Date of Authorization: May 19, 2026

FREEDOM OF INFORMATION (FOI) SUMMARY

Original Emergency Use Authorization (EUA)

EUA 006700

DECTOMAX®/DECTOMAX®-CA1

(doramectin injection)

Injectable solution

Dairy Cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older) except for calves that will be processed for veal, Horses one year and older, Swine, Sheep except for lactating sheep, and Deer

Scope of Authorization: For the prevention and treatment of infestations caused by *Cochliomyia hominivorax* larvae (myiasis) in dairy cattle (lactating dairy cows, dry dairy cows, replacement dairy heifers 20 months of age and older) except for calves that will be processed for veal; and for the prevention of infestations caused by *Cochliomyia hominivorax* larvae (myiasis) in horses one year and older, swine, sheep except for lactating sheep, and deer.

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

EUA 006700

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Names

DECTOMAX® and DECTOMAX®-CA1

D. Drug Product Established Name

doramectin injection

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

10 mg/mL

H. How Supplied

100 mL, 250 mL, and 500 mL multi-dose, rubber capped glass vials

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

1 mL (10 mg doramectin) per 110 lb of body weight (200 mcg/kg) administered in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older) by subcutaneous (SC) injection only in the neck region.

1 mL (10 mg doramectin) per 75 lb of body weight (300 mcg/kg) administered in swine by intramuscular (IM) injection only.

1 mL (10 mg doramectin) per 110 lb of body weight (200 mcg/kg) administered by IM injection only in horses one year and older, by SC or IM injection in sheep except for lactating sheep, and by SC injection only in deer.

K. Route of Administration

Administered by SC injection only in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older) and deer.

Administered by IM injection only in swine and horses one year and older.

Administered by SC or IM injection in sheep except for lactating sheep.

L. Species/Classes

Dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older) except for calves that will be processed for veal, horses one year and older, swine, sheep except for lactating sheep, and deer

M. Food and Drug Administration (FDA) Approved Indications

Cattle: DECTOMAX® (NADA 141-061) is indicated for treatment and control of gastrointestinal roundworms, lungworms, eyeworms, grubs, sucking lice, and mange mites. DECTOMAX® has been proved to effectively control infections and to protect cattle from reinfection with *Cooperia oncophora* and *Haemonchus placei* for 14 days, *Ostertagia ostertagi* for 21 days, and *C. punctata*, *Oesophagostomum radiatum*, and *Dictyocaulus viviparus* for 28 days after treatment. DECTOMAX®-CA1 (NADA 141-616) is indicated for prevention and treatment of infestations caused by New World screwworm (*Cochliomyia hominivorax*) larvae (myiasis), and the prevention of reinfestation for 21 days.

Swine: DECTOMAX® (NADA 141-061) is indicated for treatment and control of gastrointestinal roundworms, lungworms, kidney worms, sucking lice, and mange mites.

See package insert for complete indications and directions for use.

N. Emergency Authorized Uses

For the prevention and treatment of infestations caused by *Cochliomyia hominivorax* larvae (myiasis) in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older), except for calves that will be processed for veal.

For the prevention of infestations caused by *Cochliomyia hominivorax* larvae (myiasis) in horses one year and older, swine, sheep except for lactating sheep, and deer.

O. Limitations of Authorized Use

It is a violation of Federal law to use this drug product other than as directed in the fact sheets.

Lactating dairy cows, dry dairy cows, replacement dairy heifers 20 months of age and older, sheep except for lactating sheep, and deer must not be slaughtered for human consumption within 35 days of treatment. Swine must not be slaughtered for human consumption within 24 days of treatment.

Milk that has been taken during treatment and for 468 hours (19.5 days) after treatment must not be used for human consumption.

A withdrawal period has not been established for this product in pre-ruminating calves. Treated calves and calves born to treated cows and heifers must not be processed for veal.

Not for use in lactating sheep. Use in these sheep may cause drug residues in milk.

Not for use in horses less than one year of age.

Do not use in horses intended for human consumption.

DECTOMAX®/DECTOMAX®-CA1 (doramectin injection) is authorized for this use only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of DECTOMAX®/DECTOMAX®-CA1 (doramectin injection) under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or the authorization revoked sooner.

II. EFFECTIVENESS

A. Dosage Characterization

This Emergency Use Authorization does not change the previously approved 1 mL (10 mg doramectin) per 110 lb of body weight (200 mcg/kg) administered in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older) by subcutaneous injection only in the neck region. The FOI Summary for the original approval of NADA 141-061, dated July 30, 1996, contains dosage characterization information for cattle.

This Emergency Use Authorization does not change the previously approved 1 mL (10 mg doramectin) per 75 lb of body weight (300 mcg/kg) administered only by intramuscular injection in swine. The FOI Summary for the supplemental approval of NADA 141-061, dated September 18, 1997, contains dosage characterization information for swine.

B. Evidence Supporting Emergency Use Authorization

In accordance with Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the sponsor demonstrated that it is reasonable to believe that

DECTOMAX®/DECTOMAX®-CA1 may be effective for the prevention and treatment of infestations caused by New World screwworm (NWS; *Cochliomyia hominivorax*) larvae (myiasis) in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older), and prevention of NWS infestations in horses one year and older and sheep except for lactating sheep based on dose confirmation (clinical effectiveness) studies. The evidence supporting effectiveness is based on effectiveness data against NWS in non-lactating cattle, provided under the conditional approval of DECTOMAX®-CA1 (NADA 141-616), three anti-parasitic dose confirmation (clinical effectiveness) studies conducted in horses in the U.S., and three dose confirmation (clinical effectiveness) studies against NWS conducted in sheep in Brazil and Argentina. Collectively, the data support that it is reasonable to believe that DECTOMAX®/DECTOMAX®-CA1 may be effective for the prevention and treatment of infestations caused by NWS (*C. hominivorax*) larvae (myiasis) in dairy cattle and for the prevention of infestations caused by NWS (*C. hominivorax*) larvae (myiasis) in horses and sheep. The evidence supporting effectiveness in swine and deer is based on the pharmacokinetic (PK) information in these species after a single dose.

