

Date of Approval: September 9, 2010

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-314

EQUIDONE Gel

Domperidone  
Horses/Periparturient Mares

For the prevention of fescue toxicosis in periparturient mares

Sponsored by:

Dechra, Ltd.

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**I. GENERAL INFORMATION:**

- A. File Number:** NADA 141-314
- B. Sponsor:** Dechra, Ltd.  
Dechra House  
Jamage Industrial Estate  
Talke Pits  
Stoke-on-Trent  
Staffordshire, ST7 1XW  
United Kingdom
- Drug Labeler Code: 043264
- U.S. Agent: Melinda Poole  
Dechra, Ltd.  
7015 College Boulevard, Suite 525  
Overland Park, KS 66211
- C. Proprietary Name:** EQUIDONE Gel
- D. Established Name:** Domperidone
- E. Pharmacological Category:** D<sub>2</sub> dopamine receptor antagonist
- F. Dosage Form:** Gel
- G. Amount of Active Ingredient:** 110 mg/cc (11% w/w)
- H. How Supplied:** 25 cc multi-dose syringe
- I. How Dispensed:** Rx
- J. Dosage:** 0.5 mg/lb (1.1 mg/kg) once daily starting 10 to 15 days prior to expected foaling date (EFD). Treatment may be continued for up to 5 days after foaling if mares are not producing adequate milk after foaling.
- K. Route of Administration:** Oral
- L. Species/Class:** Horses/Periparturient Mares
- M. Indication:** For prevention of fescue toxicosis in periparturient

mares

## II. EFFECTIVENESS:

### A. Dosage Characterization:

Dosage characterization is based on the two pilot studies described below. Although the duration of treatment in these studies is not identical to the recommended treatment duration, these studies provide support for the premise that domperidone administered at a rate of 1.1 mg/kg (1 cc/100 kg) once daily starting 10 to 15 days prior to the expected foaling date and continuing for up to 5 days after parturition may be safe and effective to prevent fescue toxicosis in periparturient mares.

A controlled study with 24 pregnant mares evaluated the effect of continuing domperidone treatment after foaling.<sup>1</sup> Control mares were pastured on either endophyte infected (E+) or endophyte negative tall fescue (E-). Treatment groups grazed E+ pastures and received a daily oral dose of 1.1 mg/kg domperidone for either 25 days prior to foaling (D-0) or 25 days prior to foaling and 10 days after foaling (D-10). No differences were noted in milk composition, foal IgG concentrations, mammary gland development, mare and foal weight, or foal mortality between the two domperidone treated groups and control mares on E- pasture. An oral dose of 1.1 mg/kg/day domperidone given either 25 days prior to the expected date of parturition or given both 25 days pre- and 10 days postpartum was effective for prevention of fescue toxicosis in pregnant mares. No adverse events were associated with continuing domperidone treatment for 10 days post-foaling.

A shorter duration dosing study was conducted with 27 pregnant mares grazing either endophyte infected (E+) or endophyte negative (E-) pastures.<sup>2</sup> The mares received a daily dose of 1.1 mg/kg domperidone orally starting either 10 or 15 days prior to their expected foaling date and continued up to foaling. Mortality, gestation length, placental retention, body condition scores and weights, foal IgG concentration, mammary gland development, agalactia, dystocia, and endocrine responses (prolactin, immunoreactive progesterone response and estradiol-17 $\beta$  concentrations) were evaluated. The daily dose of 1.1 mg/kg domperidone prevented clinical signs of fescue toxicosis when administered for either 10 or 15 days prior to the expected foaling date.

