the original approval, is not considered the most appropriate study to determine the toxicological NOEL for deriving the acceptable daily intake (ADI). Information obtained from human studies is consistent with the finding in the 90-day dog study, with the NOEL of 0.5 mg/kg bw/day based on neurotoxicity as the most appropriate endpoint for establishing the NOEL for chronic human exposure to ivermectin residues.

The human clinical study (Report MK-0933) provides a good basis for assessing safety following acute exposure to ivermectin residues in the edible tissues and supports a NOEL of 1500 µg/kg bw (*i.e.*, 1.5 mg/kg bw) for acute oral toxicity of ivermectin.

3. Determination of Toxicological Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD)

Because the NOEL for chronic and subchronic effects from ivermectin were quantitatively similar (NADA 128-409), a 1000-fold safety factor traditionally used to derive an ADI based on data from subchronic exposure was not appropriate. In addition, human studies corroborate the findings of laboratory animal studies, and support neurotoxic effects as the primary endpoint of ivermectin toxicity, and that the 90-day toxicity study in dogs, and not the teratology study in mice, is the most appropriate for setting the

NOEL for the determination of the ADI. In addition, large quantities of human clinical safety data accumulated over many years support the use of a 100-fold safety factor to determine the ADI. The revised ADI for ivermectin is 5 µg/kg bw/day based on the NOEL of 0.5 mg/kg bw/day established from the 90-day dog study and a 100-fold safety factor.

$$\text{Toxicological Acceptable Daily Intake (ADI)} = \frac{\text{Lowest NOEL}}{\text{Safety Factor}}$$

$$= \frac{0.5 \text{ mg/kg bw/day}}{100} = 0.005 \text{ mg/kg bw/day} = 5 \text{ ìg/kg bw/day}$$

(Equation 1: Toxicological Acceptable Daily Intake (ADI) equals the lowest NOEL divided by the Safety Factor, which equals 0.5 mg/kg bw/day divided by 100, which equals 0.005 mg/kg bw/day or 5 µg/kg bw/day).

The toxicological ADI for ivermectin is 5 µg/kg bw/day.

An ARfD for ivermectin is determined based on the acute NOEL of 1.5 mg/kg bw derived from a human clinical study (Study Report MK-0933) and a 10-fold safety factor.

$$\text{Acute Reference Dose (ARfD)} = \frac{\text{Acute NOEL}}{\text{Safety Factor}}$$

$$= \frac{1.5 \text{ mg/kg bw}}{10} = 0.15 \text{ mg/kg bw} = 150 \text{ ìg/kg bw}$$

(Equation 2: Acute Reference Dose (ARfD) equals the acute NOEL divided by the Safety Factor, which equals 1.5 mg/kg bw divided by 10, which equals 0.15 mg/kg bw or 150 µg/kg bw).

The ARfD for ivermectin is 150 µg/kg bw.

D. Assignment of the Final ADI

Clorsulon: The final ADI for clorsulon is the toxicological ADI of 8 µg/kg bw/day derived from the 14-week oral toxicity study in dogs. The codified ADI is listed under 21 CFR 556.163.

Ivermectin: Because it is not necessary to determine a microbiological ADI for ivermectin, CVM establishes the toxicological ADI of 5 µg/kg bw/day as the final ADI for total ivermectin residues. CVM assigns 150 µg/kg bw as the ARfD for total ivermectin residues.

E. Safe Concentrations for Total Residues in Edible Tissues and Injection Sites

The calculation of the tissue safe concentrations is based on the General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals (FDA/CVM, revised July 2006).

The safe concentration of total drug residues in each edible tissue of cattle is calculated using the following formula with the current food consumption values:

$$\textit{Safe Concentration (SC)} = \frac{\textit{Acceptable Daily Intake (ADI)} \times \textit{Human Weight}}{\textit{Consumption Value}}$$

(Equation 3: Safe Concentration (SC) equals Acceptable Daily Intake (ADI) times Average Human Body Weight divided by the Food Consumption Value).

The average human body weight is approximated at 60 kg. The daily food consumption values of the edible tissues of cattle are approximated as 300 g for muscle, 100 g for liver, 50 g for kidney, and 50 g for fat.