1. Dose Confirmation Studies in Horses

   Three dose confirmation studies were conducted in 1997 in naturally infested horses at three different geographic locations in the U.S. These horses were naturally infected with various internal gastrointestinal parasites, including certain stages of botfly larvae (*Gasterophilus* species). Although these dose confirmation studies did not evaluate effectiveness of DECTOMAX® for the prevention of NWS myiasis, they support that DECTOMAX® can be effective as an antiparasitic in horses when administered at a dose of 200 mcg/kg. Raw data and individual animal worm count data were not provided for review (final study reports were provided), and the Center for Veterinary Medicine (CVM) was unable to confirm which parasite species had adequate infections in the control group. Therefore, the percent effectiveness for each species demonstrated for each study was not confirmed. However, the mean worm count values in the treated versus control were supportive of an antiparasitic effect in horses. Additionally, the collective 37 horses each administered the 200 mcg/kg dose of doramectin did not have any significant adverse reactions, supporting the safety of this dose in horses (see Margin of Safety Study in Horses and Injection Site Safety Study in Horses for more details).

   Collectively, the information from dose confirmation study summaries, PK information (see below), and published literature in other species support that it is reasonable to believe that DECTOMAX®/DECTOMAX®-CA1 (doramectin injection) may be effective for the prevention of infestations caused by NWS (*Cochliomyia hominivorax*) larvae (myiasis) when administered intramuscularly in horses one year and older.

2. Dose Confirmation Studies in Sheep

   Three dose confirmation studies conducted in Brazil and Argentina in 1996 and 1997 evaluated the effectiveness of DECTOMAX® (doramectin injection) for the prevention of infestations caused by NWS larvae (myiasis) in sheep. All three

studies included a group treated intramuscularly with a single dose of 200 mcg/kg body weight (BW) DECTOMAX®, and a saline-treated control group. In two of the natural infestation studies, sheep in the DECTOMAX® group were treated after shearing, and all study animals were grazed on pasture and exposed to natural infestations of NWS. In a third study with an induced NWS infection, sheep were administered DECTOMAX® two hours after two wounds were produced on each sheep. In all three studies, NWS myiasis was observed in saline-treated control animals within the first week and no animals treated with DECTOMAX® had myiasis that required a rescue treatment. Additional details about the design and results of these studies are summarized in Table II.1 below.

Table II.1. Natural and Induced Infestation Dose Confirmation Studies in Sheep

Study Number	**2049A-04-005**	**2049A-05-95-013**	**2049A-04-96-008**
Study Date	1996	1997	1997
Study Location	Brazil	Argentina	Brazil
Study Animals	Corriedale castrated male sheep (7-8 months)	Corriedale sheep (sex and age not specified)	Corriedale female sheep (10-18 months)
NWS Infestation	Natural	Natural	Induced; 2 wounds produced on each sheep
Animals/Group	30	25	10
Day of Treatment	Day 0	Day 0	Day 0
Study Duration	14 days	14 days	9 days
Incidence of Myiasis in Control Group	15/30	4/25	6/10
Incidence of Myiasis in DECTOMAX® injection Group	2/30	0/25	0/10

3. Published Literature in Sheep

Sanavria, A. & Prata M. C. A. (1996). Prophylactic efficacy of doramectin against natural infestations by *Cochliomyia hominivorax* in sheep post-castration. *Brazilian Journal of Veterinary Research and Animal Science. 33*(3):163-166.

A study conducted in Brazil and published in 1996, evaluated the effectiveness of a single subcutaneous dose of 200 mcg/kg BW doramectin for the prevention of natural infestations caused by NWS (*Cochliomyia hominivorax*) larvae (myiasis) in sheep. The control sheep did not receive any treatment. Eight sheep were assigned to two groups of four sheep each. After treatments, all sheep were surgically castrated and grazed on pasture for 14 days. One sheep from the control group died 24 hours after castration. The remaining three control sheep

developed active myiasis. Treatment with doramectin injection prevented myiasis in all doramectin-treated sheep during the 14 days after castration.

Collectively, the information from dose confirmation study summaries and published literature support that it is reasonable to believe that DECTOMAX®/DECTOMAX®-CA1 (doramectin injection) may be effective for the prevention of infestations caused by NWS (*Cochliomyia hominivorax*) larvae (myiasis) when administered at the appearance of a wound or at castration in sheep.

4. Pharmacokinetic Studies and Effectiveness Bridge

For dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older), horses one year and older, swine, and deer, there was no *in vivo* effectiveness study data against NWS to rely on; therefore, a pharmacokinetic (PK) approach was used, with further evaluation utilizing physiologically-based pharmacokinetic (PBPK) modeling to allow comparison between the plasma concentrations of injectable doramectin in non-lactating cattle and sheep to dairy cattle, horses, swine, and deer.

In the PK approach, the most relevant parameter is the PK profile at the site of the NWS infestation. The PK profile plots the concentration of doramectin in blood, plasma, or tissue, illustrating how the animal interacts with the drug from administration until it is eliminated. The level of plasma and tissue exposure required for effectiveness against NWS is not known; and it was unknown whether the relevant exposure parameter is represented by a minimum threshold concentration at a given time or an overall concentration over a period of time. This plasma concentration approach was used to predict doramectin exposure and considered a reasonable approach because there was available effectiveness data for certain species (non-lactating cattle and sheep) and the different routes of administration. Effectiveness data against NWS in non-lactating cattle were provided under the conditional approval of DECTOMAX®-CA1 (NADA 141-616), and the effectiveness data against NWS in sheep were reviewed and acceptable under this EUA (see above).