A pharmacokinetic study entitled “Pharmacokinetic and Pharmacodynamic Effects of Oral and Intravenous Domperidone in Horses” (Study #: DOM002) was performed to evaluate the pharmacokinetic properties of domperidone. The study was conducted as a

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<sup>1</sup> Kouba JM. Effect of Endophyte-Infected Tall Fescue and Pre-and Postpartum Domperidone Treatment on Pregnant Mares. Masters Thesis, Clemson University, Clemson, SC; 1995

<sup>2</sup> Dooley KM. Short Duration Dosing of Mares for Treatment of Equine Fescue Toxicosis. Masters Thesis, Clemson University, Clemson, SC; 1998

four-period crossover study in eight healthy horses (4 geldings and 4 mares), ranging in age from 4 to 15 years. Horses were randomly assigned to one of the four (n=2 horses per treatment group) treatment groups: (a) EQUIDONE Gel administered orally (PO) at 1.1 mg/kg BW; (b) EQUIDONE Gel administered PO at 5.5 mg/kg BW; (c) domperidone solution administered intravenously (IV) at 0.2 mg/kg; (d) acepromazine maleate administered IV at a dose of 0.04 mg/kg. Domperidone concentrations in blood plasma were measured using a validated LC-MS/MS method. Average terminal elimination half-life of domperidone in horses was approximately 6 and 5 hours for the oral and intravenous administration groups, respectively. Average area under the plasma concentration time curve from time 0 to 24 hr ( $AUC_{0-24}$ ) was 26.2 ( $\pm 15.3$  SD) and 182 ( $\pm 156$  SD) ng\*hr/mL, for the 1.1 and 5.5 mg/kg PO groups, respectively, and 1387 ( $\pm 1911$  SD) ng\*hr/mL, for the 0.2 mg/kg IV group. The average clearance in the 0.2 mg/kg IV group was 143 mL/hr/kg. Oral bioavailability of EQUIDONE Gel in horses was 1.2% for the 1.1 mg/kg dose and 1.4% for the 5.5 mg/kg dose.

Based on these studies, a dose of 1.1 mg/kg/day domperidone beginning 10-15 days prior to the expected foaling date and continued for up to 5 days after foaling was further evaluated in the effectiveness studies.

## **B. Substantial Evidence:**

### **1. Laboratory Effectiveness Study**

- a. **Study Title and Number:** Dose Confirmation: Domperidone Gel at 1.1 mg/kg for Prevention of Fescue Toxicosis in Periparturient Mares. Study #: DOM004.
- b. **Type of Study:** GCP laboratory effectiveness study.
- c. **Study Dates:** March – September, 2008
- d. **Investigator:** Craig R. Reinemeyer, DVM, PhD  
Rockwood, TN
- e. **Study Design:**
  1. **Objective:** To confirm the effectiveness of EQUIDONE Gel for the prevention of fescue toxicosis in periparturient mares following oral administration of 1.1 mg/kg once daily, starting 10-15 days prior to the expected foaling date and continuing for up to 5 days after foaling if needed for milk production.
  2. **Study Animals:** Thirty-two healthy, pregnant, adult (3-22 years old) Tennessee Walking Horse and Quarter Horse mares, were enrolled in the study. Pregnancy was confirmed by rectal ultrasound or rectal palpation.
  3. **Treatment Groups:**

Table 1. Treatment Groups

Treatment Group	Dose	Number of Mares Enrolled (Evaluable)
EQUIDONE	1.1 mg/kg	17 (13)
Control	0 mg/kg	15 (14)

4. *Drug Administration:* EQUIDONE Gel was administered orally at 1.1 mg/kg (1 cc/100 kg) once daily beginning 10-15 days prior to the Expected Foaling Date<sup>3</sup> (EFD) and continuing for up to 5 days after foaling. Control horses received vehicle gel administered at an equivalent dose volume and frequency. The dose calculation for each mare was based on her body weight, according to the following chart:

Table 2. Dosing Chart

Weight (lb)	Weight (kg)	cc	Domperidone (mg)
550-660	250-300	3	330
661-880	301-400	4	440
881-1100	401-500	5	550
1101-1320	501-600	6	660

5. *Duration of Study:* Mares were treated with EQUIDONE Gel or vehicle placebo beginning 10-15 days prior to EFD. Mares continued on treatment for up to 5 days after foaling. Mares and foals were evaluated through 5 days post-foaling.
6. *Inclusion Criteria:* Pregnant mares with a known EFD more than 30 days distant in good or excellent health based on physical exam.
7. *Dosage Form:*
- EQUIDONE—Final market formulation 110 mg/cc EQUIDONE Gel (domperidone).
- Control—Vehicle placebo gel.
8. *General Design:* To induce fescue toxicity, each mare was fed endophyte-infected fescue seed supplemented with endophyte-infected fescue hay (resulting in  $\geq 200$  ppb ergovaline/day) beginning approximately 30 days prior to EFD and continuing through Day 5 post-foaling. Mares were randomly allocated to treatment with EQUIDONE Gel or control (vehicle placebo gel). Mares exceeding their EFD by  $\geq 15$  days and mares not producing adequate milk were removed from the study as treatment failures and administered domperidone as rescue therapy.

