Date of Approval: September 9, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-553

VALCOR™

doramectin and levamisole injection

Cattle: Beef cattle two months of age and older and in replacement dairy heifers less than 20 months of age. Not for use in beef bulls intended for breeding over 1 year of age, dairy calves, and veal calves.

For the treatment and control of gastrointestinal roundworms (adults and fourth stage larvae) - *Ostertagia ostertagi* (including inhibited larvae), *O. lyrata*, *Haemonchus placei*, *Trichostrongylus axei*, *T. colubriformis*, *T. longispicularis*[*] *Cooperia oncophora*, *C. pectinata*[*], *C. punctata*, *C. surnabada*, *Bunostomum phlebotomum*[*], *Strongyloides papillosus*[*], *Oesophagostomum radiatum*, *Trichuris* spp.[*], and *Nematodirus helvetianus*[*]; lungworms (adults and fourth stage larvae) - *Dictyocaulus viviparus*; eyeworms (adults) - *Thelazia* spp.; grubs (parasitic stages) - *Hypoderma bovis* and *H. lineatum*; sucking lice - *Haematopinus eurysternus*, *Linognathus vituli*, and *Solenopotes capillatus*; mange mites - *Psoroptes bovis* and *Sarcoptes scabiei.*

[*]adults only

Sponsored by:

Zoetis Inc.

Executive Summary

VALCOR™ (doramectin and levamisole injection) is approved for the treatment and control of various gastrointestinal roundworms (adult and fourth stage larvae), lungworms, eyeworms, grubs, sucking lice, and mange mites in beef cattle two months of age and older and in replacement dairy heifers less than 20 months of age. The drug is not for use in beef bulls intended for breeding over one year of age, dairy calves, or veal calves.

Roundworms, lungworms, and eyeworms are internal parasites collectively called nematodes. Grubs, sucking lice, and mange mites are external parasites collectively called ectoparasites.

VALCOR™ is a combination antiparasitic drug containing two active ingredients that are already approved as single active ingredients in other antiparasitic drugs for cattle: doramectin (DECTOMAX® [doramectin injection], approved under NADA 141-061) and levamisole (TRAMISOL® [levamisole phosphate], approved under NADA 102-437). DECTOMAX® and TRAMISOL® have almost completely overlapping nematode indications, and Zoetis Inc. is also the sponsor of both drugs. TRAMISOL® has no ectoparasite indications while DECTOMAX® does. VALCOR™ is approved for all the same nematode and ectoparasite indications as DECTOMAX® with the addition of *Nematodirus helvetianus.*

Doramectin is a parasiticide belonging to the macrocyclic lactone class. It is effective against both internal and external parasites by causing paralysis of the parasites' pharyngeal pump, which affects nutrient ingestion so that the parasites starve. Levamisole is a parasiticide belonging to the imidazothiazole class. It is effective against internal parasites by blocking the transmission of signals from nerves to muscles at neuromuscular junctions in the parasites, resulting in their paralysis and allowing cattle to naturally expel the parasites in their feces.

VALCOR™ is only available by prescription. A veterinarian's expertise is required to diagnose parasites in the animal and to ensure that the antiparasitic drug is effective against the parasites present.

Safety and Effectiveness

Effectiveness
The sponsor conducted effectiveness studies to demonstrate that VALCOR™ is effective for all labeled indications and that each active ingredient contributes to the effectiveness of the combination antiparasitic drug.

VALCOR™ contains the same dose of doramectin and levamisole as DECTOMAX® and TRAMISOL®, respectively, and all three drugs have the same route of administration. The sponsor had access to the effectiveness data from the original approvals of DECTOMAX® and TRAMISOL® ; therefore, instead of showing that VALCOR™ is effective against each nematode and ectoparasite species listed in the labeled indications, the sponsor demonstrated effectiveness only for the dose-limiting nematode and ectoparasite species for DECTOMAX® and for *N. helvetianus*. A dose-

limiting parasite is the parasite that requires the highest dose of an antiparasitic drug to achieve the established minimum effectiveness, generally 90%.

The sponsor established that *Cooperia oncophora* was the dose-limiting nematode for DECTOMAX®. The sponsor was unable to confirm which ectoparasite was dose-limiting for DECTOMAX®. However, FDA determined it was acceptable for the sponsor to use the sucking louse *Linognathus vituli* as the representative ectoparasite for DECTOMAX® because *L. vituli* is the most prevalent louse species in the United States that infests cattle and its infestations are more intense than other lice infestations, typically with greater lice numbers per animal.

The sponsor used scientific literature about the mode of action and effectiveness of levamisole to show that the drug is not effective against ectoparasites. Therefore, it was not necessary for the sponsor to establish a dose-limiting ectoparasite for TRAMISOL®. In addition, because all the nematode indications that TRAMISOL® brings to the indications for VALCOR™ are already approved for DECTOMAX® (except for *Nematodirus* spp.), it was not necessary for the sponsor to establish a dose-limiting nematode for TRAMISOL®.

To demonstrate the effectiveness of VALCOR™ for all labeled indications, the sponsor conducted:

- Two dose confirmation studies showing that the combination antiparasitic drug is 99 to 100% effective against natural infections of *C. oncophora* in cattle. Because VALCOR™ is effective against the dose-limiting nematode for DECTOMAX®, FDA concluded that it is also effective against all other nematodes listed in the labeled indications for DECTOMAX®.
- Two dose confirmation studies showing that the combination antiparasitic drug is 99 to 100% effective against natural infestations of *L. vituli* in cattle. Because VALCOR™ is effective against the representative ectoparasite for DECTOMAX®, FDA concluded that the drug is also effective against all other ectoparasites listed in the labeled indications for DECTOMAX®.
- Three dose confirmation studies showing that the combination antiparasitic drug is 99 to 100% effective against adult *N. helvetianus*. In one study, the cattle were artificially infected, and in the other two studies, they were naturally infected.
- A six-site field study showing that the combination antiparasitic drug is 99 to 100% effective against a variety of nematodes in naturally infected cattle.

Also based on the above studies, the sponsor showed that doramectin contributes to the effectiveness of VALCOR™ by providing activity against ectoparasites, which levamisole does not. The sponsor demonstrated that levamisole contributes to the effectiveness of VALCOR™ by providing 99 to 100% effectiveness against adult *N. helvetianus* while doramectin was demonstrated to not be effective against this nematode.

Target Animal Safety
The sponsor conducted a safety study in three-month-old male and female dairy calves. The calves were administered VALCOR™ subcutaneously at 0X, 1X, 2X, or 3X the labeled dose every 14 days for a total of 3 injections (3X the labeled duration).

The drug caused injection site reactions and hypersalivation that were dose-dependent but resolved without treatment.

The sponsor also conducted two female reproductive safety studies. In the first study, beef heifers were administered VALCOR™ subcutaneously at 0X or 3X the labeled dose either during folliculogenesis (when the ovarian follicle is maturing) before artificial insemination or on Day 18 or 25 after artificial insemination during the early first trimester of pregnancy. In the second study, beef heifers were administered VALCOR™ subcutaneously at 0X or 3X the labeled dose at Day 43 or Day 223 after artificial insemination during either the late first trimester or the third trimester of pregnancy. In both studies, there were no clinically significant effects on conception rate, calving rate, abortion rate, stillbirth rate, or calf weights at birth and 30 days of age.

The sponsor did not conduct safety or effectiveness studies in beef calves less than two months of age, dairy calves, and veal calves; in dairy cows; or in bulls over one year of age intended for breeding. Therefore, the labeling states that VALCOR™ is not for use in these classes of animals.

Human Food Safety
FDA conducted an assessment to ensure that residues of doramectin and levamisole in the edible tissues of treated cattle do not cause safety concerns for food for human consumption. This human food safety assessment considered microbial food safety, toxicology, and residue chemistry.

For microbial food safety, FDA reviewed information submitted by the sponsor and also information that was publicly available regarding the impact of VALCOR™ on antimicrobial resistance among bacteria of public health concern in or on treated animals. Because FDA found that VALCOR™ does not exert selection pressure for the development of resistant bacteria, is not used to treat gastroenteritis or other bacterial diseases in people, is not being developed to treat a bacterial disease in people, and is not used to treat a bacterial disease in food-producing animals, the agency determined that a microbial food safety assessment was not required for VALCOR™.

The acceptable daily intake (ADI) is the quantity of drug residues in the human diet that will not cause harm to people even if they consume that amount every day. FDA previously established the ADI for total residue of doramectin as 0.75 µg/kg of body weight per day and the safe concentrations in individual edible tissues of cattle as 150 µg/kg [parts per billion (ppb)] for muscle, 450 ppb for liver, 900 ppb for kidney, and 900 ppb for fat. FDA determined it was not necessary to reassess the ADI and safe concentrations for total residue of doramectin. FDA previously determined it was not necessary to establish an ADI for total residue of levamisole.

Neurotoxicity studies evaluate a drug's toxicity to the central nervous system. After reviewing data from three acute neurotoxicity studies in rats, FDA established the acute reference dose (ARfD) for doramectin as 66 µg/kg of body weight and the injection site safe concentration as 13.2 parts per million (ppm). The ARfD is the highest oral dose of drug residues that will not cause harm to a person if he or she ingests that entire amount in a single day.

For the original approval of DECTOMAX®, FDA determined that the marker residue for doramectin is doramectin and the target tissue is liver. For the original approval of TRAMISOL®, FDA determined that the marker residue for levamisole is levamisole and didn't assign a target tissue. The marker residue is a subset of the total drug residue, and the concentration of the marker residue is in a known relationship to the concentration of the total residue in the target tissue. The target tissue is the edible tissue selected to monitor for residues and is the last tissue where the total residue depletes to its safe concentration.