PK studies of doramectin in cattle are available in the published scientific literature. Toutain et al. (1997)[1] evaluated the plasma PK of doramectin subcutaneously (SC at 200 mcg/kg in 20 cows over a 35-day period). The value of clearance (Cl) by extravascular route (Cl/F) was 0.0163 L/h/kg resulting in $AUC_{0\text{-inf}}$ = 511 ng*day/mL, where $AUC_{0\text{-inf}}$ refers to the pharmacokinetic parameter Area Under the Curve (AUC), representing the total drug exposure over time until it is completely eliminated.

[1] Toutain PL, Upson DW, Terhune TN, McKenzie ME (1997). Comparative pharmacokinetics of doramectin and ivermectin in cattle. Veterinary Parasitology 1997; 72(1):3-8.

The following table shows the results of two studies describing the PK of doramectin following single intravenous (IV) administration in non-lactating cattle and sheep, normalized to a 200 mcg/kg dose. On a per kg basis, cattle exhibited lower Cl and volume of distribution (Vd) than sheep by the same proportion, and this resulted in similar elimination half-life ($T_{1/2}$).

Table II.2. PK Parameter Estimates Following IV Administration in Cattle and Sheep.

Variable	Non-Lactating Cattle[2]	Sheep (Study 2549A-03-96-009)
Route	IV	IV
Dose (mg/kg)	0.2	0.2
N	4	6
Initial Drug Concentration (Co (ng/mL))	285	498
AUC $_{0\text{-inf}}$ (ng*day/mL)	632	157
$T_{1/2}$ (days)	3.93	3.84
Mean Residence Time (days)	5.41	4.46
Cl (L/day/kg)	0.316	1.28
Volume of Distribution at Steady State (Vss (L/kg))	1.71	5.69

Study 2549A-03-96-009 in Table II.2 was an absolute bioavailability study in sheep that were dosed IV, IM, and SC in a parallel design. Both IM and SC routes showed the relative bioavailability of the DECTOMAX® formulation in sheep was >100% (103% and 114%, respectively). Comparing the AUC from the Wick et al., 1993[3] study (583 ng*day/mL) with the IV data from the Goudie et al., 1993 study (547 ng*day/mL), both of which were studies conducted by the sponsor using the same assay, indicates 100% bioavailability in non-lactating cattle, indicating DECTOMAX®/DECTOMAX®-CA1 is highly bioavailable across these species. Table II.3 provides the PK parameter estimates for additional species. In the tables, C_{max} represents the peak (maximum) concentration that the drug reaches and represents the point where the rate of drug absorption exactly equals the rate of drug elimination, T_{max} represents the time at which the drug reaches its maximum concentration (C_{max}) after administration, and Mean Residence Time (MRT) represents that average amount of time a single molecule of the drug spends inside the body after it is eliminated.

[2] Goudie AC, Evans NA, Gration KAF, et al., (1993). Doramectin – a potent novel endectocide. Veterinary Parasitology 1993; 49(1):5-15.
[3] Wick SR, Kaye B, Weatherley AJ, et al., (1993). Effect of formulation on the pharmacokinetics and efficacy of doramectin. Veterinary Parasitology 1993; 49(1):17-26.

Table II.3. PK Parameter Estimates Following SC or IM Injection Across Species

Species**	Route	Dose (mg/kg)	N	C_{max} (ng/mL)	AUC (ng*day/mL)	T_{max} (day)	$T_{1/2}$ (days)	MRT (day)
Cattle[1]	SC	0.2	20	32.6	511	5.31	5.39	11.8
Cattle[4]	SC	0.2	6	95.9	804	2.30	7.00	6.33
Cattle[5]	SC	0.2	5	55.1	709	3.00	6.02	10.2
Horses[6]	IM	0.2	5	33.3	394	2.90	9.30	13.3
Swine[7]	IM	0.2*	8	12.9	152	3.25	6.48	10.6
Sheep[4]	SC	0.2	8	17.2	271	5.88	6.99	12.6
Sheep[8]	SC	0.2*	20	18.0	185	1.80	4.68	8.66
Sheep[8]	IM	0.2	20	17.6	166	2.33	4.44	7.74
Deer[9]	SC	0.2	4	44.8	399	2.75	3.60	7.06

*Concentration dose-normalized from the original dose of 0.3 mg/kg or 0.375 mg/kg
**Cattle are non-lactating.

[1] Toutain PL, Upson DW, Terhune TN, McKenzie ME (1997). Comparative pharmacokinetics of doramectin and ivermectin in cattle. Veterinary Parasitology 1997; 72(1):3-8.
[4] Myers MJ, Howard KD, Kawalek JC. Pharmacokinetic comparison of six anthelmintics in sheep, goats, and cattle. J Vet Pharmacol Ther. 2021;44(1):58-67.
[5] Study A431R-NZ-13-197. Comparative pharmacokinetic evaluation of three injectable solution and suspension formulations containing doramectin and levamisole versus Dectomax® (doramectin), Quadrosol® (levamisole) and Edge (doramectin + levamisole) in cattle. 2015.
[6] Pérez R, Godoy C, Palma C, Muñoz L, Arboix M, Alvinerie M. Plasma disposition and fecal elimination of doramectin after oral or intramuscular administration in horses. Veterinary Parasitology. 2010;170(1-2):112-119.
[7] Study 1525N-60-90-012 [^{3}H]Doramectin Radiotracer Residue Depletion Study at the Injection Site and in Body fluids and Excreta of Swine. 1995.
[8] Study 2549A-03-96-009. A non-clinical bioequivalence and bioavailability study in sheep: single intramuscular, subcutaneous and intravenous administration of doramectin at 300 mcg/kg. 1997.
[9] Study 25A9A-49-95-002. Pharmacokinetics of Doramectin in Blood Plasma and Tissue in Liver, Kidney, Muscle, and Abdominal Fat Following Subcutaneous Administration in Reindeer. 1996.