<sup>3</sup> Expected Foaling Date (EFD) was defined as 340 days after the median breeding date.

9. Management: Mares were dewormed and vaccinated for rhinopneumonitis prior to acclimation. Mares experiencing retained placentas were administered oxytocin. Routine foal prophylaxis measures were implemented after birth including dipping the navel in iodine solution, administration of a phosphate enema, and injection of tetanus antitoxin. Foals with serum IgG concentrations <800 mg/dL were given intravenous transfusions of equine plasma. Foals of mares with poor mammary gland development or inadequate milk production were provided with milk supplementation, if necessary.
10. Measurements and Observations: Effectiveness was assessed based on gestation length, mammary gland development,<sup>4</sup> presence of milk at foaling<sup>5</sup> and adequate lactation<sup>6</sup> for 5 days post-foaling. Mares were monitored for health during gestation, foaling observations, and post-partum examinations of the mare and placenta. Foal health was evaluated (physical exam and IgG) within 24 hours of birth, and for 5 additional days after the foaling date (observations, physical exams, body weights). Blood chemistry and hematology tests were conducted on the mares before treatment started and at the end of the study.
11. Statistical Methods: Treatment success was defined for each mare based on the actual foaling date relative to the expected foaling date, mammary gland development score on the day of foaling, postpartum lactation scores on the day of foaling and lactation scores for the 5 days following foaling. To be considered a treatment success, foaling must have occurred within 14 days of the expected foaling date, the mammary gland development score<sup>4</sup> must have been  $\geq 2$  on the day of foaling, and postpartum lactation must be present at foaling<sup>5</sup> and adequate<sup>6</sup> for the entire 5 day observation period. Mares foaling within 5 days of treatment initiation were considered non-evaluable. Mares not meeting the criteria for success and mares requiring rescue treatment were evaluated as treatment failures.

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<sup>4</sup> Mammary gland development was scored from 0 to 3:

0	No visible or palpable development of mammary gland
1	Slight distention / enlargement
2	Moderate distention; bases of teats distended with fluid
3	Mammary glands and teats fully distended

<sup>5</sup> Presence of milk at foaling was assessed as:

Present	Visible or demonstrable milk
Absent	No visible or demonstrable milk

<sup>6</sup> Lactation for 5 days post-foaling was assessed as:

Adequate	Visible or demonstrable milk and foal satiety
Inadequate	No visible or demonstrable milk and/or foal appears hungry (frequent attempts to nurse)

Secondary effectiveness variables included gestation length, occurrence of dystocia, mammary gland development, and milk production at foaling.

Inferential statistical analyses were a function of the level of measurement. For nominal levels of measurement the 2-sample test for equality of proportions was conducted. Response variables included the primary effectiveness outcome variable overall treatment success (success/failure) and the secondary effectiveness outcome variables adequate milk production at foaling (yes/no) and adequate mammary gland development at foaling (yes/no). The gestation length (ratio level of measurement) was analyzed using the two sample t-test for equality of means.

No inferential statistical analyses were performed on safety variables.

f. **Results:**

Thirty-two mares were enrolled in the study (17 treated with EQUIDONE Gel, 15 vehicle control), and 27 mares (13 treated with EQUIDONE Gel, 14 vehicle control) were included in the effectiveness analysis. Twelve of thirteen (92%) mares treated with EQUIDONE Gel and 1 of 14 control mares (7%) met the criteria for treatment success (Table 3). The success rate between treatments was statistically significantly different ( $p < 0.0000$ ). The treatment groups were also statistically significantly different ( $p < 0.0031$ ) for gestation length (mean), adequate mammary gland development (proportion success) and adequate milk production at foaling (proportion success) (Table 4). Five mares were excluded from the effectiveness analysis for foaling within 5 days of treatment initiation, giving birth to a mule foal, or lack of exposure to endophyte.

