Date of Approval: April 16, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-327

LONGRANGE

(eprinomectin)

Extended Release Injectable Parasiticide

Cattle on Pasture

For the treatment and control of *Bunostomum phlebotomum* (adults and L4s) and for the protection of cattle from reinfection with *Bunostomum phlebotomum* for 150 days following treatment.

Sponsored by:

Merial Ltd.

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I. GENERAL INFORMATION

A. File Number

NADA 141-327

B. Sponsor

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

Drug Labeler Code: 050604

C. Proprietary Name

LONGRANGE

D. Established Name

Eprinomectin

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

5% w/v eprinomectin
(50 mg eprinomectin per mL)

H. How Supplied

50 mL, 250 mL, and 500 mL rubber-capped glass bottles

I. Dispensing Status

Rx

J. Dosage Regimen

1 mg eprinomectin per kg body weight
(1 mL/110 lb body weight)

K. Route of Administration

Subcutaneous injection

L. Species/Class

Cattle/Pastured

M. Indication

For the treatment and control of *Bunostomum phlebotomum* (adults and L4s) and for the protection of cattle from reinfection with *Bunostomum phlebotomum* for 150 days following treatment.

N. Effect of Supplement

This supplement provides for the approval of a new indication for the treatment and control of *Bunostomum phlebotomum* (adults and L4s) and for the protection of cattle from reinfection with *Bunostomum phlebotomum* for 150 days following treatment.

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 NADA 141-327 dated September 26, 2011, contains dosage characterization information for species, dosage, or other applicable information.

B. Substantial Evidence for Treatment and Control Indication:

Five dose confirmation studies were performed, evaluating the 1 mg eprinomectin/kg body weight dose (1 mL/110 lb or 1 mL/50 kg) for the treatment and control of *Bunostomum phlebotomum* using artificially induced infections.

Studies were considered acceptable for providing substantial evidence of effectiveness if they had an adequate level of infection (at least 6 control animals with 50 *Bunostomum phlebotomum*), showed a statistically significant difference between the treated and control groups, and showed an efficacy > 90%.

Table 1: Summary of Five Dose Confirmation Studies Used to Demonstrate the Efficacy of LONGRANGE for the Treatment and control of *Bunostomum phlebotomum*.

Study #	Parasite Stage Evaluated	Study Location	# of Adequately Infected Control Animals (Actual Worm Counts)	% Efficacy
PR&D 0052002	Adult	Germany	8 (290, 360, 380, 530, 300, 580, 150, 370)	100%
PR&D 0052003	Adult	UK	6 (67, 123, 81, 22, 313, 161, 141, 20)	100%
PR&D 0052102	L_4	Germany	7 (170, 20, 210, 80, 90, 110, 50, 120)	100%
PR&D 0272301	L_4 & Adults	Germany	8 (600, 310, 40, 0, 270,370, 285, 575, 320, 350)	100%
PR&D 0272302	L_4 & Adults	US (MO)	7 (21, 161, 31, 201, 96, 159, 40, 76, 172, 149)	100%

The individual studies are summarized below.

1. Dose Confirmation Study PR&D 0052102

This study was previously published in the original Freedom of Information Summary dated September 26, 2011, to support the approval of other nematode species. Only *B. phlebotomum* is reported here.

a. Title: Effectiveness of a Single Subcutaneous Injection of Eprinomectin Long Acting Injection Solution Against Induced Infections of Fourth Stage Larvae of Internal Parasites in Cattle.

b. Investigator: S. Rehbein, Dr. med. vet. habil., DipEVPC, Merial GmbH, Kathrinenhof Research Center, Rohrdorf, Germany

c. Study Design:

1) Objective: To confirm the efficacy of eprinomectin extended release injection (ERI) when administered subcutaneously at 1.0 mg/kg bodyweight as an extended-release solution to cattle against induced infections of immature nematodes.

2) Study Animals: Sixteen male Braunvieh calves, approximately 5.5 months of age and weighing 109 to 159 kg, were ranked by decreasing body weights and allocated consecutively to eight replicates of two animals each. Animals within each replicate were randomly assigned to one of two treatment groups.

3) Treatment Groups: Eprinomectin ERI was the test article and vehicle containing no eprinomectin was the control article. The study used two treatment groups with eight animals per group. One group received the vehicle at 1 mL /110 lb or 1 mL/50 kg body weight. The second group received eprinomectin ERI at 1.0 mg/kg body weight (1 mL /110 lb or 1 mL/50 kg).