Table II.4. Doramectin Levels in Fat at 7 Days Post Dose Across Species

Species**	Route	Dose (mg/kg)	N/time	Concentration (ng/g)
Cattle[10]	SC	0.2	6	351
Cattle[11]	IM	0.2	6	212
Cattle[12]	SC	0.2	2	52
Cattle[13]	IM	0.2	4	493
Horses[14]	IM	0.2	2	481
Swine[15]	IM	0.2*	6	143
Swine[16]	IM	0.2*	6	251
Swine[17]	IM	0.2*	2	161
Sheep[18]	SC	0.2*	4	54.7
Sheep[19]	Oral	0.2*	6	95.1
Deer[20]	SC	0.2	3	50.6

*Concentration dose-normalized from the original dose of 0.3 mg/kg or 0.375 mg/kg
**Cattle are non-lactating

[10] Study 1531N-60-90-049. Doramectin Residue Depletion Study in Edible Tissues of Cattle. 1991.
[11] Study 1531N-60-91-050. Depletion of Drug Residues in Cattle Tissues Treated Parenterally with Doramectin. 1992.
[12] Study 1535N-60-89-009. [^{3}H]UK-67994 Radiotracer Residue Depletion Study in Edible Tissues of Cattle. 1990.
[13] Study 1535N-60-93-016. Radiotracer Residue Depletion Study in Edible Tissues and Injection Site of Cattle Treated Intramuscularly with [^{3}H]-Doramectin. 1994.
[14] Study 1555N-03-97-158. Liver metabolic profile of horses administered a single dose of 3H-doramectin intramuscularly. 1997.
[15] Study 1521N-60-91-005. Doramectin Residue Depletion Study in Edible Tissues of Swine. 1991.
[16] Study 1521N-60-94-007. Marker Residue Depletion Study in Edible Tissues and Injection Site of Swine Treated Intramuscularly with Doramectin. 1995.
[17] Study 1525N-60-90-011. [^{3}H]UK-67,994 Radiotracer Residue Depletion Study in Edible Tissues of Swine. 1993.
[18] Study 2549A-03-96-085. [^{3}H]Doramectin Re-Analysis of Injection sites from Sheep after Subcutaneous Administration. 1996. Original study 2549A-03-94-008.
[19] Study 2549C-14-96-058. Tissue residue depletion of doramectin following oral administration to sheep at a dose of 300 µg/kg. 1997.
[20] Study 2509A-03-98-011. Residue Depletion Study in Deer Administered a Single Subcutaneous Injection of Doramectin at a Dose Rate of 200 a.i./kg Bodyweight. 1999.

Table II.5. Mean PK Parameters and Statistical Comparison Following an IM Dose of 300 mcg/kg

PK Variable	Cattle Least Squares Mean	Horse Least Squares Mean
$AUC_{0\text{-inf}}$ (ng*day/mL)	1302	1054
T_{max} (days)	3	3
C_{max} (ng/mL)	85.63	77.88

The mean values in Table II.3 were used to compare doramectin exposures across species and consider the likelihood that doramectin may be as effective in other species (dairy cattle, horses, swine, and deer) against NWS as in cattle or in sheep. The data presented in Table II.3, based on body size, show cattle and horses reaching higher C_{max} and AUC than the smaller species (swine, sheep, and deer). The larger animals (cattle and horses) clear the drug much more slowly on a per-kg basis than the smaller species. The smaller species exhibit much lower dose-adjusted exposures than those observed in cattle and horses. For the smaller species (swine and deer), sheep served as the appropriate reference species since sheep effectiveness data against NWS were available.

For **dairy cattle**, lactating cows, particularly those with high milk production, there were differences in drug clearance (Cl) as compared to non-lactating animals. For this reason, it could not be assumed that the effectiveness data in non-lactating cattle against NWS, as provided under the conditional approval of DECTOMAX®-CA1 (NADA 141-616), could be directly applied to lactating dairy cattle. Therefore, a PK approach was used along with PBPK modeling, which allowed for comparison between the plasma levels of injectable doramectin in non-lactating cattle to lactating cattle. This modeling indicated that both lactating and non-lactating cattle appear to have very similar rapid increases in doramectin plasma levels within the first day of administration and that doramectin plasma levels in lactating cattle appear to be higher within the first week after administration as compared to non-lactating cattle. This information coupled with the clinical effectiveness data in NWS to support both a prevention and treatment indication under NADA 141-616 provided enough evidence to reasonably conclude that DECTOMAX®/DECTOMAX®-CA1 may be effective for the prevention and treatment of infestations caused by NWS myiasis in lactating dairy cattle. Based on the PBPK modeling, blood levels of injectable doramectin are lower at 21 days for lactating dairy cattle as compared to the blood levels of injectable doramectin in non-lactating dairy cattle, which results in more rapid clearance of doramectin. There was not enough evidence to support that doramectin injectable may be effective in lactating dairy cattle for this duration of time; therefore, a prevention of reinfestation for 21 days indication is not granted in lactating dairy cattle.

For **horses**, the plasma concentration versus time profiles of doramectin were close to cattle. Mean cattle exposure parameters (AUC, C_{max}) were generally higher than those in the horse (see Table II.5.). C_{max} values were 85.63 and

77.88 ng/mL in cattle and horses, respectively, and were reached at 3 days in both species. Mean AUC values were 1302 and 1054 ng*day/mL whereas $T_{1/2}$ values were 6.86 and 6.20 days in cattle and horses, respectively. Drug exposure is similar enough between cattle and horses to consider that the prevention of infestation results observed in cattle clinical studies of NWS to be extrapolated for horses. The observed differences between AUC and C_{max} are not of concern for a prevention indication. The lack of bioequivalence across species and the lower duration of plasma concentrations above a critical threshold in horses, do not support the extrapolation of the treatment of existing infestations and the prevention of reinfestation for 21 days from cattle to horses.