The sponsor conducted a residue depletion study to measure the concentrations of the marker residues, doramectin and levamisole, in edible tissues of cattle at various timepoints after a single subcutaneous injection of VALCOR™. FDA used the information from the residue depletion study and the toxicology studies, in combination with the ADI and safe concentrations, to establish a tolerance of 300 ppb for doramectin in cattle liver, 30 ppb for doramectin in cattle muscle, and 100 ppb for levamisole in cattle liver, kidney, muscle, and fat. FDA assigned a withdrawal period of 15 days for cattle treated with VALCOR™. The tolerance is the highest concentration of the marker residue that can legally remain in an edible tissue of a treated animal. When the marker residue is at or below the tolerance in the target tissue, the total drug residues in all edible tissues should be at or below their respective (individual) safe concentrations. The withdrawal period allows the marker residue in the target tissue to get to a level that is at or below the target tissue tolerance.

FDA evaluated the validated analytical methods for detecting residues of doramectin and levamisole for the original approvals of DECTOMAX® and TRAMISOL®, respectively, and found them acceptable.

Conclusions
Based on the data submitted by the sponsor for the approval of VALCOR™, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-553

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

VALCOR™

D. Drug Product Established Name

doramectin and levamisole injection

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

5 mg/mL doramectin and 150 mg/mL levamisole hydrochloride

H. How Supplied

100 mL, 250 mL, and 500 mL multiple dose bottles

I. Dispensing Status

Rx

J. Dosage Regimen

Inject subcutaneously as a single dose at a dosage of 0.2 mg doramectin and 6 mg of levamisole hydrochloride per kg of body weight.

K. Route of Administration

Subcutaneous

L. Species/Class

Cattle: beef cattle two months of age and older and in replacement dairy heifers less than 20 months of age. Not for use in beef bulls intended for breeding over 1 year of age, dairy calves, and veal calves.

M. Indication

For the treatment and control of gastrointestinal roundworms (adults and fourth stage larvae) - *Ostertagia ostertagi* (including inhibited larvae), *O. lyrata*, *Haemonchus placei*, *Trichostrongylus axei*, *T. colubriformis*, *T. longispicularis*[*], *Cooperia oncophora*, *C. pectinata*[*], *C. punctata*, *C. surnabada*, *Bunostomum phlebotomum*[*], *Strongyloides papillosus*[*], *Oesophagostomum radiatum*, *Trichuris* spp.[*], and *Nematodirus helvetianus*[*]; lungworms (adults and fourth stage larvae) - *Dictyocaulus viviparus*; eyeworms (adults) - *Thelazia* spp.; grubs (parasitic stages) - *Hypoderma bovis* and *H. lineatum*; sucking lice - *Haematopinus eurysternus*, *Linognathus vituli*, and *Solenopotes capillatus*; mange mites - *Psoroptes bovis* and *Sarcoptes scabiei.*

[*]adults only

II. EFFECTIVENESS

A. Dosage Characterization

Levamisole: The effectiveness of levamisole phosphate for the treatment of cattle infected with the nematodes *Haemonchus*, *Ostertagia*, *Trichostrongylus*, *Cooperia*, *Nematodirus*, *Bunostomum*, *Oesophagostomum*, *Chabertia,* and *Dictyocaulus,* was provided under the original approval of Tramisol® levamisole phosphate Injectable Solution, 13.65% under NADA 102-437 on May 12, 1978.

Doramectin: The effectiveness of doramectin for the treatment of cattle infected with the parasites Gastrointestinal roundworms (adults and fourth-stage larvae) - *Ostertagia ostertagi* (including inhibited larvae)*, O. lyrata, Haemonchus placei, Trichostrongylus axei, T. colubriformis,* adult *T. longispicularis, Cooperia oncophora,* adult *C. pectinata, C. punctata, C. surnabada,* adult *Bunostomum phlebotomum,* adult *Strongyloides papillosus, Oesophagostomum radiatum,* and adult *Trichuris* spp.; Lungworms (adults and fourth-stage larvae) - *Dictyocaulus viviparus*; Eyeworms (adults) –*Thelazia* spp.; Grubs (parasitic stages) - *Hypoderma bovis and H. lineatum;* Sucking lice - *Haematopinus eurysternus, Linognathus vituli,* and *Solenopotes capillatus*; and Mange mites - *Psoroptes bovis* and *Sarcoptes scabiei,* was provided with the original approval of Dectomax® Injectable Solution under NADA 141-061 on July 30, 1996.

Collectively, the dosage characterization data previously accepted for levamisole phosphate under NADA 102-437 and doramectin under NADA 141-061 provide the basis for the doses used in the final formulation demonstrating the effectiveness of VALCOR™.

B. Substantial Evidence

Three dose confirmation studies and one clinical field study were conducted to evaluate the effectiveness of VALCOR™ against gastrointestinal nematodes. Two studies were conducted to evaluate the effectiveness of VALCOR™ against sucking lice.

1. Dose Confirmation Study

Title: "Efficacy of a Doramectin Injectable Formulation and a Doramectin Levamisole Fixed-Dose Injectable Co-Formulation Against Artificially Infected Adult Stage *Nematodirus helvetianus* in Cattle." (Study No. A131C-US-17-530)

Study Dates: October 11, 2017, to August 10, 2018

Study Location: Richland, Michigan, United States

Study Design:

Objective: To compare the effectiveness of Dectomax®, a doramectin injectable formulation and VALCOR™, a doramectin and levamisole hydrochloride fixed-dose combination injectable to saline-treated controls against an artificially established patent infection of adult *Nematodirus helvetianus*. This study was conducted in accordance with Good Clinical Practice guidelines.

Study Animals: Twenty-four Holstein steers approximately nine weeks old at inoculation were used.

Experimental Design: Calves with ≥ five eggs per gram of feces prior to Day 0 were blocked by body weight and randomized to treatment according to a completely randomized block design to one of three treatment groups:

Table IIB.1. Treatment Groups

Treatment Group	Test Article	Number of Animals	Treatment Day
1	Saline (control)	8	0
2	Dectomax® (0.2 mg/kg doramectin)	8	0
3	VALCOR™ (0.2 mg/kg doramectin and 6.0 mg/kg levamisole)	8	0

Drug Administration: Saline was the control article for Group 1. Dectomax® was administered to Group 2 at a dose of 0.2 mg/kg body weight (bw). VALCOR™ was administered to Group 3 at a dose of 0.04 mL/kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg of body weight (1 mL/25 kg body weight). All test and controls articles were administered once on Day 0 by a single subcutaneous injection in front of the shoulder.

Infection: Study animals were inoculated with third-stage larvae as outlined in Table IIB.2.

Table IIB.2. Parasite Details

Species	Approximate number of infective larvae	Days of Inoculation	Approximate age of strain
Nematodirus helvetianus	14,850 total; 4,950 daily over three days	33 to 35 days prior to Day 0	2 years

Measurements and Observations: Prior to treatment on Day 0 and again 14 days after treatment, fecal samples were collected from each animal and a fecal egg count reduction test was conducted. All animals were necropsied on Day 14. Based on morphological characteristics, nematodes were identified to species and stage. The number of each species/stage was counted. General health observations were conducted daily.

Statistical Method: The primary assessment of effectiveness was the post-treatment *N. helvetianus* adult worm count on Day 14. Efficacy was calculated using the formula: [(C-T)/C] x 100, where C = geometric mean of worm counts for the saline-treated group and T = geometric mean of worm counts for the Dectomax® and the VALCOR™-treated groups independently. A general linear mixed model was used to analyze the natural log-transformed counts + 1 with treatment group as a fixed effect and block and error as random effects.

Pre-treatment (Day -7) versus post-treatment (Day 14) fecal egg counts from each group were evaluated using the fecal egg count reduction test (FECRT) formula: FECRT = 100 x [(pre-treatment arithmetic mean – post-treatment arithmetic mean)/(pre-treatment arithmetic mean)].

Results:

Table IIB.3. Geometric Mean Worm Counts on Day 14, Treated Compared to Control Group

Treatment	Number of Animals	Geometric Mean Worm Counts	% Efficacy
Saline	8	2983.9	N/A
Dectomax®	8	2837.4	4.9%
VALCOR™	8	0	100%

Table IIB.4. Fecal Egg Count Reduction Test (FECRT) Results Using Arithmetic Mean Fecal Egg Counts from Day -7 and Day 14

Treatment	Day -7 Arithmetic Mean	Day 14 Arithmetic Mean	% Fecal Egg Count Reduction
Saline	49.5	77.8	-56.94%
Dectomax®	47.4	40.0	15.66%
VALCOR™	55.0	0	100%

Adverse Reactions: One VALCOR™-treated animal was observed with injection site swelling on Day 7. This swelling resolved by Day 12.

Conclusions: This study demonstrates that VALCOR™ administered as a single subcutaneous injection at a dose of 1 mL/25 kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg body weight is effective for the treatment and control of adult *Nematodirus helvetianus* in cattle and demonstrates doramectin is not effective for the treatment and control of *N. helvetianus*, thus establishing the contribution of levamisole hydrochloride to the combination.

2. **Dose Confirmation Study**

Title: "Efficacy of a Doramectin Injectable Formulation and a Doramectin Levamisole Fixed-Dose Injectable Co-Formulation Against Naturally Acquired Adult Stage *Nematodirus helvetianus* and *Cooperia oncophora* in Cattle." (Study No. A131C-US-17-538)

Study Dates: November 30, 2017, to November 6, 2018

Study Location: Richland, Michigan, United States

Study Design:

Objective: To compare the effectiveness of Dectomax®, a doramectin injectable formulation and VALCOR™, a doramectin and levamisole fixed-dose combination injectable to saline-treated controls against naturally established infections of adult *Nematodirus helvetianus* and adult *Cooperia oncophora*. This study was conducted in accordance with Good Clinical Practice guidelines.

Study Animals: Thirty-six beef and dairy crossbred cattle approximately four to ten months of age were used.