4) Drug Administration: Test and control articles were administered once on Day 0 by a single subcutaneous injection in the front of the shoulder.

5) Infection: Study animals were inoculated with approximately 1500 third stage larvae on Day -14 so that nematodes were fourth stage larvae (L_4) on Day 0. The age of the strain was three years.

6) Pertinent Measurements/Observations: All animals were necropsied at 21 or 22 days post-treatment. Nematodes recovered from animals at necropsy were counted.

d. Statistical Analysis: The Wilcoxon rank sum test was used to compare the distribution of speciated parasite counts for the treated group to that of the control group. All testing was two-sided at the significance level $\alpha=0.05$. Speciated parasite counts for each animal were transformed to the natural logarithm of (count + 1) for analysis and calculation of geometric means.

e. Results: The study had an adequate level of infection in the control animals. Seven of the eight control animals had worm counts of 50 or higher. Eprinomectin ERI had a 100% efficacy against *B. phlebotomum*.

f. Adverse Reactions: No adverse reactions were reported in the study.

g. Conclusions: This study demonstrates that eprinomectin ERI administered as a single subcutaneous injection at a dose of 1 mg eprinomectin/kg body weight (1 mL/ 110 lb [50 kg]) is effective for the treatment and control of L_4 *Bunostomum phlebotomum* in cattle.

2. Dose Confirmation Study PR&D 0052002

The Freedom of Information Summary for the original approval of NADA 141-327 dated September 26, 2011, contains the relevant information for this European study. Eprinomectin ERI demonstrated 100% efficacy against *B. phlebotomum* adults.

3. Dose Confirmation Study PR&D 0052003

This study was previously published in the original Freedom of Information Summary dated September 26, 2011, to support the approval of other nematode species. Only *B. phlebotomum* is reported here.

a. Title: Effectiveness of a Single Subcutaneous Injection of Eprinomectin Long-Acting Injection Solution Against Induced Infections of Adult Internal Parasites in Cattle.

b. Investigator: D.G. Baggott, PhD, BVSc, MRCVS, Merial, Highfield Research Centre, Hertford, Hertfordshire, UK

c. Study Design:

1) Objective: To confirm the efficacy of Eprinomectin ERI when administered subcutaneously at 1.0 mg/kg body weight as an extended-release solution to cattle against induced infections of adult nematodes.

2) Study Animals: Sixteen Limousin or Limousin cross calves, approximately four to seven months of age and weighing 129 to 153.5 kg, were ranked by decreasing body weights and allocated consecutively to eight replicates of two animals each. Animals within each replicate were randomly assigned to one of two treatment groups.

3) Treatment Groups: Eprinomectin ERI was the test article and vehicle containing no eprinomectin was the control article. The study used two treatment groups with eight animals per group. One group received the vehicle at 1 mL /110 lb or 1 mL/50 kg body weight. The second group received eprinomectin ERI at 1.0 mg/kg body weight (1 mL /110 lb or 1 mL/50 kg).

4) Drug Administration: Test and control articles were administered once on Day 0 by a single subcutaneous injection in the front of the shoulder.

5) Infection: Study animals were inoculated with approximately 1700 third stage larvae on Day -55. The age of the strain was 3.5 years.

6) Pertinent Measurements/Observations: All animals were necropsied at 14 or 15 days post-treatment. Nematodes recovered from animals at necropsy were counted.

d. Statistical Analysis: The Wilcoxon rank sum test was used to compare the distribution of speciated parasite counts for the treated group to that of the control group. All testing was two-sided at the significance level $\alpha=0.05$. Speciated parasite counts for each animal were transformed to the natural logarithm of (count + 1) for analysis and calculation of geometric means.

e. Results: The study had an adequate level of infection in the control animals. Six of the eight infected control animals had worm counts higher than 50. Eprinomectin ERI had a 100% efficacy against *B. phlebotomum*.

f. Adverse Reactions: No adverse reactions were reported in the study.

g. Conclusions: This study demonstrates that eprinomectin ERI administered as a single subcutaneous injection at a dose of 1 mg eprinomectin/kg body weight (1 mL/ 110 lb [50 kg]) is effective for the treatment and control of adult *Bunostomum phlebotomum* in cattle.