Table 3. Treatment Success

Treatment Group (number mares)	Treatment Success	Pearson $\chi^2$ Test
Vehicle Control (14)	7% (1 / 14)	Test statistic = 16.320 p-value < 0.0000
EQUIDONE Gel (13)	92% (12 / 13)	

Table 4. Gestation Length, Milk Production and Mammary Gland Development

Treatment Group (number mares)	Mean gestation length in days	Percent adequate milk production at foaling	Percent adequate mammary gland development at foaling
Vehicle Control (14)	346	33% (3 / 9) <sup>1</sup>	30% (3 / 10) <sup>2</sup>
EQUIDONE Gel (13)	337	100% (13 / 13)	100% (13 / 13)
Test Statistic	t statistic = 3.754 p=0.0014	Pearson $\chi^2$ = 8.793 p=0.0030	Pearson $\chi^2$ = 9.984 p=0.0016

<sup>1</sup>Three mares rescued prior to foaling for exceeding EFD by  $\geq 15$  days, 1 euthanized after foaling, 1 missing observation

<sup>2</sup>Three mares rescued prior to foaling for exceeding EFD by  $\geq 15$  days, 1 euthanized after foaling

One mare treated with EQUIDONE Gel was carrying twins; one twin foal was stillborn and the other foal was born alive and healthy. Six foals of control mares were stillborn, died or were euthanized within 5 days of birth. Two control mares were euthanized within 5 days of foaling due to bacterial metritis and colic. Dystocia occurred in 1 mare treated with EQUIDONE Gel and 4 control mares. Two mares treated with EQUIDONE Gel and 6 control mares had assisted deliveries (limited to manual assistance/manipulation outside the vulva). One mare treated with EQUIDONE Gel and three control mares experienced retained placentas.

**g. Adverse Reactions:**

Foal IgG concentrations were evaluated in 25 of the 33 total foals born in this study. Of the 25 foals evaluated for IgG, 16 were born to EQUIDONE Gel treated mares and 9 were born to control mares. Failure of passive transfer (IgG <800 mg/dL) occurred in 13/16 (81%) foals of mares treated with EQUIDONE Gel and 8/9 (89%) foals of control mares. Three of the 17 EQUIDONE Gel treated mares were noted to drip milk for a single day prior to foaling. Failure of passive transfer in foals of mares treated with EQUIDONE Gel was not solely due to physical loss of colostrum through premature lactation, because 77% of EQUIDONE Gel treated mares that did not drip milk prior to foaling had foals with failure of passive transfer.

**h. Conclusions:**

EQUIDONE Gel was effective in preventing clinical signs of fescue toxicosis when administered at 1.1 mg/kg orally once daily in periparturient mares challenged with endophyte-infected fescue seed and hay.

## 2. Field Effectiveness Study:

a. **Study Title and Number:** A Clinical Trial of Efficacy of Domperidone Oral Gel (Final Formulation) in Periparturient Mares for the Prevention and Treatment of Fescue Toxicosis and Related Agalactia.  
Study #: ETIdomEFTCTE02.

b. **Type of Study:** Open label, uncontrolled, field effectiveness study.

c. **Study Dates:** February – May 1999

d. **Investigators:**

Michael J. Beyer, DVM  
Versailles, KY

James P. Klyza, DVM  
Paris, KY

Richard Holder, DVM  
Lexington, KY

e. **Study Design:**

1. **Objective:** To determine the effectiveness and field safety of EQUIDONE Gel.

2. **Study Animals:** Two hundred seventy-nine periparturient mares (278 Thoroughbred and 1 draft mare; 4 to 24 years of age) grazing endophyte-infected fescue pasture.

3. **Treatment Groups:** This was an uncontrolled, open-label study. All horses were treated with EQUIDONE Gel.

4. **Drug Administration:** EQUIDONE Gel was administered orally at a 1.1 mg/kg (1 cc/100 kg) once daily beginning 10-15 days prior to the Expected Foaling Date<sup>7</sup> (EFD) and continuing after foaling as necessary. Only mares treated at the recommended dose and duration were included in the effectiveness analysis.