Experimental Design: Cattle confirmed with patent infections of *N. helvetianus* and with positive cultures of *C. oncophora* prior to Day 0 were blocked by body weight and randomized to treatment according to a completely randomized block design to one of three treatment groups:

Table IIB.5. Treatment Groups

Treatment Group	Test Article	Number of Animals	Treatment Day
1	Saline (control)	12 (males)	0
2	Dectomax® (0.2 mg/kg doramectin)	12 (10 males, 2 females)	0
3	VALCOR™ (0.2 mg/kg doramectin and 6.0 mg/kg levamisole)	12 (10 males, 2 females)	0

Drug Administration: Saline was the control article for Group 1. Dectomax® was administered to Group 2 at a dose of 0.2 mg/kg body weight. VALCOR™ was administered to Group 3 at a dose of 0.04 mL/kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg of body weight (1 mL/25 kg body weight). All test and control articles were administered once on Day 0 by a single subcutaneous injection in front of the shoulder.

Measurements and Observations: Three days prior to treatment on Day 0 and again 14 days after treatment, fecal samples were collected from each animal and a fecal egg count reduction test and coproculture were conducted. All animals were necropsied on Day 14. Based on morphological characteristics, nematodes were identified to species and stage. The number of each species/stage was counted. General health observations were conducted daily.

Statistical Method: The primary assessment of effectiveness was the post-treatment adult *N. helvetianus* and adult *C. oncophora* worm counts on Day 14. Efficacy was calculated using the formula: [(C-T)/C] x 100, where C = geometric mean of worm counts for the saline-treated group and T = geometric mean of worm counts for the Dectomax® and the VALCOR™-treated groups independently. A general linear mixed model was used to analyze the natural log-transformed counts + 1 with treatment group as a fixed effect and block and error as random effects.

Pre-treatment (Day -3) versus post-treatment (Day 14) fecal egg counts from each group were evaluated using the fecal egg count reduction test (FECRT) formula: FECRT = 100 x [(pre-treatment arithmetic mean – post-treatment arithmetic mean)/(pre-treatment arithmetic mean)].

Results:

Table IIB.6. Geometric Mean Worm Counts and % Efficacy on Day 14, Treated Compared to Control Group

Treatment	Number of Animals	Geometric Mean *N. helvetianus* Worm Counts	Geometric Mean *C. oncophora* Worm Counts	% Efficacy for *N. helvetianus*	% Efficacy for *C. oncophora*
Saline	12	695.5	1014.1	N/A	N/A
Dectomax®	12	84.0	6.1	87.9%	99.4%
VALCOR™	12	0.0	0.0	100%	100%

Table IIB.7. Fecal Egg Count Reduction Test (FECRT) Results Using Arithmetic Mean Fecal Egg Counts from Day -3 and Day 14

Treatment	Day -3 Arithmetic Mean	Day 14 Arithmetic Mean	% Fecal Egg Count Reduction
Saline	226.6	196.0	13.53%
Dectomax®	162.5	8.1	94.99%
VALCOR™	137.1	0	100%

Adverse Reactions: Nine VALCOR™-treated animals were observed with injection site swellings beginning on Day 5. Swellings in four animals had not resolved by Day 14.

Conclusions: This study demonstrates that VALCOR™ administered as a single subcutaneous injection at a dose of 1 mL/25 kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg body weight is effective for the treatment and control of adult *Nematodirus helvetianus* in cattle and demonstrates doramectin is not effective for the treatment and control of *N. helvetianus*, thus establishing the contribution of levamisole hydrochloride to the combination. This study also demonstrates that VALCOR™ is effective for the treatment and control of adult *Cooperia oncophora* in cattle. This parasite is the dose-limiting parasite of doramectin and this demonstration of effectiveness allows the granting of indications to all the remaining nematodes on the doramectin injectable solution label to VALCOR™.

3. **Dose Confirmation Study**

Title: "Efficacy of a Doramectin Injectable Formulation and a Doramectin Levamisole Fixed-Dose Injectable Co-Formulation Against Naturally Acquired Adult Stage *Nematodirus helvetianus* and *Cooperia oncophora* in Cattle." (Study No. A136C-US-17-554)

Study Dates: November 1, 2017, to January 6, 2018

Study Location: Fayetteville, Arkansas, United States

Study Design:

Objective: To compare the effectiveness of Dectomax®, a doramectin injectable formulation and VALCOR™, a doramectin and levamisole hydrochloride fixed-dose combination injectable to saline-treated controls against naturally established infections of adult *Nematodirus helvetianus* and adult *Cooperia oncophora*. This study was conducted in accordance with Good Clinical Practice guidelines.

Study Animals: Thirty crossbred beef cattle approximately seven months of age were used.

Experimental Design: Cattle confirmed with patent infections of *N. helvetianus* and with positive cultures of *C. oncophora* prior to Day 0 were blocked by body weight and randomized to treatment according to a completely randomized block design to one of three treatment groups:

Table IIB.8. Treatment Groups

Treatment Group	Test Article	Number of Animals	Treatment Day
1	Saline (control)	10 (2 males, 8 females)	0
2	Dectomax® (0.2 mg/kg doramectin)	10 (6 males, 4 females)	0
3	VALCOR™ (0.2 mg/kg doramectin and 6.0 mg/kg levamisole hydrochloride)	10 (4 males, 6 females)	0

Drug Administration: Saline was the control article for Group 1. Dectomax® was administered to Group 2 at a dose of 0.2 mg/kg body weight. VALCOR™ was administered to Group 3 at a dose of 0.04 mL/kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg of body weight (1 mL/25 kg body weight). All test and control articles were administered once on Day 0 by a single subcutaneous injection in front of the shoulder.

Measurements and Observations: Five days prior to treatment on Day 0 and again 14 days after treatment, fecal samples were collected from each animal and a fecal egg count reduction test and coproculture were conducted. All animals were necropsied on Day 14. Based on morphological characteristics, nematodes were identified to species and stage. The number of each species/stage was counted. General health observations were conducted daily.

Statistical Method: The primary assessment of effectiveness was the post-treatment adult *N. helvetianus* and adult *C. oncophora* worm counts on Day 14. Efficacy was calculated using the formula: [(C-T)/C] x 100, where C = geometric mean of worm counts for the saline-treated group and T = geometric mean of worm counts for the Dectomax® and the VALCOR™-treated groups independently. A general linear mixed model was used to analyze the

natural log-transformed counts + 1 with treatment group as a fixed effect and block and error as random effects.

Pre-treatment (Day -5) versus post-treatment (Day 14) fecal egg counts from each group were evaluated using the fecal egg count reduction test (FECRT) formula: FECRT = 100 x [(pre-treatment arithmetic mean – post-treatment arithmetic mean)/(pre-treatment arithmetic mean)].

Results:

Table IIB.9. Geometric Mean Worm Counts and % Efficacy on Day 14, Treated Compared to Control Group

Treatment	Number of Animals	Geometric Mean *N. helvetianus* Worm Counts	Geometric Mean *C. oncophora* Worm Counts	% Efficacy for *N. helvetianus*	% Efficacy for *C. oncophora*
Saline	10	1059.9	1261.3	N/A	N/A
Dectomax®	10	790.7	639.5	25.4%	49.3%
VALCOR™	10	9.1	4.1	99.1%	99.7%

Table IIB.10. Fecal Egg Count Reduction Test (FECRT) Results Using Arithmetic Mean Fecal Egg Counts from Day -5 and Day 14

Treatment	Day -5 Arithmetic Mean	Day 14 Arithmetic Mean	% Fecal Egg Count Reduction
Saline	999.4	2005.1	-105.63%
Dectomax®	1136.2	519.9	54.25%
VALCOR™	1134	0.2	99.98%

Adverse Reactions: Several animals across treatment groups were observed with signs of bovine respiratory disease during the study. One saline-treated and one VALCOR™-treated animal died during the study due to bovine respiratory disease. None of these adverse events were related to the test article.

Conclusions: This study demonstrates that VALCOR™ administered as a single subcutaneous injection at a dose of 1 mL/25 kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg body weight is effective for the treatment and control of adult *Nematodirus helvetianus* in cattle and demonstrates doramectin is not effective for the treatment and control of *N. helvetianus*, thus establishing the contribution of levamisole hydrochloride to the combination. This study also demonstrates that VALCOR™ is effective for the treatment and control of adult *Cooperia oncophora* in cattle. This parasite is the dose-limiting parasite of doramectin and this demonstration of effectiveness allows the granting of indications to all the remaining nematodes on the doramectin injectable solution label to VALCOR™.

4. **Clinical Field Study**

Title: "Efficacy of a Doramectin Levamisole Fixed-Dose Combination Injectable Formulation Against Field Nematode Infections in Cattle." (Study No. A131C-US-16-504)

Study Dates: September 2017 to December 2017

Study Locations: This was a six-site study at the following U.S. locations: Sites 01 and 07 Lodi, Wisconsin, United States; Sites 02 and 03 Fayetteville, Arkansas, United States; Sites 05 and 06 Manhattan, Kansas, United States. Site 04 was removed due to inadvertent dosing of study animals with doramectin prior to study start.

Study Design:

Objective: To evaluate the effectiveness of VALCOR™ against naturally acquired mixed infections of gastrointestinal nematodes under field conditions. This study was conducted in accordance with Good Clinical Practice guidelines.

Study Animals:

Table IIB.11. Animal Summary

Site number	Control cattle #	Treated Cattle #	Cattle class
01	18*	54*	Stocker calves
02	18	54	Stocker calves
03	18	54	Stocker calves
05	18	54	Stocker calves
06	17	50	Late lactation cows
07	18	54	Early/mid gestation heifers and early/mid gestation gestation/late-lactating cows

*One animal from each group removed from analysis due to mis-dosing.

Experimental Design: At each site, between 17 and 54 animals per treatment group with ≥ 20 strongylid eggs per gram of feces (stockers only; cows enrolled if fecal positive) were randomized to treatment according to a completely randomized design with one-way treatment structure replicated across the six sites. Cattle from both treatment groups were commingled on native grass pastures at each site.