4. Dose Confirmation Study PR&D 0272301

a. Title: Efficacy of a Single Treatment with eprinomectin (5% w/v) Extended-Release Injection (1 mg Eprinomectin/kg) Administered Once Subcutaneously Against Fourth-Stage Larval and Adult *Bunostomum phlebotomum* in Cattle Following Induced Infection.

b. Investigator: Martin Visser, Biologist, Merial GmbH, Kathrinenhof Research Center, Rohrdorf, Germany

c. Study Design:

1) Objective: To confirm the efficacy against fourth-stage larval and adult *Bunostomum phlebotomum* in cattle following induced infections of Eprinomectin (5% w/v) extended-release injection when administered as a single subcutaneous dose (1 mg eprinomectin/kg).

2) Study Animals: Thirty, male intact, Fleckvieh (German Simmental) aged approximately five to eight months and weighing 144.5 to 190.0 kg. Animals were ranked by decreasing pre-treatment body weight and allocated consecutively to ten blocks of three animals each. Within blocks, the cattle were randomly allocated to one of three treatment groups.

3) Treatment Groups:

Table 2: Treatment Groups Used in Dose Confirmation Study PR&D 0272301

Treatment Group	IP	Route	Treatment Day	Total # of Animal
1	Saline (control)	SQ	0	10
2	Eprinomectin (5% w/v) ERI	SQ	0	10
3	Eprinomectin (5% w/v) ERI	SQ	42	10

4) Drug Administration: Eprinomectin ERI was the test article and 0.9% Normal Saline Solution was the control article. Test and control articles were administered once on Day 0 (Treatment Groups 1 and 2) and Day 42 (Treatment Group 3) by a single subcutaneous injection in the front of the shoulder 1 mL /110 lb or 1 mL/50 kg body weight. The dose of eprinomectin provided 1.0 mg eprinomectin/kg body weight.

5) Infection: Study animals were inoculated with approximately 1800 third stage larvae on Day -15 so that nematodes were fourth stage larvae (L_4) on Day 0 (Group 2) and adults by Day 42 (Group 3). The age of the strain was seven years.

6) Pertinent Measurements/Observations: All animals were necropsied on Study Day 56. Nematodes recovered from animals at necropsy were counted.

d. Statistical Analysis: The mixed procedure in SAS was used for the analysis of log-transformed parasite counts, with the treatment groups listed as a fixed effect, and the allocation blocks listed as a random effect. All testing was two-sided at the significance level $\alpha=0.05$.

e. Results: The study had an adequate level of infection in the control animals. Eight of the ten control animals had worm counts higher than 50.

The percent efficacy for Treatment Group 2 (Eprinomectin ERI treatment on Day 0) was 100% and there were significantly lower *B. phlebotomum* counts compared to the control group. The percent efficacy for Treatment Group 3 (Eprinomectin ERI on Day 42) was 100%.

f. Adverse Reactions: No adverse reactions were reported in the study.

g. Conclusions: This study demonstrates that eprinomectin ERI administered as a single subcutaneous injection at a dose of 1 mg eprinomectin/kg body weight (1 mL/ 110 lb [50 kg]) is effective for the treatment and control of L_4 and adult *Bunostomum phlebotomum* in cattle.

5. Dose Confirmation Study PR&D 0272302

a. Title: Efficacy of a Single Treatment with Eprinomectin (5% w/v) Extended-Release Injection (1 mg Eprinomectin/kg) Administered Once Subcutaneously Against Fourth-Stage Larval and Adult *Bunostomum phlebotomum* in Cattle Following Induced Infection.

b. Investigator: Bruce Kunkle, DVM, PhD; Senior Veterinary Scientist II/Investigator; Merial Limited, Missouri Research Center, Fulton, MO

c. Study Design:

1) Objective: To confirm the efficacy against fourth-stage larval and adult *Bunostomum phlebotomum* in cattle following induced infections of eprinomectin (5% w/v) extended-release injection when administered as a single subcutaneous dose (1 mg eprinomectin/kg).

2) Study Animals: Thirty, male intact, Holstein cattle aged approximately three to four months and weighing 67 to 136 kg. Animals were ranked by decreasing pre-treatment body weight and allocated consecutively to ten blocks of three animals each. Within blocks, the cattle were randomly allocated to one of three treatment groups.

3) Treatment Groups:

Table 3: Treatment Groups Used in Dose Confirmation Study PR&D 0272302

Treatment Group	IVP	Route	Treatment Day	Total # of Animal
1	Saline (control)	SQ	0	10
2	Eprinomectin (5% w/v) ERI	SQ	0	10
3	Eprinomectin (5% w/v) ERI	SQ	42	10

4) Drug Administration: Eprinomectin ERI was the test article and 0.9% Normal Saline Solution was the control article. Test and control articles were administered once on Day 0 by a single subcutaneous injection in the front of the shoulder at a dose of 1 mL /110 lb or 1 mL/50 kg body weight. The dose of eprinomectin provided 1.0 mg eprinomectin/kg body weight.