Clorsulon

The safe concentrations for total residues of clorsulon in the edible tissues are recalculated as (summarized in Table 1):

$$\text{SC (muscle)} = \frac{8\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{300\ \text{g/day}} = 1.6\ \text{ìg/g} = 1.6\ \text{ppm}$$

(Equation 4: SC (muscle) equals 8 µg/kg bw/day times 60 kg divided by 300 g/day, which equals 1.6 µg/g or 1.6 ppm).

$$\text{SC (liver)} = \frac{8\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{100\ \text{g/day}} = 4.8\ \text{ìg/g} = 4.8\ \text{ppm}$$

(Equation 5: SC (liver) equals 8 µg/kg bw/day times 60 kg divided by 100 g/day, which equals 4.8 µg/g or 4.8 ppm).

$$\text{SC (kidney)} = \frac{8\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{50\ \text{g/day}} = 9.6\ \text{ìg/g} = 9.6\ \text{ppm}$$

(Equation 6: SC (kidney) equals 8 µg/kg bw/day times 60 kg divided by 50 g/day, which equals 9.6 µg/g or 9.6 ppm).

$$\text{SC (fat)} = \frac{8\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{50\ \text{g/day}} = 9.6\ \text{ìg/g} = 9.6\ \text{ppm}$$

(Equation 7: SC (fat) equals 8 µg/kg bw/day times 60 kg divided by 50 g/day, which equals 9.6 µg/g or 9.6 ppm).

Table 1. Safe concentrations for Total Clorsulon Residues in the Edible Tissues of Cattle using the Food Consumption Value

Edible Tissue	Food Consumption Value (Amount Consumed/Day)	Safe Concentration
Muscle	300 g	1.6 ppm
Liver	100 g	4.8 ppm
Kidney	50 g	9.6 ppm
Fat	50 g	9.6 ppm

Ivermectin

The safe concentrations for total residues of ivermectin in the edible tissues are calculated as (summarized in Table 2):

$$\text{SC (muscle)} = \frac{5\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{300\ \text{g/day}} = 1\ \text{ìg/g} = 1\ \text{ppm}$$

(Equation 8: SC (muscle) equals 5 µg/kg bw/day times 60 kg divided by 300 g/day, which equals 1 µg/g or 1 ppm).

$$\text{SC (liver)} = \frac{5\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{100\ \text{g/day}} = 3\ \text{ìg/g} = 3\ \text{ppm}$$

(Equation 9: SC (liver) equals 5 µg/kg bw/day times 60 kg divided by 100 g/day, which equals 3 µg/g or 3 ppm).

$$\text{SC (kidney)} = \frac{5\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{50\ \text{g/day}} = 6\ \text{ìg/g} = 6\ \text{ppm}$$

(Equation 10: SC (kidney) equals 5 µg/kg bw/day times 60 kg divided by 50 g/day, which equals 6 µg/g or 6 ppm).

$$\text{SC (fat)} = \frac{5\ \text{ìg/kg bw/day} \times 60\ \text{kg bw}}{50\ \text{g/day}} = 6\ \text{ìg/g} = 6\ \text{ppm}$$

(Equation 11: SC (fat) equals 5 µg/kg bw/day times 60 kg divided by 50 g/day, which equals 6 µg/g or 6 ppm).

The safe concentration for the injection site is calculated as:

$$\text{SC (injection site) muscle} = \frac{\text{ARfD} \times \text{human body weight}}{\text{Muscle food consumption Value}}$$

$$= \frac{0.15\ \text{mg/kg bw x 60 kg bw}}{0.3\ \text{kg}} = 30\ \text{mg/kg} = 30\ \text{ppm}$$

(Equation 12: SC (injection site) equals ARfD (150 µg/kg bw) times human body weight divided by muscle food consumption value, which equals 0.150 mg/kg bw times 60 kg divided by 300 g/day, which equals 30 µg/g or 30 ppm).

Table 2. Safe concentrations for Total Ivermectin Residues in Edible Tissues of Cattle using the Food Consumption Value

Edible Tissue	Food Consumption Value (Amount Consumed/Day)	Safe Concentration
Muscle	300 g	1 ppm
Liver	100 g	3 ppm
Kidney	50 g	6 ppm
Fat	50 g	6 ppm
Injection Site	300 g	30 ppm

F. Residue Chemistry

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Studies

CVM did not require total residue and metabolism studies for this supplemental approval. The FOI Summaries for the original approval of NADA 128-409 dated February 13, 1984, and NADA 140-841 dated August 30, 1990, contain summaries of the total residue and metabolism studies for ivermectin in cattle.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-409 dated February 13, 1984, contains a summary of residue chemistry studies for ivermectin in cattle.

c. Study to Establish Withdrawal Period and/or Milk Discard Time

(1) Tissue Residue Depletion Study

Study Title: "Determination of the Depletion of Ivermectin and Clorsulon in Bovine Tissues Following a Single Administration of IVOMEC®-F". Study Number PR&D 0127201

A statement is provided describing adherence to the OECD Principles of Good Laboratory Practice.

Study Director: Matthias Pollmeier, Dr. med. Vet.

Study Dates: August 1, 2005, to January 27, 2006

Test Facility: Merial GmbH, Rohrdorf, Germany

Test Animals: Forty-four Fleckvieh/Fleckvieh cross cattle were used (22 male, 22 female). Body weights ranged from 255 to 382 kg.

Dosing: Forty cattle were administered IVOMEC-F (ivermectin clorsulon injection) by a single subcutaneous injection at a dose rate of 1 mL/50 kg body weight (200 µg ivermectin/kg, 2 mg clorsulon/kg). Four animals (2 male, 2 female) served as controls.