Table IIB.12. Treatment Groups

Treatment	Dose (mL/kg)	Total Number and Sex of Animals	Day of Treatment
Saline	0.04	106 (60 female, 46 male)	0
VALCOR™	0.04	319 (182 female, 137 male)	0

Drug Administration: VALCOR™ was the test article and saline was the control article. Test and control articles were administered once on Day 0 by a single subcutaneous injection in front of the shoulder at a dose of 0.04 mL/kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg of body weight (1 mL/25 kg body weight).

Measurements and Observations: Prior to treatment and 14 days after treatment, fecal samples were collected from each animal for determination of fecal egg counts per gram of feces, coproculture, and a fecal egg count reduction test. Fecal samples with ≥ 20 strongylid eggs per gram were cultured for the recovery and identification of resultant larvae. General health observations were conducted daily during the study.

Statistical Methods: The primary assessment of effectiveness was the post-treatment fecal egg count of all animals on Day 14. The fecal egg counts, computed as the number of eggs per gram of feces on Day 14, were log-transformed, LN (count + 1), prior to analysis. The percent effectiveness of the treated group was calculated using the formula: [(C-T)/C] x 100, where C = saline-treated group geometric mean and T = VALCOR™-treated group geometric mean.

Pre-treatment versus post-treatment (Day 14) fecal egg counts in the VALCOR™-treated group were evaluated using the fecal egg count reduction test (FECRT) formula: FECRT = 1 – (Day 14 arithmetic mean fecal egg counts)/(pre-treatment arithmetic mean fecal egg counts).

Results:

Table IIB.13. Geometric Mean Fecal Egg Counts on Day 14, Treated Compared to Control Groups

Site	Treatment	Geometric Mean Fecal Egg Counts	% Efficacy
01	Saline VALCOR™	63.63 0.1	99.8%
02	Saline VALCOR™	213.82 0	100%
03	Saline VALCOR™	487.66 0.11	100%
05	Saline VALCOR™	244.37 0	100%
06	Saline VALCOR™	3.03 0	100%
07	Saline VALCOR™	2.17 0.01	99.4%

Table IIB.14. Fecal Egg Count Reduction Test (FECRT) Results Using Arithmetic Mean Fecal Egg Counts from Day 0 and Day 14, VALCOR™-treated Animals

Site	Treatment	Day 0 Arithmetic Mean	Day 14 Arithmetic Mean	% Fecal Egg Count Reduction
01	VALCOR™	314.15	0.17	99.9%
02	VALCOR™	480.00	0.00	100%
03	VALCOR™	516.30	0.17	100%
05	VALCOR™	280.93	0.00	100%
06	VALCOR™	8.5	0.00	100%
07	VALCOR™	19.76	0.02	99.9%

Adverse Reactions: No test article-related adverse reactions were reported in this study.

Conclusions: This study demonstrates that VALCOR™ administered as a single subcutaneous injection at a dose of 1 mL/25 kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg body weight is effective for the treatment and control of natural infections of gastrointestinal nematodes in cattle.

5. **Dose Confirmation Study**

Title: "Therapeutic Efficacy of a Doramectin Levamisole Fixed-Dose Combination Injectable Formulation Administered Subcutaneously to Cattle Naturally Infested with Sucking Lice." (Study No. A136C-US-18-629)

Study Dates: January 15, 2019, to March 12, 2019

Study Location: Lodi, Wisconsin, United States

Study Design:

Objective: To evaluate the efficacy of VALCOR™ against naturally established infestations of immature and adult sucking lice (*Linognathus vituli, Haematopinus eurysternus,* and/or *Solenopotes capillatus*) when administered once subcutaneously to cattle at a dose of 1 mL/25 kg of body weight (0.04 mL/kg body weight) to deliver 0.2 mg/kg doramectin and 6.0 mg/kg levamisole hydrochloride. This study was conducted in accordance with Good Clinical Practice guidelines.

Study Animals: Twenty-four cattle, representing beef and dairy breeds including both males and females, ranging from 119 to 288 kg (262 to 634 lbs) were used.

Experimental Design: Cattle with natural infestations of ≥ 40 live, motile, sucking lice on Day -7 were blocked by pre-treatment lice count and pen location and randomized to treatment according to a completely randomized block design to one of two treatment groups. The experimental unit was the pen.

Table IIB.15. Treatment Groups

Treatment Group	Test Article	Treatment Day	Animals per Treatment
1	Sterile water (control; 0.04 mL/kg)	0	12 (4 pens of 3 animals each)
2	VALCOR™ (0.2 mg/kg doramectin and 6.0 mg/kg levamisole; 0.04 mL/kg)	0	12 (4 pens of 3 animals each)

Drug Administration: Sterile water was the control article for Group 1. VALCOR™ was administered to Group 2 at a dose of 0.04 mL/kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg of body weight (0.04 mL/kg body weight). Test and control articles were administered once on Day 0 by a single subcutaneous injection in front of the shoulder.

Measurements and Observations: Prior to treatment on Day 0 and again on Days 14, 21, 28, 35, 42, and 56 after treatment, lice counts were conducted by observing and recording the number of motile sucking lice at 9 predilection sites on each animal. General health observations were conducted daily during the entire study and injection sites were observed once daily after treatment for the first 14 days.

Statistical Method: The primary effectiveness variable was the total motile immature and adult sucking lice count (total immature and adult *L. vituli*, *H. eurysternus,* and/or *S. capillatus*) from all the sampled predilection sites on Days 14, 21, 28, 35, 42, and 56. The total lice counts were averaged over each pen then log transformed prior to analysis. The log transformed average counts were analyzed using a general linear mixed model separately for each time point. The model included treatment as a fixed effect and the block as a random effect. A ≥95% effectiveness and a statistically significant ($p \leq 0.05$) difference between the VALCOR™-treated group compared with the placebo-treated group was required for the product to be considered effective. Percent effectiveness at each timepoint was calculated using the formula [(C-T)/C] X 100, where C=Geometric mean back-transformed from the Least Squares mean of the lice count for the placebo-treated group and T=Geometric mean back-transformed from the Least Squares mean of the lice count for the VALCOR™-treated group. Comparisons of lice counts between the treatment groups were tested using a 2-sided test with 5% level of significance.

Results:

Table IIB.16. Post-treatment Geometric Means Sucking Lice Counts, Treated Compared to Control Group

Day of Study	Treatment	# Pens	Geometric mean lice counts	% efficacy
14	Control	4	83.5	n/a
14	VALCOR™	4	0	100
21	Control	4	96.3	n/a
21	VALCOR™	4	0	100
28	Control	4	87.1	n/a
28	VALCOR™	4	0	100
35	Control	4	101.1	n/a
35	VALCOR™	4	0	100
42	Control	4	85.8	n/a
42	VALCOR™	4	0.1	99.9
56	Control	4	70.3	n/a
56	VALCOR™	4	0.1	99.9

Adverse Reactions: There were no treatment-related adverse reactions observed during the study.

Conclusions: This study demonstrates that VALCOR™ administered as a single subcutaneous injection at a dose of 1 mL/25 kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg body weight is effective for the treatment and control of sucking lice in cattle. Because levamisole is known to not be effective against ectoparasites, this study also establishes the contribution of doramectin to the combination. This also allows the granting of indications to all the remaining ectoparasites on the doramectin injectable solution label to VALCOR™.

6. **Dose Confirmation Study**

Title: "Therapeutic Efficacy of a Doramectin Levamisole Fixed-Dose Combination Injectable Formulation Administered Subcutaneously to Cattle Naturally Infested with Sucking Lice." (Study No. A136C-GB-19-717)

Study Date: April 24, 2019, to June 19, 2019

Study Location: Stratford-on-Avon, Warwickshire, United Kingdom

Study Design:

Objective: To evaluate the efficacy of VALCOR™ against naturally established infestations of immature and adult sucking lice (*Linognathus vituli, Haematopinus eurysternus,* and/or *Solenopotes capillatus*) when administered once subcutaneously to cattle at a dose of 1 mL/25 kg of body weight (0.04 mL/kg body weight) to deliver 0.2 mg/kg doramectin and 6.0 mg/kg levamisole hydrochloride. This study was conducted in accordance with Good Clinical Practice guidelines.

Study Animals: Twenty-four cattle, representing beef and dairy breeds including both males and females, ranging from 57 to 123 kg (125 to 271 lbs) were used.

Experimental Design: Cattle with natural infestations of ≥ 40 live, motile, sucking lice on Day -7 were blocked by pre-treatment lice count and pen location and randomized to treatment according to a completely randomized block design to one of two treatment groups. The experimental unit was the pen.

Table IIB.17. Treatment Groups

Treatment Group	Test Article	Treatment Day	Animals per Treatment
1	Sterile saline (control; 0.04 mL/kg)	0	12 (4 pens of 3 animals each)
2	VALCOR™ (0.2 mg/kg doramectin and 6.0 mg/kg levamisole; 0.04 mL/kg)	0	12 (4 pens of 3 animals each)

Drug Administration: Sterile saline was the control article for Group 1. VALCOR™ was administered to Group 2 at a dose of 0.04 mL/kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg of body weight (0.04 mL/kg body weight). Test and control articles were administered once on Day 0 by a single subcutaneous injection in front of the shoulder.

Measurements and Observations: Prior to treatment on Day 0 and again on Days 14, 21, 28, 35, 42, and 56 after treatment, lice counts were conducted by observing and recording the number of motile sucking lice at 9 predilection sites on each animal. General health observations were conducted daily during the entire study and injection sites were observed once daily after treatment for the first seven days and then every subsequent lice count day if an injection site reaction was present.