The PK data for **swine** (AUC = 152 ng*day/mL, C_{max} = 13 ng/mL) were lower than sheep (AUC = 207 ng*day/mL, C_{max} = 18 ng/mL); therefore, the concentration of doramectin in fat tissue was considered. This is because the subcutaneous fat represents 80% of total fat in pigs, and the NWS larvae would be expected to burrow deep into the SC tissues including the fat layer and deeper tissues. A fat/plasma ratio was calculated using the drug concentration in fat (ng/g) from Table II.4, and the plasma AUC from Table II.3. For sheep, the fat/plasma ratio was 0.36 and for swine it was 1.22; suggesting that for a given plasma exposure, a substantially higher drug concentration may be achieved in the subcutaneous fat of pigs compared to sheep. A limitation for the data presented in Table II.2 is that the typical dose level for swine (300 mcg/kg) was normalized to a 200 mcg/kg dose to allow for comparison to sheep and the other species; meaning the results do not show the data and results for the true dose in swine. Therefore, for further comparisons, a population-PK (pop-PK) evaluation was conducted of the swine PK data (Study S1525N-60-90-012) to estimate what systemic exposure might be in a population of swine relative to that of sheep. The doramectin blood-level PK data used were from the sponsor's study (Study S1525N-60-90-012) and Meyers MJ et al., 2021[4] to simulate 10,000 AUC and C_{max} values that were physiologically relevant. Based on the pop-PK simulation data, the *in vivo* derived mean simulated C_{max} values for swine (300 mcg/kg BW, IM injection) exceed the mean C_{max} value reported for sheep (200 mcg/kg BW, SC injection), suggesting that peak systemic exposure in swine treated with 300 mcg/kg BW is expected to be comparable to that in sheep treated with 200 mcg/kg BW. Further, for AUC, the *in vivo* mean AUC value for swine is less than the mean AUC value reported for sheep. The 75th percentile AUC in a population of 10,000 swine (272.7 ng*d/mL) is expected to be comparable to the reported mean AUC for sheep (270.8 ± 530.3 ng*d/mL); thereby suggesting that systemic exposure in approximately 25% of treated swine is expected to exceed the mean value reported for treated sheep. Together, these data provide support that the administration of doramectin at 300 mcg/kg as a single dose may be effective for the prevention of NWS larvae infestation in swine. The data do not support extrapolating the indications of treatment of existing infestations and prevention of reinfestation for 21 days from cattle to pigs.

[4] Myers MJ, Howard KD, Kawalek JC. Pharmacokinetic comparison of six anthelmintics in sheep, goats, and cattle. J Vet Pharmacol Ther. 2021;44(1):58-67.

For the purpose of this EUA, it is reasonable to consider that preventative effectiveness in **deer** (AUC = 399, C_{max} = 45) is comparable to that observed in sheep (AUC = 207, C_{max} = 18). The administration of doramectin SC at 200 mcg/kg as a single dose may be effective for the prevention of NWS larvae infestation in deer. Taken together with the United States Department of Agriculture (USDA)'s report[21] from the 2016 NWS outbreak in the endangered Key deer population in Florida, where doramectin was administered extensively via medicated feed, topically treated rollers, and subcutaneous injection, the data support extrapolation of the prevention of NWS infestations. The data do not support extrapolation of the treatment of existing NWS infestations and the prevention of reinfestation for 21 days from cattle to deer.

III. TARGET ANIMAL SAFETY

FDA did not require target animal safety studies for this authorization in dairy cattle and swine. The FOI Summary for the original approval of NADA 141-061 dated July 30, 1996, and a supplemental approval dated September 18, 1997, contain summaries of target animal safety studies for cattle and swine. It was concluded that the safety information submitted under NADA 141-061 for the full approval of DECTOMAX® for various endo- and ectoparasites in cattle supports the safety of doramectin injectable in dairy cattle as well.

Safety information for horses, sheep, and deer is described below.

A. Margin of Safety Study in Horses

Title: Multiple-Dose Safety-Margin Study for Doramectin in Horses. (Study No. 1452N-60-97-163)

Study Dates: June 1997 to March 1998

Study Location: Fort Collins, CO

Study Design:

Objective: To assess the safety of 300, 900, or 1500 mcg/kg doramectin when administered by intramuscular injection on three consecutive days to horses.

Study Animals: Twenty-four healthy horses (12 males and 12 females) of various breeds approximately 1 to 5 years old were enrolled in the study. The horses weighed 222 to 445.5 kg at the start of the study.

Experimental Design: Horses were randomized to pen and treatment group. There were four treatment groups, with three males and three females in each group (See Table III.1). Horses were euthanized and necropsy was performed on Day 16. Clinical observations were conducted by the study veterinarian who remained

[21] USDA APHIS NWS Response. Final Report for APHIS Veterinary Services (VS) Response to the 2016–2017 Outbreak of New World Screwworm (NWS) in Florida.

unaware of specific treatment assignments. The study was conducted according to Good Laboratory Practices.