Sampling: Groups of 4 cattle (2 male, 2 female) were slaughtered at 3, 10, 17, 28, 45, 52, 60, 70, and 80 days after treatment. Liver, kidneys, perirenal fat, skeletal muscle, core injection site, and concentric ring around the core injection site were collected for analysis of ivermectin and clorsulon residues.

Analysis: The marker residue for ivermectin, 22,23-dihydroavermectin B_{1a} (H_2B_{1a}), was measured in tissues by HPLC with fluorescence detection. Clorsulon was measured in tissues and plasma by HPLC with ultraviolet detection.

Results:

Table 3. Summary of average tissue residue levels found for ivermectin (H_2B_{1a} ng/g)

Time post dose (days)	IS* inner	IS outer	Muscle	Liver	Kidney	Fat
3	3286	72.6	7.48	336	57.4	123
10	16,300	226	15.6	356	36.2	162
17	1180	11.6	6.74	183	20.2	88.3
28	455	< LOQ	< LOQ	64.1	7.46	42.3
45	< LOQ	< LOQ	< LOQ	11.4	< LOQ	6.46
52	1330	20.9	NA	34.4	< LOQ	11.8
60	< LOD	< LOQ	NA	15.1	< LOQ	< LOQ
70	< LOD	< LOD	NA	< LOD	< LOD	< LOD
80	< LOD	NA	NA	< LOQ	NA	< LOD
LOQ (ng/g)	5.12	5.12	5.12	5.12	5.12	5.12
LOD (ng/g)	0.99	0.99	0.99	0.99	0.99	0.99

NA - not assayed
*IS = injection site

Table 4. Summary of average tissue residue levels found for clorsulon (ng/g)

Time post dose (days)	IS inner	IS outer	Muscle	Liver	Kidney	Fat
3	745	141	139	390	1340	67.9
10	367	< LOQ	< LOD	< LOQ	116	< LOD
17	470	636	6.88	< LOQ	< LOQ	< LOD
28	35.5	< LOD	NA	NA	< LOQ	NA
45	< LOD	< LOD	NA	NA	NA	NA
52	< LOQ	NA	NA	NA	NA	NA
60	NA	NA	NA	NA	NA	NA
70	NA	NA	NA	NA	NA	NA
80	NA	NA	NA	NA	NA	NA
LOD (ng/g)	10	10	10	10	10	10
LOQ (ng/g)	15	15	15	50	100	25

NA - not assayed

2. Target Tissue and Marker Residue

The target tissue and marker residue for ivermectin residues remain as previously determined (21 CFR 556.344). The target tissue is liver and the marker residue is 22,23-dihydroavermectin $B1_a$.

The target tissue and marker residue for clorsulon residues in cattle remain as previously determined (21 CFR 556.163). The target tissue is kidney and the marker residue is parent clorsulon.

3. Tolerance(s)

Using a marker to total residue ratio of 53% for ivermectin residues in liver and a liver safe concentration of 3 ppm, a tolerance of 1.6 ppm is assigned for 22,23-dihydroavermectin $B1_a$ in cattle liver.

Using a marker to total residue ratio of 65% for muscle residues and a safe concentration of 1 ppm in muscle, a tolerance of 0.65 ppm is assigned for 22,23-dihydroavermectin $B1_a$ residues in cattle muscle.

Using a marker to total residue ratio of 65% for the injection site ivermectin residues and an injection site safe concentration of 30 ppm, a tolerance of 20 ppm is assigned for 22,23-dihydroavermectin $B1_a$ at the injection site.

The tolerance for clorsulon residues in kidney remains as previously determined (21 CFR 556.163). Tolerances for parent clorsulon in kidney and muscle are 1 ppm and 0.1 ppm, respectively.

4. Withdrawal Period and Milk Discard Time

Because ivermectin residues are more persistent, the withdrawal calculation is based on the ivermectin depletion data (section F.1.(c) above). The withdrawal period for IVOMEC Plus (ivermectin plus clorsulon) Injection for Cattle is 21 days.

G. Analytical Method for Residues

1. Description of Analytical Method

The FOI Summary for the original approval of NADA 128-409 dated February 13, 1984, contains the analytical method summaries for ivermectin residues in cattle.

2. Availability of the Method

The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to IVOMEC Plus Injection for Cattle:

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, to obtain an MSDS, or for assistance, contact Merial at 1-888-637-4251.

VI. 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. The data demonstrate that IVOMEC Plus Injection for Cattle, when used according to the label, is safe and effective for the treatment and control of internal parasites, including adult liver flukes, and external parasites. Additionally, data demonstrate that residues in food products derived from species treated with IVOMEC Plus Injection for Cattle will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

IVOMEC Plus Injection for Cattle, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the Federal Food, Drug, and Cosmetic Act.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.