Statistical Method: The primary effectiveness variable was the total motile immature and adult sucking lice count (total immature and adult *L. vituli*, *H. eurysternus,* and/or *S. capillatus*) from all the sampled predilection sites on days 14, 21, 28, 35, 42, and 56. The total lice counts were averaged over each pen then log transformed prior to analysis. The log transformed average counts were analyzed using a general linear mixed model separately for each time point. The model included treatment as a fixed effect and the block as a random effect. A ≥95% effectiveness and a statistically significant difference between the VALCOR™-treated group compared with the placebo-treated group was required for the product to be considered effective. Percent effectiveness at each timepoint was calculated using the formula [(C-T)/C] X 100, where C=Geometric mean back-transformed from the Least Squares mean of the lice count for the placebo-treated group and T=Geometric mean back-transformed from the Least Squares mean of the lice count for the

VALCOR™-treated group. Comparisons of lice counts between the treatment groups were tested using a 2-sided test with 5% level of significance.

Results:

Table IIB.18. Post-treatment Geometric Means Sucking Lice Counts, Treated Compared to Control Group

Day of Study	Treatment	# Pens	Geometric mean lice counts	% efficacy
14	Control	4	588.0	n/a
14	VALCOR™	4	3.6	99.4
21	Control	4	427.3	n/a
21	VALCOR™	4	0.0	100
28	Control	4	328.8	n/a
28	VALCOR™	4	0.0	100
35	Control	4	210.2	n/a
35	VALCOR™	4	0.0	100
42	Control	4	144.1	n/a
42	VALCOR™	4	0.0	100
56	Control	4	124.4	n/a
56	VALCOR™	4	0.0	100

Adverse Reactions: Signs of bovine respiratory disease and ringworm were observed in a few animals in both treatment groups. Conjunctivitis was observed in two control animals. These conditions responded to concomitant treatment and none were considered test article related. Injection site reactions were observed in one control animal and nine VALCOR™-treated animals. The reactions observed in the VALCOR™-treated animals were considered test article related. All injection site reactions except for one resolved without treatment prior to the end of the study. The injection site reaction that was still present at Day 56 had decreased in size since its initial observation on Day 6.

Conclusions: This study demonstrates that VALCOR™ administered as a single subcutaneous injection at a dose of 1 mL/25 kg body weight to provide 0.2 mg doramectin and 6 mg levamisole hydrochloride per kg body weight is effective for the treatment and control of sucking lice in cattle. As noted previously, because levamisole is known to not be effective against ectoparasites, this study also establishes the contribution of doramectin to the combination. This also allows the granting of indications to all the remaining ectoparasites on the doramectin injectable solution label to VALCOR™.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: "Evaluation of the Margin of Safety of Doramectin:Levamisole Fixed Dose Combination Anthelmintic in Young Calves." (Study No. A332N-US-16-498)

Study Dates: May 5, 2017, to October 24, 2018

Study Location: Parma, Idaho, United States

Study Design:

Objective: To evaluate the margin of safety of VALCOR™ in young calves when administered in three subcutaneous doses 14 days apart. This study was conducted in accordance with the Good Laboratory Practice (GLP) Regulations for Non-Clinical Laboratory Studies.

Study Animals: 32 healthy Holstein calves (16 males, 16 females) approximately three months of age and weighing between 61 and 103 kg (134 to 227 lbs) at the start of the study were enrolled.

Experimental Design: The study was a masked, randomized margin of safety study with a negative control. The experimental unit was the individual calf. Blocking was based on pen location and order of processing (i.e., truck offloading). Calves were randomly assigned within sex to one of four treatment groups (8 calves per group). Calves were individually housed. The control group calves received saline at 0.12 mL/kg; 1X dose group calves received VALCOR™ at 0.04 mL/kg [0.2 mg doramectin/kg body weight, 6 mg levamisole/kg body weight]; 2X dose group calves received VALCOR™ at 0.08 mL/kg [0.4 mg doramectin/kg body weight, 12 mg levamisole/kg body weight]; and 3X dose group calves received VALCOR™ at 0.12 mL/kg [0.6 mg doramectin/kg body weight, 18 mg levamisole/kg body weight].

Drug Administration: Test and control articles were administered once on Days 0, 14, and 28, by a single subcutaneous injection in front of the shoulder.

Measurements and Observations: Body weights were measured on Days -14, 0, 14, and 28. Health observations were conducted once daily from Days -14 to -1, then twice daily from Day 0 to Day 31. In addition, animals were observed after each dose administration within 15 minutes of injection and 4 and 8 hours post-injection. Injection site observations occurred on Days 0, 7, 14, 21, and 28. Additional observations occurred 24 hours post-dose administration on Days 1, 15, and 29. Neurologic examinations were conducted on Day -6 and following dosing on Days 0, 14, and 28 at 4 hours, 8 hours, and 24 hours after dosing. Feed and water consumption were measured daily from Days -7 to 30/31. Blood was collected for hematology and clinical chemistry on Days -14, -6, 0, 2, 14, 16, 28, and 30. Urine was collected for analysis on Days -14/-13, -5, 2, 10, 16, and on necropsy Day 30/31. Physical examinations occurred on Days -13, -6, 0, 7, 14, 21, 28, and 29. On Days 30/31, animals were necropsied and tissues from all major organs were collected for histopathology.

Statistical Methods: Endpoints that were measured multiple times post-treatment, which included body weight, feed and water consumption, and clinical pathology and urine data, were analyzed using a general linear mixed model with repeated measures. For all quantitative variables, descriptive statistics were provided. Categorical data were summarized by treatment and time point using frequency distribution tables, by sex and across sex.

Results:

Clinical observations: There were no clinically relevant treatment-related effects on physical examination parameters, food/water consumption, or body weight. The 1X, 2X, and 3X treatment groups had an increased number of palpable injection site reactions when compared to the control group; these injection site reactions were dose dependent. Injection site swelling in the 1X group from Day 0 dose administration resolved between 21 and 28 days post-injection. Anatomic pathology evaluations confirmed the presence of test article-related injection site reactions with injection site swelling, edema, inflammation, muscle necrosis, and fibrosis. Clinical observations and histopathology findings indicated that over time, injection site reactions progressed toward resolution. The 1X, 2X, and 3X treatment groups also had dose-dependent increases in incidence of hypersalivation after treatment administration when compared to the control group. All cases of hypersalivation were mild, transient, and resolved without further medical intervention.

Clinical chemistry parameters: Some statistically significant variations from normal reference ranges were observed for some parameters. However, these were determined to not be test article-related because there was no dose-dependent trend, and the abnormalities were sporadic and did not worsen over the course of the study with continued drug exposure. The differences were not considered clinically relevant.

Adverse Reactions: Injection site reactions and hypersalivation as described above.

Conclusions: The study demonstrates that VALCOR™ is safe for use in beef cattle when administered as a subcutaneous injection at the recommended label dose and there is an acceptable margin of safety.

B. Reproductive Safety Study

Title: "Safety of Doramectin:Levamisole Fixed Combination Anthelmintic on Folliculogenesis, Implantation, and Organogenesis in Reproducing Female Cattle." (Study No. A333N-US-16-477).

Study Dates: November 29, 2016, to August 13, 2019

Study Location: Parma, Idaho, United States

Study Design:

Objective: To evaluate the reproductive safety of VALCOR™ when administered once via subcutaneous route to heifers at 0.12 mL/kg (3X the therapeutic dose; [0.6 mg doramectin/kg body weight, 18 mg levamisole/kg body weight]) at folliculogenesis, implantation, or organogenesis. This study was conducted in accordance with the Good Laboratory Practice (GLP) Regulations for Non-Clinical Laboratory Studies.

Study Animals: Two hundred mixed beef breed heifers between one and two years of age were enrolled.

Experimental Design: The study was a masked, randomized female reproductive safety study with a negative control. The experimental unit was the individual animal. Heifers were randomly assigned to one of four treatment groups (50 heifers per group). Heifers were estrus synchronized on Day -10 and bred via artificial insemination on Day 0. Heifers were pregnancy checked on Days 39, 92, and 224. Heifers across treatment groups were commingled.

Table IIIB.1. Treatment Groups (Day 0 is day of artificial insemination)

Group	Dose Volume	Dose Administration	Animal Number
T01; 0X (control)	0.12 mL/kg saline	Day -5; Day 18; Day 25	49*
T02; 3X	0.12 mL/kg VALCOR™	Day -5	50
T03; 3X	0.12 mL/kg VALCOR™	Day 18	50
T04; 3X	0.12 mL/kg VALCOR™	Day 25	48*

*One heifer was removed from T01 prior to Day 39 pregnancy evaluation and two heifers were removed from T04 prior to test article administration.

Drug Administration: Test and control articles were administered by a subcutaneous injection in front of the shoulder. A maximum of 10 mL was administered at a single injection site. Multiple injection sites were used to accommodate the total dose volume administered.

Measurements and Observations: Health observations were conducted on heifers twice daily through the entire study. Conception rate, calving rate, abortion rate, stillbirth rate, dystocia scores, and calf health and body weight at birth and 30 days post-partum were evaluated.

Statistical Methods: Conception status (yes/no), calving status (yes/no), abortion status (yes/no), stillbirth status (0 or 1), and dichotomized dystocia scores (0-1 vs. ≥ 2) were analyzed using a generalized linear mixed model for binomial distribution with logit link. The differences between treated groups and the control group were assessed using two-sided tests with unadjusted 10% level of significance. Frequency distribution tables were used to summarize categorical data by either treatment group or time point or both while descriptive statistics were used to summarize continuous data.

Results:

Table IIIB.2. Results of Reproductive Variables (Day 0 is Day of Artificial Insemination)

Variable	T01 (Saline Control)	T02 (VALCOR™-treated Day -5)	T03 (VALCOR™-treated Day 18)	T04 (VALCOR™-treated Day 25)
Conception Rate: (# pregnant Day 40/ # bred)	28/49 57%	28/50 56%	25/50 50%	26/48 54%
Calving Rate: (# live full term calves delivered/# bred)	23/49 47%	28/50 56%	21/50 42%	23/48 48%
Abortion Rate: (# lost pregnancies/# pregnant Day 40)	4/28 14%	0/28 0%	2/25 8%	2/25* 8%
Stillbirth Rate: (# full-term calves born dead/# pregnant Day 40)	1/28 4%	0/28 0%	2/25 8%	0/25* 0%
Calf birth weights (mean)	29.9 kg	29.0 kg	27.1 kg	27.4 kg
Calf weight gain in 30 days (mean)	24 kg	22.4 kg	22.8 kg	22.7 kg

*One animal found dead due to bloat and removed from this calculation.