5) Infection: Study animals were inoculated with approximately 4000 third stage larvae on Day -15 so that nematodes were fourth stage larvae (L_4) on Day 0 (Group 2) and adults by Day 42 (Group 3). The age of the strain was two to four weeks old.

6) Measurements and Observations: All animals were necropsied on Study Day 56 or 57. Nematodes recovered from animals at necropsy were counted.

d. Statistical Analysis: The mixed procedure in SAS was used for the analysis of log-transformed parasite counts, with the treatment groups listed as a fixed effect, and the allocation blocks listed as a random effect. All testing was two-sided at the significance level $\alpha=0.05$.

e. Results: The study had an adequate level of infection in the control animals. Seven of the ten control animals had worm counts higher than 50. Efficacy was 100% in cattle in Treatment Group 2. Efficacy was 100% in cattle in Treatment Group 3.

f. Adverse Reactions: No adverse reactions were reported during the study.

g. Conclusions: This study demonstrates that eprinomectin ERI administered as a single subcutaneous injection at a dose of 1 mg/kg body weight (1 mL/110 lb [50 kg]) is effective for the treatment and control of L_4 and adult *Bunostomum phlebotomum* in cattle.

C. Substantial Evidence for Persistent Activity:

Two dose confirmation studies were performed to evaluate eprinomectin ERI at a 1 mg eprinomectin/kg body weight dose (1 mL /110 lb or 1 mL/50 kg) against artificially induced infections of *B. phlebotomum*. One study was conducted in Europe and the other was conducted in the United States.

The studies demonstrating effectiveness for this indication are summarized below.

1. Dose Confirmation Study PR&D 0135301

The Freedom of Information Summary for the original approval of NADA 141-327 dated September 26, 2011, contains the relevant information for this European study. Eprinomectin ERI demonstrated 95.6% efficacy against *B. phlebotomum* at 150 days post-treatment.

2. Dose Confirmation Study PR&D 0272701

a. Title: A Study to Evaluate the Persistent Efficacy of a Single Treatment with Eprinomectin (5% w/v) Extended-Release Injection (1 mg Eprinomectin/kg) Administered Once Subcutaneously Against an Induced Infection of *Bunostomum phlebotomum* in Cattle.

b. Investigator(s): Bruce Kunkle, DVM, PhD, Merial Limited, Missouri Research Center (MRC); Fulton, MO

c. Study Design:

1) Objective: : To confirm the persistent efficacy of Eprinomectin (5% w/v) extended-release injection when administered as a single subcutaneous dose (1 mg eprinomectin/kg) against induced infections of *Bunostomum phlebotomum* at 150 days post-treatment in cattle.

2) Study Animals: Twenty-four, male castrate, Holstein calves aged three to four months and weighing 109 to 130 kg. Animals were ranked based on decreasing pre-treatment body weight and allocated consecutively to blocks of two animals. Within blocks, cattle were randomly allocated to one of the two treatment groups.

3) Treatment Groups:

Table 4: Treatment Groups Used in Dose Confirmation Study PR&D 0272701

Treatment Group	IVP	Route	Treatment Day	Total # of Animal
1	Saline (0.9%; control)	SQ	0	12
2	Eprinomectin (5% w/v) ERI	SQ	0	12

4) Drug Administration: Eprinomectin ERI was the test article and 0.9% Normal Saline Solution was the control article. Test and control articles were administered once on Day 0 by a single subcutaneous injection in the front of the shoulder at a dose volume of 1 mL /110 lb or 1 mL/50 kg body weight. The dose of eprinomectin provided 1.0 mg eprinomectin/kg body weight.

5) Infection: Study animals were inoculated with approximately

4000 third stage larvae on Day 150 with an aliquot of infective (third stage) larvae. The age of the strain was less than seven years old.

6) Measurements and Observations: All animals were necropsied at 182 or 183 days post-treatment. Nematodes recovered from animals at necropsy were counted.

d. Statistical Analysis: The mixed procedure in SAS was used for the analysis of log-transformed parasite counts, with the treatment groups listed as a fixed effect, and the allocation blocks listed as a random effect. All testing was two-sided at the significance level $\alpha=0.05$.

e. Results: The study had an adequate level of infection in the control animals. Eleven of the twelve control animals had worm counts higher than 50. Geometric mean efficacy for eprinomectin ERI against *B. phlebotomum* at was 99.8%.

f. Adverse Reactions: No adverse reactions were observed during this study.

g. Conclusions: This study demonstrates that eprinomectin ERI administered as a single subcutaneous injection at a dose of 1 mg/kg body weight (1 mL/ 110 lb [50 kg]) is effective to protect cattle from reinfection of *Bunostomum phlebotomum* for 150 days .