Table III.1. Treatment groups – Margin of Safety Study

Group	Treatment assignment	Dosage	Number of Horses per group
T1	Saline	1.5 ml/50 kg (equivalent to T2 volume)	3 males; 3 females
T2	Doramectin	300 mcg/kg	3 males; 3 females
T3	Doramectin	900 mcg/kg	3 males; 3 females
T4	Doramectin	1500 mcg/kg	3 males; 3 females

Drug Administration: The test article was doramectin 10 mg/mL in an injectable solution (DECTOMAX®). The control article was 0.9% Sodium Chloride Injection, USP. The assigned treatment (saline or doramectin) was administered by intramuscular injection once daily for three days (Days 0, 1, and 2).
Measurements and Observations: Body weight was recorded by scale on Days -7, 0, and 16 (or at death for unscheduled euthanasia). Feed intake (hay and grain) was determined from Day -14 through Day 15 (or the last survival day). Routine animal observations were conducted by animal technicians twice daily for the entire period that horses were housed at the site. A veterinarian performed physical examinations at the time of horse arrival and at Day -7. Rectal temperature was taken on Days 0, 5, and 15. Veterinarian-performed clinical observations occurred twice daily on Days -2,
-1, before treatment, about 1 to 2 hours post-treatment, 4 to 5 hours post-treatment, twice daily through Day 15, and once on the morning of Day 16. Blood and urine were collected on Day -14, Day 0 prior to treatment, and on Days 5 and 15.

All study horses were humanely euthanized and a necropsy was performed. Microscopic examination was performed on all tissues in the control and 1500 mcg/kg group, and in other cases based on gross pathology findings or microscopic pathology in the evaluated treatment group.

Statistical Method: Not reviewed.

Results: There were dose-dependent clinical signs of toxicity associated with doramectin injection, most prominently in the 900 mcg/kg and 1500 mcg/kg groups. In the 300 mcg/kg group, the most common clinical sign was multiple observations of unformed feces in 3 horses (compared with 1 observation in 1 horse in the saline group). Clinical signs that occurred in both the 900 mcg/kg and 1500 mcg/kg groups included listlessness, depression, drooping lips, mydriasis, excitability, feed held in mouth, recumbency, gauntness, and ataxia. Urine dribbling was reported in one 900 mcg/kg horse. Head pressing, weakness, tremors, and weight shifting were reported in the 1500 mcg/kg groups. Two horses in the T4 group were prematurely euthanized because they were considered moribund on Day 4. Prior to humane euthanasia, the two horses were reported to be recumbent, have no pupillary light reflex (normal palpebral reflex), would not retract their tongues, had cold extremities, were dehydrated, and were hypothermic.

The two euthanized horses lost the most weight during the study, and two other T4 horses also lost weight. All horses in T1, T2, and T3 gained weight during the study except one in T3 which neither lost nor gained weight. Group T4 had lower average daily grain intake than the saline group. T3 and T4 had lower hay intake.

Clinical pathology changes that were considered possibly related to doramectin included mild elevations in sorbitol dehydrogenase (SDH) in 4 horses in T4. There were other abnormalities seen in the moribund horses that could be attributed to being moribund rather than due to direct organ-specific toxicity.

No gross or histopathological findings were attributed to doramectin.

Conclusions: DECTOMAX®/DECTOMAX®-CA1 (doramectin injection) has a relatively narrow margin of safety in horses, with only a 1.5X multiple (300 mcg/kg) of the intended dose (200 mcg/kg) demonstrating a margin of safety in this study. Adverse reactions in this dose group included episodes of unformed feces in the days following doramectin administration. At doses of 900 mcg/kg (4.5X) and above, doramectin was associated with significant clinical abnormalities and resulted in humane euthanasia of two horses administered 1500 mcg/kg (7.5X) due to moribundity. Clinical abnormalities appeared to be consistent with neurotoxicity and included listlessness, depression, lower lip flaccidity (drooping lips), mydriasis, excitability, ataxia, recumbency, incomplete mastication/deglutition (feed held in mouth), weakness, weight shifting, tremors, urine dribbling, and head pressing. These clinical signs may occur in sensitive animals when administered at the proposed dose to a broader population of horses. Therefore, for the purposes of this EUA, users should be advised to monitor horses for these clinical signs following doramectin injection.

There are limitations of the data as presented, especially the limited histopathologic assessment. Raw data and complete individual animal data listings were not provided to CVM for review. However, based on the provided information there does not appear to be clinically significant gross or microscopic pathology associated with DECTOMAX®/DECTOMAX®-CA1 administration in horses.

B. Injection Site Safety in Horses

Title: Doramectin Injection-Site Toleration in Horses. (Study No. 1453N-60-97-164)

Study Dates: August 1997 to April 1998

Study Location: Fort Collins, CO

Study Design:

Objective: To evaluate the effect of intramuscular injection of doramectin at 300 mcg/kg (1.5 mL per 50 kg) upon tissue at the site of injection.

Study Animals: Twenty horses approximately 1 to 3 years of age, various breeds, non-pregnant females, geldings, and stallions

Experimental Design: Horses were randomly assigned to a necropsy time of 7 (T1) or 30 days (T2) (n = 10 per group). Clinical observations and injection site observations were conducted by a study veterinarian masked to specific treatment assignment. The study was conducted according to Good Laboratory Practices. Horses were euthanized at the scheduled study day for postmortem examination of injection sites and collection of injection site tissues for histopathology.

Drug Administration: Each horse received two intramuscular injections of doramectin (one in the neck and one in a gluteal muscle) and two of saline (one in the neck and one in a gluteal muscle) on Day 0. Treatments were randomized to side of animal.

Measurements and Observations: General health observations, post-dosing clinical observations, and injection site observations occurred during the study period. Gross and microscopic examination of injection site tissues was conducted after necropsy. Injection sites were only evaluated microscopically if there were gross lesions observed. If gross lesions were observed, tissue of the corresponding site on the contralateral side was collected for comparative histopathological examination.

Statistical Method: Not reviewed.

Results: One horse had loose feces post-dosing. Transient lower lip flaccidity was incidentally observed by the study veterinarian outside of scheduled observation times within the first two days post-dose. There were no palpable or visual abnormalities at any of the injection site examinations. In horses necropsied at Day 7, the following microscopic abnormalities were found at more than one doramectin site: hemorrhage, subacute inflammation, edema, Zenker's degeneration, and fibrosis. In horses necropsied at Day 30, a single doramectin site had gross discoloration, which was associated with microscopic findings of mild, multifocal histiocytic inflammation.