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<sup>7</sup> Expected Foaling Date (EFD) was defined as 340 days after breeding.

5. Duration of Study: Mares were treated with EQUIDONE Gel beginning 10-15 days prior to EFD. Mares and foals were evaluated through 5 days post-foaling.
6. Enrollment Inclusion/Exclusion Criteria: Inclusion criteria included healthy, reproductively sound, pregnant mares in the last trimester of gestation remaining on fescue until 2 days prior to their EFD. Mares with a history of reproductive problems, twins, and mares not consuming endophyte infected fescue were excluded from enrollment.
7. Criteria for Inclusion in the Effectiveness Database: Mares with a known EFD, documented exposure to endophyte infected fescue, and treated at the recommended dose and duration with EQUIDONE Gel.
8. Dosage Form: Final market formulation 110 mg/cc EQUIDONE Gel (domperidone).
9. Measurements and Observations: Levels of pasture fescue and endophyte were recorded for each farm. Mares were monitored for gestation length, udder development, presence or absence of milk at foaling, lactation at end of treatment, foaling observations, and mare and foal mortality. Udder development and lactation at the end of treatment were scored on a scale of 1 to 5 (poor to excellent) with a score of 3 or more being considered adequate.
10. Evaluation of Effectiveness: The results of this study are intended to corroborate the findings of the laboratory effectiveness study (DOM004) in horses with naturally occurring disease. A control group was not included in this study due to the life-threatening nature of fescue toxicosis, the lack of an adequate active control, and the inability to provide adequate rescue treatment. Ingestion of endophyte infected fescue is known to cause clinical signs of fescue toxicosis as demonstrated in the literature and the laboratory effectiveness study DOM004.<sup>8,9,10</sup> The results of this study were interpreted in relation to the laboratory effectiveness study DOM004, historical controls (references 8, 9 and 10), and published literature.

f. **Results:**

One hundred ninety-three mares were included in the effectiveness analysis. Mares grazed pastures with an average fescue content of 50% and an average endophyte

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<sup>8</sup> Monroe JL, et al. Effect of Selenium and Endophyte-Contaminated Fescue on Performance and Reproduction in Mares. *Journal of Equine Veterinary Science* 8(2): 148-153; 1988

<sup>9</sup> Earle WE, et al. Effect of Energy Supplementation on Gravid Mares Grazing Endophyte-Infected Fescue. *Journal of Equine Veterinary Science* 10(2): 126-130; 1990

<sup>10</sup> Putnam MR, et al. Effects of the Fungal Endophyte *Acremonium coenophialum* in Fescue on Pregnant Mares and Foal Viability. *American Journal of Veterinary Research* 52(12): 2017-2074; 1991

contamination level of 80%. Individual pastures in this study ranged from 20-95% fescue and were 40-100% positive for endophyte. All horses included in the effectiveness analysis were exposed to endophyte infected fescue up to foaling. The most common reason for exclusion from the effectiveness database was a treatment duration of more than 15 or less than 10 days prior to EFD.

The 193 mares included in the effectiveness analysis had a mean gestation length of 340 days. Gestation lengths ranged from 326 to 360 days with 5 mares (3%) exceeding their EFD<sup>11</sup> by more than 14 days. Underdeveloped udders (scores of 1 or 2) at the time of foaling were reported in 5 (3%) mares. Two out of 187 mares (1%) were agalactic at the time of foaling (6 mares were missing lactation data at the time of foaling). All mares continuing on treatment after foaling had adequate lactation at the end of treatment. Five mares (3%) experienced dystocia, and 6 mares (3%) had retained placentas.

Of the 279 total mares treated with EQUIDONE Gel, 3 mares (1%) died or were euthanized within 5 days of foaling due to dystocia or uterine artery rupture. Eight foals (3%) were either stillborn, died, or were euthanized within 5 days of foaling. Causes of death included dystocia, ruptured pulmonary artery, placentitis, asphyxia, or undetermined. Five mares (2%) experienced premature placental separation.

**g. Adverse Reactions:**

Of the 279 total mares treated with EQUIDONE Gel, premature lactation was reported in 3 (1%) mares and failure of passive transfer was reported in 3 (1%) foals.