There were no clinically significant differences between treated groups and the control group in the reproductive variables tabulated above. There were also no clinically significant differences in dystocia scores between treated groups and the control group. Treatment-related injection site swellings occurred across all treated groups. One animal in T03 showed agitation, hypersalivation, and tongue-chewing following treatment on Day 18. These signs resolved without treatment one hour after observation. Some calves across all groups were observed with diarrhea/pneumonia during the 30-day post-partum period. These illnesses were considered common for the class/age of animal and not related to treatment.

Conclusions: The study demonstrates that VALCOR™ is safe for use in reproducing female beef cattle when administered as a subcutaneous injection at the recommended label dose during folliculogenesis and early first trimester.

C. Reproductive Safety Study

Title: "Reproductive Safety of Doramectin:Levamisole Fixed Combination in Reproducing Female Cattle in Early and Late Gestation." (Study No. A333N-US-16-478)

Study Dates: December 22, 2016, to August 13, 2019

Study Location: Parma, Idaho, United States

Study Design:

Objective: To evaluate the reproductive safety of VALCOR™ when administered once via subcutaneous route to heifers at 0.12 mL/kg (3X the therapeutic dose; [0.6 mg doramectin/kg body weight, 18 mg levamisole/kg body weight]) at either early (44 ± 2 days) or late (224 ± 2 days) time points of gestation. This study was conducted in accordance with the Good Laboratory Practice (GLP) Regulations for Non-Clinical Laboratory Studies.

Study Animals: One hundred twenty mixed beef breed heifers between one and two years of age were enrolled.

Experimental Design: The study was a masked, randomized female reproductive safety study with a negative control. The experimental unit was the individual animal. Heifers were randomly assigned to one of three treatment groups (40 heifers per group). Heifers were estrus synchronized and bred via artificial insemination on Day 0. Heifers were pregnancy checked on Day 39 and enrolled if pregnant. Heifers were pregnancy checked again on Days 89 and 223. Heifers across treatment groups were commingled.

Table IIIB.3. Treatment Groups (Day 0 is day of artificial insemination)

Group	Dose Volume	Dose Administration	Animal Number
T01; 0X (control)	0.12 mL/kg saline	Day 43; Day 223	40
T02; 3X	0.12 mL/kg VALCOR™	Day 43	40
T03; 3X	0.12 mL/kg VALCOR™	Day 223	39*

*One heifer aborted prior to dosing and was removed from the study.

Drug Administration: Test and control articles were administered by a subcutaneous injection in front of the shoulder. A maximum of 10 mL was administered at a single injection site. Multiple injection sites were used to accommodate the total dose volume administered.

Measurements and Observations: Health observations were conducted on heifers twice daily through the entire study. Calving rate, abortion rate, stillbirth rate, dystocia scores, and calf health and body weight at birth and 30 days post-partum were evaluated.

Statistical Methods: Calving status (yes/no), abortion status (yes/no), stillbirth status (0 or 1), and dichotomized dystocia scores (0-1 vs. ≥ 2) were analyzed using a generalized linear mixed model for binomial distribution with logit link. The differences between treated groups and the control group were assessed using two-sided tests with unadjusted 10% level of significance. Frequency distribution tables were used to summarize categorical data by either treatment group or time point or both while descriptive statistics were used to summarize continuous data.

Results:

Table IIIB.4. Results of Reproductive Variables (Day 0 is Day of Artificial Insemination)

Variable	T01 (Saline Control)	T02 (VALCOR™-treated Day 43)	T03 (VALCOR™-treated Day 223)
Calving Rate: (# live full term calves delivered/# pregnant Day 40)	34/40 85%	37/40 93%	37/39* 95%
Abortion Rate: (# lost pregnancies/# pregnant Day 40)	6/40 15%	2/40 5%	0/39 0%
Stillbirth Rate: (# full-term calves born dead/# pregnant Day 40)	0/40 0%	0/40 0%	0/39 0%
Calf birth weights (mean)	28.4 kg	27.9 kg	27.2 kg
Calf weight gain in 30 days (mean)	20.1 kg	21.3 kg	21.5 kg

*One heifer aborted prior to dosing and was removed from the study.

There were no clinically significant differences between treated groups and the control group in the reproductive variables tabulated above. There were also no clinically significant differences in dystocia scores between treated groups and the control group. Treatment-related injection site swellings occurred across all treated groups. One animal in T01 and two animals in T03 had hypersalivation on Day 223 dosing. These signs resolved without treatment no more than 30 minutes after observation. Three calves were born with congenital malformations. One calf in T01 was born with multiple congenital abnormalities including a septal heart defect, dome shaped skull with cerebellar dysplasia and abiotrophy,

abnormal dentition, thymic tissue deficiency, and limb hyperextension. This calf was euthanized. One calf in T02 was found dead within 24 hours of birth and found to have an intraventricular septal heart defect. Another calf in T02 was also born with multiple congenital abnormalities including an undescended testicle, carpal valgus deformity, thymic hypoplasia, abnormal dentition, and focal cerebellar dysplasia. This calf was euthanized. At necropsy, this calf was positive for cryptosporidium, coronavirus, and found to be severely deficient in vitamin A and selenium. It was determined the congenital defects seen in T02 calves were likely not test article-related due to the overlap between abnormalities seen in both treated and control calves in addition to a lack of increased incidence in the treated group as compared to the control group. Some calves across all groups were observed with diarrhea/pneumonia during the 30-day postpartum period. These illnesses were considered common for the class/age of animal and not related to treatment.

Conclusions: The study demonstrates that VALCOR™ is safe for use in reproducing female beef cattle when administered as a subcutaneous injection at the recommended label dose during first and third trimester.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

The Agency evaluated the need to address the impact of the use of VALCOR™ on antimicrobial resistance among bacteria of public health concern in or on VALCOR™-treated cattle. After reviewing information (literature, data, etc.) both submitted by the sponsor and available in the public domain, the Agency determined:

- VALCOR™ is not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
- VALCOR™ is not used to treat gastroenteritis or other bacterial diseases in humans,
- VALCOR™ (or a similar class representative) is not under development to treat a bacterial disease in humans, and
- VALCOR™ is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined that a microbial food safety assessment was not required for VALCOR™.

B. Toxicology

1. Doramectin

Reassessment of the codified ADI or safe concentration was not needed for this approval. The codified ADI for total residue of doramectin is 0.75 µg/kg of body weight *per* day, as listed under 21 CFR §556.222. The safe concentrations for total residue of doramectin in individual edible tissues of cattle are 150 µg/kg (ppb) for muscle, 450 ppb for liver, 900 ppb for kidney, and 900 ppb for fat.

The FOI Summary for the original approval of NADA 141-061, dated July 30, 1996 contains summaries of all toxicology studies and information used in determining the ADI.

Toxicology studies conducted to determine an Acute Reference Dose (ARfD) are summarized below:

a. Acute Neurotoxicology Study in Rodents

Title: Single Dose Oral Gavage Neurobehavioral Study with Doramectin in Rats

Study Number: 8360429

Report Date: December 17, 2018

Study Location: Madison, Washington, United States

Study Design: This GLP study was conducted in accordance to the FDA Guidance for Industry, Single Dose Acute Toxicity Testing for Pharmaceuticals (CDER, August 1996); and the FDA CDER/ICH Harmonized Tripartite Guidelines ICH-S7A, Safety Pharmacology Studies for Human Pharmaceuticals (CDER, July 2001); the FDA CDER/ICH (R2), Nonclinical Safety Studies for the conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CDER, January 2010); OECD Environment, Health and Safety Publications Series on Testing and Assessment, No. 124, Guidance for the Derivation of an Acute Reference Dose. The study was designed to evaluate the potential of the test article to induce acute neurotoxicity when administered as a single (acute) oral dose via gavage in rats and to derive an ARfD.

A single oral dose of the test article, doramectin in vehicle (1.0% (w/v) medium viscosity carboxymethylcellulose and 0.5% (v/v) Tween 80 in reverse osmosis water) or vehicle only in 10 mL/kg dose volume was administered *via* gavage to 4 groups of 7 week old RccHan® WIST rats (23 per sex *per* treatment groups divided into toxicity group, interim group and toxicokinetic group) at 0, 15, 30 and 60 mg/kg bw. From days 1 to 15, cage side clinical observations, detailed physical observations, body weight and food consumption data were collected.

Functional observational battery (FOB) and locomotor activity (LMA) assessments were made on all animals, once during the predosing phase. Toxicity and interim animals were examined approximately 24 hours post dosing on day 2, and animals assigned to terminal sacrifice were evaluated once on day 14 of the dosing phase.

FOB assessment included but not limited to, body temperature, pupillary status, muscle tone, piloerection, respiration, appearance of fur, foot splay, grip strength, open field observations, *etc*. Each animal was evaluated during handling (hand-held observations) and in an open field (open field observations) and was assessed for sensory reactivity to stimuli (elicited behaviors).

LMA was conducted in a sound-attenuated, dark chamber on all toxicity and interim sacrifice animals, after they had completed the FOB. Each rat for the LMA assessments was placed in the chamber, which was an automated photocell activity recording device. Locomotor activity was conducted within 10 minutes of FOB examinations, and the activity was recorded for 40 minutes. The intervals for reporting and data presentation were in 20 2-minute bins with the following parameters analyzed: basic movement, X + Y ambulation, fine movements and rearing activity.

Blood was collected from all rats in the satellite group approximately 24 hours post dosing and repeated on days 3 and 15. Blood plasma was assessed for the maximum observed concentration (C_{max}), time to peak concentration (T_{max}), and area under the concentration-time curve (AUC).