Conclusions: Mild clinical signs (transient lower lip flaccidity) were associated with two simultaneous injections of 300 mcg/kg each (3X proposed dose) in some horses. These clinical signs were poorly documented during the study and therefore not well characterized for number of animals involved or duration of signs. There were no reported injection site reactions. There are limitations of the data as presented, especially the limited histopathologic assessment. However, based on the provided information there does not appear to be clinically significant gross or microscopic pathology at the injection sites associated with DECTOMAX® (doramectin injection). Further, a single 3X systemic dose of doramectin in two injections was not associated with clinically significant adverse effects, supporting the safety of DECTOMAX®/DECTOMAX®-CA1 in horses at 200 mcg/kg.

C. Target Animal Safety in Sheep

The target animal safety of DECTOMAX® (doramectin injection) in sheep has not been established in controlled laboratory or field studies in the U.S. Available safety information is limited to the three dose confirmation effectiveness studies cited above that were conducted in Brazil and Argentina. In these studies, DECTOMAX® (200 mcg/kg body weight) was administered either following routine management procedures (e.g., shearing) with subsequent natural exposure to NWS or following

induced wounds. Across the studies, no adverse reactions attributable to doramectin administration were reported. Treated animals were monitored for up to 14 days, and no safety concerns were identified. In the published literature described above, no adverse effects related to treatment were reported in doramectin-treated animals. Based on the available data, DECTOMAX® (doramectin injection) administered at 200 mcg/kg body weight is well tolerated in sheep under the conditions of these studies.

D. Target Animal Safety in Deer

The target animal safety of doramectin in deer has not been established in controlled laboratory or field studies. Available safety information is limited to residue depletion studies in deer[9,20] and a USDA report[21] from a 2016 NWS outbreak in the endangered Key deer population in Florida. In the residue depletion studies, the PK profile of doramectin (200 mcg/kg) was studied in male deer after a single SC administration. Doramectin was well tolerated by deer when treated with the proposed dosing, but no target animal safety or tolerance studies were conducted.

During the Florida Keys outbreak, doramectin was administered to Key deer by either medicated feed (oral route), treated rollers at feeding stations (topical route), or by subcutaneous injection, with over 10,000 doses reportedly administered. However, these data are not derived from controlled studies in a controlled dosing environment; deer were free-ranging and repeated exposure was possible as deer could revisit stations and treatment administrators could have accidentally re-dosed animals. Deer were monitored after treatment administrations through trail cameras, animal tagging, and visual observations; and no population-level adverse events were clearly attributable to doramectin. The severe adverse events reported were morbidity and mortality related to NWS infestation and did not appear to be drug-product related. Due to the lack of controlled safety studies, there is uncertainty regarding the safety profile of doramectin in deer. However, the absence of reports of adverse effects in the residue depletion studies and the large-scale field use in Key deer in the U.S. provides supportive evidence of tolerance.

IV. HUMAN FOOD SAFETY

The product fact sheet contains the following Warning statement: Do not use in horses intended for human consumption.

The human food safety assessment for the EUA of DECTOMAX®/DECTOMAX®-CA1 Injectable Solution for Cattle and Swine for use in lactating dairy cows, dry dairy cows, replacement dairy heifers, swine, sheep and deer was based on the following information and data:

---

[9] Study 25A9A-49-95-002. Pharmacokinetics of Doramectin in Blood Plasma and Tissue in Liver, Kidney, Muscle, and Abdominal Fat Following Subcutaneous Administration in Reindeer. 1996.
[20] Study 2509A-03-98-011. Residue Depletion Study in Deer Administered a Single Subcutaneous Injection of Doramectin at a Dose Rate of 200 a.i./kg Bodyweight. 1999.
[21] USDA APHIS NWS Response. Final Report for APHIS Veterinary Services (VS) Response to the 2016–2017 Outbreak of New World Screwworm (NWS) in Florida.

1. The human food safety information and data for the original approvals of NADA 141-061, dated July 30, 1996, and NADA 141-553, dated September 09, 2022.

2. The maximum residue limit (MRL) adopted by the Codex Alimentarius Commission for doramectin in milk (15 ppb)[22].

3. One milk residue depletion study evaluated by the 62nd meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[23,24]:

   A field and laboratory study to determine the residue depletion profile of doramectin in milk following administration of a 10 mg/mL doramectin injectable formulation in lactating dairy cattle. Volume 5, April 2003. Study Report 2539A-14-01-003 (PFD 1205).

4. One total residue and metabolism study conducted in sheep and submitted by the sponsor:

   [^{3}H]-Doramectin Metabolism and Residues Following Subcutaneous Administration to Sheep. Study number 2546A-03-94-008.

5. One marker residue depletion study conducted in sheep and two marker residue depletion studies conducted in deer and submitted by the sponsor:

   Tissue Residues of Doramectin in Sheep Following Intramuscular Injection. Study number 2549A-03-96-010.

   Residue Depletion Study in Deer Administered a Single Subcutaneous Injection of Doramectin at a Dose Rate of 200 mcg/kg Bodyweight. Study number 2509A-03-98-011.

   Pharmacokinetics of Doramectin in Blood Plasma and Tissue Residues in Liver, Kidney, Muscle and Abdominal Fat Following Subcutaneous Administration in Reindeer. Study number 25A9A-49-95-002.

6. Publicly available information:

   Toutain, P. L., Upson, D. W., Terhune, T. N., & McKenzie, M. E. (1997). Comparative pharmacokinetics of doramectin and ivermectin in cattle. *Veterinary Parasitology 72*, 3-8.