**h. Conclusions:**

The results of this study corroborate the findings of the laboratory effectiveness study DOM004, and support the effectiveness of EQUIDONE Gel under field conditions for the prevention of fescue toxicosis in periparturient mares.

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<sup>11</sup> EFD calculations were performed by each farm. EFDs were calculated based on gestation lengths ranging from 335-340 days.

### III. TARGET ANIMAL SAFETY:

#### A. Laboratory Safety

##### 1. Margin of Safety Study

- a. **Study Title and Number:** Target Animal Safety Study of Domperidone Oral Gel in Pregnant Adult Female Horses. Study #: DOM001.
- b. **Type of Study:** GLP laboratory study.
- c. **Study Dates:** March 24, 2007 to May 6, 2008
- d. **Study Director and Location:** Craig R. Reinemeyer, DVM, PhD  
Rockwood, TN
- e. **Study Design:**
  1. *Objective:* To determine the safety of EQUIDONE Gel in periparturient mares and their foals after oral administration in the mare at 1X, 3X, and 5X the recommended maximum dose (1.46 mg/kg) once daily beginning approximately 45 days (Cohort 1) or 15 days (Cohort 2) prior to Expected Foaling Date<sup>12</sup> (EFD), and continuing for 15 days after foaling (3X the maximum duration).
  2. *Study Animals:* Thirty-two periparturient Quarter Horse and Tennessee Walking Horse mares, 4-18 years of age, and weighing 416 to 598 kg.
  3. *Dosage Form:*

EQUIDONE—Final market formulation 110 mg/cc EQUIDONE Gel (domperidone).

Control—Vehicle placebo gel.
  4. *Drug Administration:* Treated mares received 0X, 1X, 3X, or 5X the maximum potential exposure dose for a 550 lb mare once a day starting at either 45 or 15 days prior to their EFD and continuing for 13-17 days after foaling.

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<sup>12</sup> Expected Foaling Date (EFD) was calculated as 340 days after the median breeding date.

Table 5. Treatment Groups

Treatment Group	Dose	Number of mares started on treatment:	
		45 days before EFD (Cohort 1)	15 days before EFD (Cohort 2)
1	(0X) 0.0 mg/kg *	4	4
2	(1X) 1.46 mg/kg	4	4
3	(3X) 4.38 mg/kg	4	4
4	(5X) 7.30 mg/kg	4	4

\*Control mares were administered vehicle at a volume equivalent to the 3X group

5. *Inclusion/Exclusion Criteria:* Pregnant mares with a known EFD more than 60 days distant (Cohort 1) or more than 30 days distant (Cohort 2). Mares with a single fetus in good or excellent health based on physical exams, reproductive exams, and clinical pathology evaluations.
6. *General Design:* Mares were treated 45 days (Cohort 1) or 15 days (Cohort 2) prior to EFD with either a placebo gel control or EQUIDONE Gel at 1X, 3X or 5X the recommended dose. Mares continued treatment for 15 (+/-2) days after foaling. Mares in the 0X and 3X groups were rebred and followed through 50 days of gestation or until the mare was determined not pregnant after two failed breeding attempts. Foals of mares in all treatment groups were evaluated through day 15 post-foaling. Foals of mares in the 0X and 3X groups continued to be evaluated until the mare reached 50 days of gestation or was removed from the study after two failed breeding attempts.
7. *Measurements and Observations:* Physical examinations, body weights, and clinical pathology for mares (hematology, serum chemistry, coagulation, and reproductive hormones) were evaluated pre-treatment, at least once during treatment prior to foaling, the day of foaling, and 15 days after foaling. Urinalysis was performed pre-treatment and 15 days after foaling. Control and 3X mares were also evaluated at rebreeding. Observations of parturition, the placenta, foal behavior and health at birth, and gestation length were recorded at the time of foaling. Mammary gland development and lactation scores were evaluated beginning prior to treatment and continued through the day of foaling. Foal IgG concentrations were evaluated on the day of foaling. Foal body weight, physical exams, and clinical pathology (hematology and serum chemistry) were evaluated on the day of foaling, Day 7, and Day 15 post foaling. Control and 3X foals were also evaluated on the days the mare was bred. Mares and foals received general health observations throughout the study. Mares in the 0X and 3X groups were followed for re-breeding success. Mares with liver enzymes elevated above twice the upper limit of the reference range had a liver

biopsy. Foals that died or were euthanized received complete necropsy and histopathology evaluations. Mares of foals that died during the treatment phase were euthanized and received complete necropsy and histopathology evaluations.