At necropsy, all animals were subjected to a complete gross pathological examination and organ weights were measured. Histopathological examination was conducted on tissues collected from toxicity and interim rats. Microscopic evaluations were conducted on tissues from toxicity and interim animals of the control and high dose groups and all animals that died or sacrificed at an unscheduled interval.

Results and Conclusions: Doramectin was systemically absorbed following a single oral administration of doramectin at nominal doses of 15, 30, and 60 mg/kg bw in rats. Systemic absorption generally increased with increasing dose levels and there was no test article detected in blood plasma of control animals.

The single (acute) oral administration of doramectin to RccHan® WIST rats (males and females) was well tolerated, producing no overt clinical signs of toxicity. Clinical signs, body weights, body weight changes, food consumption and gross pathology were not significantly affected. In males, foot splay was increased at all dose levels tested, and basic movement and X+Y ambulation motor activity were significantly decreased at all dose levels. Biologically relevant reduction in testis weight was noted at all dose levels. Microscopical changes of the kidneys and epididymis, and low sperm volume and increased incidence of luminal cell debris were noted. No effects on FOB parameters, motor activity, organ weights and microscopic changes were noted in females.

A no-observed-effect level (NOEL)/no-observed-adverse-effect level (NOAEL) could not be established from this study because of increased motor deficits, increased foot splay that remained elevated on day 14, increased testis weight, increased incidence of basophilic tubule of the kidney, and increased incidence of luminal cell debris and hypospermia. A lowest-observed-effect level (LOEL)/lowest-observed-adverse-effect level (LOAEL) for doramectin was established at 15 mg/kg bw based on reduction in motor activity (most sensitive endpoints) in males.

b. Acute Neurotoxicity Study in Rodents (Male Rats)

Title: **Single Dose Oral Gavage Neurobehavioral Study with Doramectin in Male Rats**

Study Number: 8360207

Report Date: November 27, 2018

Study Location: Madison, Washington, United States

Study Design: This non-GLP study was conducted in accordance with the Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology – Guidance for the Derivation of an Acute Reference Dose – Annex 2: Guidance for Conducting a Single Exposure Toxicity Study. The study was designed to evaluate the potential of the test article to induce acute neurotoxicity when administered as a single oral dose *via* gavage in rats and to derive an ARfD.

A single oral dose of the test article, doramectin in vehicle (1.0% (w/v) medium viscosity carboxymethylcellulose and 0.5% (v/v) Tween 80 in reverse osmosis water) or vehicle only in 10 mL/kg dose volume was administered via gavage to 9 groups, in two separate cohorts of 7 weeks old RccHan® WIST rats. Cohort 1 (8 males *per* group, subdivided into toxicity and satellite groups) were dosed at 0 (control), 50, 100, 300 and 500 mg/kg bw. Cohort 2 (5 males per group) were dosed at 40, 50, 60 and 80 mg/kg bw.

Detailed clinical observations were made, and body weight collected on all animals during the predosing phase. While during the dosing phase, days 1 to 3, cage side clinical observations, detailed physical observations and food consumption data were collected. FOB and LMA assessments were made 24 hours post dosing on day 2 with terminal sacrifice on day 3. FOB and motor activity were measured using the procedure described under Study Number: 8360207 above. The intervals for reporting and data presentation were in 20 2-minute bins. The following parameters were analyzed: basic movement, X + Y ambulation, fine movements and rearing activity.

Blood was collected from rats in the satellite group on day 1 (24 hours post dosing) for plasma analysis of doramectin concentration.

At necropsy, all animals were subjected to a complete gross pathological examination and organ weights recorded. Microscopic evaluations were conducted on tissues from all animals of the control and high dose groups and all animals that died or were sacrificed at an unscheduled interval.

Results and Conclusions: Doramectin was systemically absorbed following a single oral administration of doramectin at nominal doses of 40, 50, 60, 80, 100, 300 and 500 mg/kg bw. Systemic absorption generally increased with increasing dose levels. There was no test article detected in blood plasma of control animals.

A single (acute) oral administration of doramectin to RccHan® WIST male rats produced overt toxicity at ≥50 mg/kg bw. While food consumption was unremarkable in animals administered ≤80 mg/kg bw, significantly decreased motor activity was observed in animals administered ≥50 mg/kg bw. Moreover, dose-dependent doramectin-related neurological findings were

evident in the FOB and LMA assessments of all animals administered the test article at levels ≥50 mg/kg bw. In addition, organ weight changes (thymus, thyroid gland, adrenal and spleen) were noted, some of those changes were correlated with microscopic effects such as single cell necrosis of the thymus. Statistical non-significant neurological signs in animals administered ≤40 mg/kg bw included piloerection, low reactivity to handling, splayed stance, hunched posture, increased auditory reactivity, decreased approach response. Following necropsy, doramectin-related microscopic anatomical findings included slight to minimal hypertrophy of chief cells and of the acini in mandibular salivary gland of animals administered ≥50 mg/kg bw. A NOEL/NOAEL was established at 40 mg/kg bw.

The results from this study were used to set the doses used to conduct the definitive study (Study No. 8360429) discussed above.

c. Acute Neurotoxicity Study in Rodents (Female Rats)

Title: **Single Dose Oral Gavage Neurobehavioral Study with Doramectin in Female Rats**

Study Number: 8374146

Report Date: December 12, 2018

Study Location: Madison, Washington, United States

Study Design: This non-GLP study was conducted in accordance with the Environment, Health and Safety Publications Series on Testing and Assessment, No. 124, Guidance for the Derivation of an Acute Reference Dose and on the Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology – Guidance for the Derivation of an Acute Reference Dose – Annex 2: Guidance for Conducting a Single Exposure Toxicity Study. The study was designed to evaluate the potential of doramectin to induce acute toxicity when administered as a single oral dose via gavage in females and to derive an ARfD.

A single oral dose of the test article, doramectin in vehicle (1.0% (w/v) medium viscosity carboxymethylcellulose and 0.5% (v/v) Tween 80 in reverse osmosis water) or vehicle only in 10 mL/kg dose volume was administered via gavage to 5 groups of 7 weeks old RccHan® WIST rats (13 *per* treatment groups divided into toxicity and satellite groups) at 0, 20, 30, 40 and 80 mg/kg bw.

All clinical observations, body weight, blood collection, FOB and LMA assessments were conducted in a similar manner to those described above under Study No., 8360207 (males). In addition, the procedures used at necropsy for gross pathology, organ weights, and microscopic evaluations on tissues from all animals of the control and high dose groups were similar to those used in the male study (discussed above under Study No. 8360207).

Results and Conclusions: Doramectin was systemically absorbed following a single oral administration of doramectin at doses of 20, 30, 40 and

80 mg/kg bw. Systemic absorption generally increased with increasing dose levels. There was no test article detected in blood plasma of control animals.

A single (acute) oral administration of doramectin to RccHan® WIST female rats produced overt toxicity at ≥40 mg/kg bw. Dose-dependent doramectin-related neurological findings were evident on day 2 of the dosing phase during the FOB and LMA assessments of animals administered ≥40 mg/kg bw, with associated doramectin-related mortality, mild ataxia, excessive salivation, piloerection and impaired righting reflex noted. Significantly decreased motor activity also was observed on day 2 of the dosing phase in animals administered ≥40 mg/kg. Recovery could not be assessed due to the scheduled or unscheduled sacrifice of affected animals prior to follow up testing on day 14 of the dosing phase. A NOEL/NOAEL was established at 30 mg/kg bw.

The results from this study were used to support the doses selected to conduct the definitive acute neurotoxicity study (Study No. 8360429) discussed above.

Establishment of an Acute Reference Dose

Benchmark dose (BMD) modeling on locomotor activity data for male rats from the two single dose neurotoxicity studies (Study No. 8360429 and Study No. 8360207) was conducted to determine the point of departure (POD) for derivation of the ARfD. The BMDS estimated BMD_{1SD} and $BMDL_{1SD}$ are presented in Table IV.1 below.

Table IV.1. Summary of Benchmark Dose Modeling Results for Male Rats in Neurobehavioral Toxicity Studies; Study No. 8360429 and Study No. 8360207.

Endpoints	BMD_{1SD}, mg/kg	$BMDL_{1SD}$, mg/kg
Basic Motor Activity	22	7.8
X-Y Ambulation	13	**6.6**

The lowest BMDL of 6.6 mg/kg bw was selected as the POD. A safety factor of 100 was applied to account for intraspecies (animal-to-human) and interspecies (human-to-human) extrapolations in toxicity. The ARfD for total residue of doramectin is calculated using the following formula.

$$\text{Toxicological ARfD} = \frac{\text{BMDL 1SD}}{\text{Safety Factor}} = \frac{6.6\,\text{mg/kg bw}}{100}$$

$$= 0.066\ \text{mg/kg bw} = 66\ \mu\text{g/kg bw}$$

The ARfD for total residue of doramectin is 66 µg/kg bw.

Safe Concentrations for Injection Site:

Based on the ARfD of 66 µg/kg bw, the safe concentration of residues at the injection site is calculated as:

$$\text{Safe Concentration (injection Site)} = \frac{66\ \mu g/kg\ bw \times 60\ kg\ body\ weight}{300\ g}$$

$$= 13.2\ \mu g/g$$

The Safe Concentration for the injection site is 13.2 ppm.

2. Levamisole

The toxicology studies that support the assessment of levamisole are summarized in the FOI summary for the supplemental approval of NADA 102-437 (Tramisol© for Cattle) dated December 29, 1978. There is no codified ADI for levamisole, however, a tolerance of 0.1 ppm was established for edible tissues (excluding milk) (21 CFR §556.350).

There is no concern for synergistic or additive effect of levamisole and doramectin residues with regards to human consumption of edible tissues from treated cattle.