D. Clinical Field Studies

Three studies (PR&D 0011504, PR&D 0011505, and PR&D 0011509) were conducted under field conditions to confirm the effectiveness of eprinomectin ERI against naturally-acquired nematode infections that included *Bunostomum phlebotomum*. The Freedom of Information Summary for the original approval of NADA 141-327 dated September 26, 2011, contains the relevant information for these studies.

III. TARGET ANIMAL SAFETY:

Target animal safety studies were not required for this supplemental approval. The FOI Summary for the original approval of NADA 141-327 dated September 26, 2011, contains a summary of target animal safety studies for species, dosage, or other applicable information.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

The Agency carefully reviewed information submitted by the sponsor regarding the development of antimicrobial resistance following use of eprinomectin among bacteria of public health concern in or on treated cattle. Based on available information, the Agency concludes that it is unlikely that the use of eprinomectin

in cattle would cause a microbial food safety hazard with respect to antimicrobial resistance development among bacteria of public health concern at this time.

B. Impact of Residues on Human Intestinal Flora:

The Agency carefully reviewed information submitted by the sponsor regarding the impact of residues or metabolites of eprinomectin in the edible tissues of cattle on human intestinal flora. Based on available information, the Agency determined that an assessment of the impact of residues or metabolites of eprinomectin in the edible tissues of cattle on human intestinal flora was not necessary at this time.

C. Toxicology:

Reassessment of the toxicological Acceptable Daily Intake (ADI) or Acceptable Single-Dose Intake (ASDI) for the active ingredient, eprinomectin, was not needed for this supplemental approval. The FOI Summaries for the original approval of NADA 141-079 dated April 16, 1997, a supplemental approval dated August 9, 1998, and the original approval of NADA 141-327, dated September 26, 2011, contain summaries of all toxicology studies and information for eprinomectin.

Reassessment of the S_o for the excipient, N-methyl-2-pyrrolidone (NMP), was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-327 dated September 26, 2011, contains a summary of all toxicology studies and information for NMP.

D. Assignment of the Final Acceptable Daily Intake, Acceptable Single-Dose Intake, and S_o:

The final ADI for eprinomectin is the toxicological ADI of 0.01 mg/kg bw/day derived from the 53-week oral toxicity study in dogs. The ASDI for eprinomectin is 0.8 mg/kg bw derived from an acute oral toxicity study in rats. The codified ADI is listed under 21 CFR 556.227.

The S_o, the concentration of NMP residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to the human consumer, is 67 ppm.

E. Safe Concentrations and S_m for Total Residues:

The safe concentrations of total eprinomectin residues in each edible tissue of cattle are 1.92 ppm for muscle, 5.76 ppm for liver, 11.52 ppm for kidney, 11.52 ppm for fat, and 160 ppm for the injection sites.

The S_m, the concentration of NMP residue of carcinogenic concern in each edible tissue of cattle corresponding to no significant increase in the risk of cancer to the human consumer, is 334 ppm for muscle, 1002 ppm for liver, 2004 ppm for kidney, and 2004 ppm for fat.

F. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-327 dated September 26, 2011, contains a summary of residue chemistry studies for cattle.

G. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-327 dated September 26, 2011, contains the analytical method summaries for eprinomectin and N-methyl-2-pyrrolidone in cattle.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to LONGRANGE:

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.

No special handling or protective clothing is necessary.

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 LONGRANGE, when used according to the label, is safe and effective for the treatment and control of *Bunostomum phlebotomum* (adults and L4s) and for the protection of cattle from reinfection with *Bunostomum phlebotomum* for 150 days following treatment. Additionally, data demonstrate that residues in food products derived from species treated with LONGRANGE will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because a proper diagnosis of the parasites present in a herd of animals and the follow-up required to ensure the drug maintains effectiveness is important for the safe and effective use of this product. A veterinarian is trained in the parasitological procedures necessary for safe and effective use of this product.

B. Exclusivity:

This supplemental approval for LONGRANGE qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental approval included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the new claim that is approved in this supplemental application.

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.