8. *Statistical Methods*: Statistical analyses were a function of the level of measurement and the number of times a measurement was taken. For interval/ratio levels of measurement where the response variable was measured more than once, the data were analyzed as a completely randomized design with a two-way treatment structure (dose and time) using an analysis of variance with a linear model. For interval/ratio levels of measurement where the response variable was measured once, the data were analyzed as a completely randomized design with a one-way treatment structure (dose) using an analysis of variance with a linear model.

In the case of nominal/ordinal levels of measurement where the response level was measured more than once, the data were analyzed as a completely randomized design with a two-way treatment structure (dose and time) using an analysis of variance with a generalized linear model. For nominal/ordinal levels of measurement where the response variable was measured once the Fisher's Exact test was used to evaluate difference from the control.

f. **Results:**

1. *Gestation length*: The first 4 horses enrolled in each treatment group in the study began treatment 45 days prior to their EFD (Cohort 1). Due to premature foaling in treated mares, the study protocol was amended, and the next 4 horses in each treatment group began treatment 15 days prior to EFD (Cohort 2). In Cohort 1, gestation lengths were statistically significantly shorter for foals in all treated groups as compared to controls (p-value=0.0006). Treated mares in Cohort 1 foaled an average of 27 days prior to EFD with a range of 12 to 40 days prior to EFD. These mares received treatment for an average of 18 days prior to foaling. In Cohort 2, two treated horses inadvertently began treatment 33 and 47 days prior to EFD. These mares foaled 23 and 39 days prior to EFD. Cohort 2 mares that began treatment 15 days prior to EFD foaled an average of 5 days prior to EFD with a range of 12 days prior to 5 days after EFD. Control mares in Cohort 1 foaled an average of 5 days after EFD while control mares in Cohort 2 foaled an average of 6 days prior to EFD. One control mare in Cohort 2 foaled 30 days prior to EFD.
2. *Foal health*: The incidence of morbidity and mortality in foals during the first 14 days of life was similar between foals of treated mares (17%) and controls (12.5%). Four of the twelve foals born to treated mares in Cohort 1 died or were euthanized within 11 days of birth. These foals were born 12 to 40 days prior to EFD. One foal born to a control mare in Cohort 2 died at

14 days of age. This foal was born 30 days prior to EFD. No treated foals in Cohort 2 died. One other control foal was healthy at birth and throughout the treatment phase, but was euthanized due to severe pneumonia at 2 months of age. On necropsy, one 1X foal (a Tennessee Walking Horse) was noted to have severe lymphoid and thymic depletion of unknown cause. This foal was born 25 days prior to EFD and was weak and unable to stand. The foal was euthanized due to severe respiratory disease on Day 5 post-foaling. One 3X foal born to a systemically ill mare 40 days prior to EFD was noted to have cerebral edema on necropsy; however, no specific cause of death could be determined. Findings in the other foals were limited to bronchopneumonia, fibrinous arthritis, and omphalitis. Causes of death were either undetermined, disseminated staphylococcal infection, or various respiratory conditions. The deaths occurring during the first 14 days of life may be related to premature parturition and foal immaturity.

Foals of treated mares in Cohort 1 had lower mean body weights than foals in the control group at all evaluations. The low body weight is likely a result of premature parturition due to treatment with EQUIDONE Gel.

Foals of treated mares experienced more diarrhea and loose stool than foals of control mares during the first 15 days of life (while mares were being treated with EQUIDONE Gel). All episodes of diarrhea were self-limiting and resolved without treatment.