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

   b. Total Residue and Metabolism Studies were not required for this approval. The FOI Summary for the original approval of NADA 141-061 dated July 30, 1996, contains a summary of total residue and metabolism studies for doramectin in cattle. The FOI Summary for the approval of NADA 102-437 dated December 29, 1978, contains a summary of total residue and metabolism studies for levamisole in cattle.

   c. Comparative Metabolism Study

   d. Comparative Metabolism Studies were not required for this approval. The FOI Summaries for the original approval of NADA 141-061 dated July 30, 1996, contains a summary of total residue and metabolism studies for doramectin in cattle. The FOI Summary for the approval of NADA 102-437 dated December 29, 1978, contains a summary of total residue and metabolism studies for levamisole in cattle.

   e. Study to Establish Withdrawal Period and/or Milk Discard Time, and/or Honey Discard Time

      Title: Pivotal Tissue Residue Depletion Study in Beef Cattle Administered a Single Subcutaneous Injection of a 0.5% Doramectin (5 mg/mL)/15% Levamisole Hydrochloride (150 mg/mL) Combination Formulation at a

Dose Level of 0.2 mg/kg Doramectin and 6.0 mg/kg Levamisole Hydrochloride Administered at the Maximum Label Dose Level of 0.23 mg/kg Doramectin and 6.9 mg/kg Levamisole hydrochloride (Study No. A433N-AU-17-532)

Study Dates: September 2017 to December 2021

Study Location: Armidale, New South Wales, Australia

Study Design:

Objective: The purpose of the study was to measure concentrations of doramectin and levamisole in edible cattle tissues (liver, muscle, kidney, fat, and injection site) at 2, 4, 7, 14, 21, 28, 35, 42, and 49 days withdrawal after a single subcutaneous injection of doramectin and levamisole injection (0.23 mg/kg Doramectin and 6.9 mg/kg Levamisole hydrochloride).

Study Animals: Thirty-eight beef British breeds and cross cattle (19 castrated male/19 female) approximately 12 months of age upon receipt and weighing 329-415 kg were enrolled in the study.

Experimental Design: In a GLP-compliant study, thirty-six of the animals were randomized to 9 treatment groups (2 male and 2 female in each group). All groups received the same treatment then were slaughtered after withdrawal periods of 2, 4, 7, 14, 21, 28, 35, 42, or 49 days. Liver, kidney, muscle, peri-renal fat, and injection site samples were collected, processed, and stored at ≤-10 °C.

Drug Administration: Doramectin and levamisole injection was administered at a target dose rate of 0.23 mg/kg Doramectin and 6.9 mg/kg Levamisole hydrochloride subcutaneously in the neck of the animal. A maximum injection volume of 10 mL was used on one side of the neck, with the remaining dose injected on the opposite side.

Measurements and Observations: Kidney, liver, muscle, fat, and injection site samples were analyzed by a validated HPLC-fluorescence method for doramectin and an LC-MS/MS method for levamisole.

Result(s): Kidney, liver, muscle, fat, and injection site samples were analyzed. Values below the limit of quantitation were reported as BLOQ. The limits of quantitation for levamisole were:

- Kidney: 4.92 ppb
- Liver: 6.47 ppb
- Muscle: 12.6 ppb
- Fat: 5.53 ppb

The limits of quantitation for doramectin were:

- Kidney: 1.3 ppb
- Liver: 2.6 ppb
- Muscle: 0.44 ppb

- Fat: 2.6 ppb

The results for levamisole are presented in Table IV.C.c.1 and for doramectin in Table IV.C.c.2 below. Levamisole residues in all tissues decreased quickly following dose administration and were below the LOQ in all tissues by 14 days withdrawal. Doramectin residues were highest in the injection site followed by fat, liver, kidney, and muscle. Doramectin residues depleted slower than levamisole. Doramectin residues in the injection site were below the injection site safe concentration after 14-days withdrawal.

Table IV.C.c.1. Mean Concentrations (ppb) ± Standard Deviation of Levamisole in Edible Tissues of Beef Cattle Treated with 0.23 mg/kg doramectin + 6.9 mg/kg levamisole hydrochloride.

Withdrawal Time (days)	Liver	Kidney	Loin Muscle	Fat	Injection Site Core
2	205 ± 59.9	30.1 ± 14.9	BLOQ	BLOQ	196 ±99.4
4	40.9 ± 7.5	5.96*	BLOQ	BLOQ	BLOQ
7	20.2 ± 6.3	BLOQ	BLOQ	BLOQ	23.1*
14	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ

BLOQ: Below the calculated limit of quantitation
*Results from only one animal. Results from the other 3 animals in the treatment group were BLOQ.

Table IV.C.c.2. Mean Concentrations (ppb) ± Standard Deviation of Doramectin in Edible Tissues of Beef Cattle Treated with 0.23 mg/kg doramectin + 6.9 mg/kg levamisole hydrochloride.

Withdrawal Time (days)	Liver	Kidney	Loin Muscle	Fat	Injection Site Core
2	282.3 ± 82.7	105.7 ± 23	31.3 ± 7.9	443.9 ± 110.1	21802.4 ± 9672.7
4	289.7 ± 30.9	102.3 ± 4.3	31.4 ± 3.4	547.6 ± 13.8	8632.6 ± 2399.3
7	207.4 ± 43.0	87.2 ± 15.8	23.3 ± 3.0	420.4 ± 30.5	13093.6 ± 5258.2
14	123.4 ± 29.7	40.0 ± 7.6	13.0 ± 2.7	234.8 ± 34.3	1415.3 ± 1276.3
21	63.3 ± 40.7	19.3 ± 10.7	6.4 ± 3.8	125.0 ± 76.9	235.1 ± 229.7
28	31.8 ± 6.5	10.8 ± 2.9	3.9 ± 1.3	63.8 ± 13.1	29.1 ± 9.3
35	19.8 ± 6.0	6.4 ± 2.7	2.8 ± 0.98	45.1 ± 19.6	93.2 ± 85.4
42	7.2 ± 1.7	3.5 ± 0.8	1.3 ± 0.28	15.9 ± 4.6	58.2 ± 46.7
49	4.5 ± 0.8	1.9 ± 0.3	0.94 ± 0.25	10.8 ± 2.2	2.53 ± 1.7

Conclusion(s): Tissue residue data from study A433N-AU-17-532 were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99th percentile of the population with 95% confidence. The data support the assignment of a 15-day withdrawal period. A withdrawal period of 15 days is consistent with the safety of residues at the injection site.

2. Target Tissue and Marker Residue

- As described in the FOI summary for the approval of NADA 141-061 dated July 30, 1996, the marker residue for doramectin is doramectin, and the target tissue is liver.
- As described in the FOI summary for the approval of NADA 102-437 dated December 29, 1978, the marker residue for levamisole is levamisole, and no target tissue is assigned.

3. Tolerances

- As described in the FOI summary for the approval of NADA 141-061 dated July 30, 1996, a tolerance of 100 ppb was assigned for doramectin in cattle liver. For the original approval, the tolerance was adjusted from 300 ppb to 100 ppb to ensure safety of residues at the injection site. With the establishment of the ARfD and a new safe concentration for residues at the injection site, the adjusted tolerance in liver is no longer necessary.

We re-assign the tolerance for doramectin in cattle liver (the target tissue) to 300 ppb. The tolerance for doramectin in muscle remains 30 ppb.

- The tolerances for levamisole in cattle liver, kidney, muscle, and fat are 100 ppb.

4. Withdrawal Period

Doramectin residue depletion data from Study Number A433N-AU-17-532 were analyzed using a statistical algorithm that calculated the upper tolerance limit for the 99th percentile with 95% confidence. The data support the assignment of 15-day withdrawal period.

D. Analytical Method for Residues

1. Description of Analytical Method

   a. The FOI summary for the original approval of NADA 141-061 dated July 30, 1996,contains the analytical method for doramectin in cattle liver.

   b. The FOI summary for the original approval of NADA 102-437 dated December 29, 1978, contains the analytical method for levamisole in cattle tissues.

2. Availability of the Method

   The validated analytical methods for analysis of residues of doramectin and levamisole are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

V. USER SAFETY

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

"USER SAFETY WARNINGS: Not for human use. If accidental eye contact occurs, flush eyes immediately with water for 15 minutes and seek medical attention. If wearing contact lenses, flush eyes immediately with water before removing lenses then continue rinsing for at least 15 minutes. Do not eat, drink or smoke while handling the product. Wash hands after use. Take care to avoid accidental self-injection. If accidental injection occurs, seek medical attention and provide product package insert to medical professional. To obtain a Safety Data Sheet(s), contact Zoetis Inc. at 1-888-963-8471 or www.zoetis.com."

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that VALCOR™, when used according to the label, is safe and effective in beef cattle two months of age and older and in replacement dairy heifers less than 20 months of age (not for use in beef bulls intended for breeding over 1

year of age, dairy calves, and veal calves) for the treatment and control of gastrointestinal roundworms (adults and fourth stage larvae) - *Ostertagia ostertagi* (including inhibited larvae), *O. lyrata*, *Haemonchus placei*, *Trichostrongylus axei*, *T. colubriformis*, *T. longispicularis*[*], *Cooperia oncophora*, *C. pectinata*[*], *C. punctata*, *C. surnabada*, *Bunostomum phlebotomum*[*], *Strongyloides papillosus*[*], *Oesophagostomum radiatum*, *Trichuris* spp.[*], and *Nematodirus helvetianus*[*]; lungworms (adults and fourth stage larvae) - *Dictyocaulus viviparus*; eyeworms (adults) - *Thelazia* spp.; grubs (parasitic stages) - *Hypoderma bovis* and *H. lineatum*; sucking lice - *Haematopinus eurysternus*, *Linognathus vituli*, and *Solenopotes capillatus*; mange mites - *Psoroptes bovis* and *Sarcoptes scabiei* ([*]adults only). Additionally, data demonstrate that residues in food products derived from species treated with VALCOR™ 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 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

VALCOR™, as approved, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of VALCOR™.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.