   Lin, Z., Li, M., Wang, Y-S., Tell, L. A., Baynes, R. E., Davis, J. L., Vickory, T. W., & Riviere, J. E. (2020). Physiological parameter values for physiologically based pharmacokinetic models in food-producing animals. Part I: Cattle and swine. *Journal of Veterinary Pharmacology and Therapeutics, 43*, 385-420.

---

[22] CXM 2. Maximum Residue Limits (MRLs) and Risk Management Recommendations (RMRs) for Residues of Veterinary Drugs in Foods.
[23] Joint FAO/WHO Expert Committee on Food Additives (2004: Rome, Italy). Evaluation of certain veterinary drug residues in food: sixty-second report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series; 925).
[24] Doramectin. FAO Food and Nutrition Paper 41/16.

Chou, W-C., Tell, L. A., Baynes, R. E., Davis, J. L., Maunsell, F. P., Riviere, J. E., & Lin, Z. (2022). An Interactive Generic Physiologically Based Pharmacokinetic (igPBPK) Modeling Platform to Predict Drug Withdrawal Intervals in Cattle and Swine: A Case Study on Flunixin, Florfenicol, and Penicillin G. *Toxicological Sciences,188*, 180-197.

FDA concluded that the food products obtained from treated animals are safe for human consumption when the conditions of use granted by the Emergency Use Authorization are followed, including the withdrawal periods and milk discard time.

For meat tissues, FDA reviewed the aforementioned information and data and concluded the following:

- A 35-day withdrawal period is assigned to lactating dairy cows, dry dairy cows, and replacement dairy heifers administered a subcutaneous injection of DECTOMAX®/DECTOMAX®-CA1 at up to 200 mcg doramectin/kg bw. A withdrawal period has not been established for this product in pre-ruminating calves. Treated calves and calves born to treated cows and heifers must not be processed for veal.

- A 24-day withdrawal period is assigned to swine administered an intramuscular injection of DECTOMAX®/DECTOMAX®-CA1 at up to 300 mcg doramectin/kg bw.

- A 35-day withdrawal period is assigned to sheep administered an intramuscular or subcutaneous injection of DECTOMAX®/DECTOMAX®-CA1 at up to 300 mcg doramectin/kg bw.

- A 35-day withdrawal period is assigned to deer administered an intramuscular or subcutaneous injection of DECTOMAX®/DECTOMAX®-CA1 at up to 200 mcg doramectin/kg bw.

For milk, FDA evaluated the milk residue depletion studies reported by the 62nd meeting of JECFA. In addition, to overcome limitations of the data, FDA developed a population-based physiologically-based pharmacokinetic (pop-PBPK) model for residues of doramectin in milk. Based on the totality of evidence (Codex MRL, JECFA data, and pop-PBPK model), FDA concluded the following:

- A 468-hour (19.5 days) milk discard time is assigned to lactating dairy cows, dry dairy cows, and replacement dairy heifers administered a subcutaneous injection of DECTOMAX®/DECTOMAX®-CA1 at up to 200 mcg doramectin/kg bw.

A. USER SAFETY

The product Fact Sheets contain the following information regarding safety to humans handling, administering, or exposed to DECTOMAX®/DECTOMAX®-CA1:

Not for use in humans. Keep out of reach of children.

The safety data sheet (SDS) contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain an SDS, call 1-888-963-8471.

V. AGENCY CONCLUSIONS

Based on the totality of scientific evidence available to FDA, including data from clinical effectiveness, PK, and margin of safety studies, and published scientific literature, it is reasonable to believe that DECTOMAX®/DECTOMAX®-CA1, when used as authorized, may be effective for the prevention and treatment of infestations caused by *Cochliomyia hominivorax* larvae (myiasis) in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older), except for calves that will be processed for veal, and for the prevention of infestations caused by *Cochliomyia hominivorax* larvae (myiasis) in horses one year and older, swine, sheep except for lactating sheep, and deer. The known and potential benefits of DECTOMAX®/DECTOMAX®-CA1 when used as authorized outweigh the known and potential risks since NWS infestations can have significant adverse health consequences and can be fatal if left untreated due to the extensive tissue damage caused by *Cochliomyia hominivorax* larvae. The benefit of preventing or treating this potentially fatal disease outweighs the health risks of using this product in these species. Additionally, data demonstrate that residues in food products derived from lactating dairy cows, dry dairy cows, replacement dairy heifers 20 months of age and older except for lactating sheep treated with DECTOMAX®/DECTOMAX®-CA1 will not represent a public health concern when the product is used as authorized.

There is no adequate, approved,[25] and available alternative to the product for the treatment and prevention of NWS myiasis in dairy cattle (lactating dairy cows, dry dairy cows, and replacement dairy heifers 20 months of age and older); and for prevention of NWS myiasis in horses one year and older, swine, sheep except for lactating sheep, and deer. The conditional approval for indications against NWS for DECTOMAX®-CA1 does not include these additional species and subclasses of cattle.

For additional information on all products authorized or conditionally approved for use to treat and/or prevent New World screwworm, please see FDA's "New World Screwworm: Information for Veterinarians" webpage at https://www.fda.gov/animal-veterinary/safety-health/new-world-screwworm-information-veterinarians.

A. Duration of Authorization: Revision and Revocation

This EUA will be effective until revoked under Section 564(g) of the FD&C Act or until the Secretary's declaration of emergency or threat justifying emergency authorized use is terminated (Section 564(f)(1)), with exception for continued use permissible under Section 564(f)(2). FDA may revoke or revise this authorization if emergency use of this animal drug for NWS myiasis is no longer justified, if the product no longer meets the criteria for issuance of an EUA under Section 564(c) of the FD&C Act, or other circumstances make such revocation or revision of the authorization appropriate to protect the public health or safety (Section 564(g)(2) of the FD&C Act).

---

[25] "Approved" products include conditionally approved products for purposes of EUAs issued under Section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.

B. Marketing Status

This product is authorized to be marketed OTC because the authorized labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.