Table 6. Foals Experiencing At Least One Episode of Diarrhea or Loose Stool

Treatment group (n=8 foals /group)	# Foals (percentage)
0X	1 (12.5%)
1X	4 (50%)
3X	6 (75%)
5X	5 (63%)

3. *Mare health*: No mares died during this study. Five mares whose foals died during the treatment phase were euthanized in order to capture pathology data. One 3X mare was systemically ill prior to and during treatment. The mare exhibited anorexia, diarrhea, respiratory disease, and severely elevated BUN and creatinine values. The mare was treated with EQUIDONE Gel for 5 days before foaling 40 days prior to EFD. The effect of treatment on the mare's early parturition and the death of the mare's foal could not be determined due to the severity of the mare's illness.
4. *Lactation*: Mares treated with EQUIDONE Gel had a higher incidence of dripping milk (96%) prior to parturition than control mares (50%). More mares treated with EQUIDONE Gel (71%) dripped milk for 3 or more days prior to parturition than control mares (0%). The duration of treatment did not affect premature lactation.

5. *Foal IgG concentrations*: Failure of passive transfer of immunoglobulins occurred in all treatment groups; however, there was a greater incidence of IgG concentrations <400 mg/dL in foals of treated mares. The incidence of failure of passive transfer also increased with dose. All mares that dripped milk for 3 or more days prior to parturition had foals with IgG concentrations <800 mg/dL, and one treated mare that did not drip milk had a foal with an IgG concentration of 400-800 mg/dL.

Table 7. Foal IgG Concentrations

Treatment group	# Foals	# Foals (percentage)			Overall incidence of <800 mg/dL
		<400 mg/dL	400-800 mg/dL	≥800 mg/dL	
0X	8	3 (38%)	2 (25%)	3 (38%)	63%
1X	6*	3 (50%)	1 (17%)	2 (33%)	67%
3X	7*	5 (71%)	1 (14%)	1 (14%)	86%
5X	8	7 (88%)	1 (13%)	0 (0%)	100%

\* IgG concentrations were not determined for 3 foals

6. *Parturition parameters*: Time to nursing, mammary gland development, lactation, milk specific gravity, parturition and placenta scores were not affected by treatment. Time to standing was not affected by treatment in foals in Cohort 1; however, 5X foals in Cohort 2 took longer to stand than control foals. (One 5X foal took over 24 hours to stand unassisted). Time for the placenta to be expelled, placental weight, gestation length, and foal body weight were lower/shorter in mares dosed with EQUIDONE Gel as compared to control mares in Cohort 1, but not in Cohort 2. Six treated mares (one 1X, two 3X and three 5X) and one control mare received assistance (limited to manual assistance/manipulation outside the vulva) during parturition. One control mare and three treated mares (two 1X and one 3X) had retained placentas that were expelled within approximately 5 hours of parturition after oxytocin treatment. One 3X and one 5X mare had abnormally thickened placentas. These mares required assistance during parturition and their foals were born healthy. The significance of the thickened placentas and their relationship to treatment with EQUIDONE Gel could not be determined.
7. *Mare clinical pathology*: In Cohort 1, treated mares had higher granulocyte, neutrophil and white blood cell counts as compared to control mares. In Cohort 2, treated mares had higher white blood cell counts as compared to controls and granulocyte and white blood cell counts appeared to increase with increasing dose. More treated mares had alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) concentrations above the reference range than control mares. GGT and ALP elevations generally occurred at time points surrounding foaling. The elevated GGT and ALP concentrations generally declined post-foaling, but the concentrations were still above the

reference range in some mares at Day 15 post-foaling. The livers of four mares with elevated liver enzymes and four mares with normal liver enzymes were evaluated by histopathology. There were no findings indicative of hepatobiliary disease.

8. Foal clinical pathology: More foals of treated mares had granulocyte and/or neutrophil counts below the reference range on the day of foaling than foals born to control mares. Most decreased neutrophil counts in treated foals occurred in foals born more than 25 days prior to EFD. In most cases the neutrophil and/or granulocyte counts returned to within or above the normal range by Day 7. In Cohort 1 foals, globulin and total protein values were lower for foals from mares treated with EQUIDONE Gel on the day of foaling. This is due to the increased incidence of failure of passive transfer in foals of treated mares. AST and GGT values were higher in Cohort 1 foals as compared to control foals. Additionally, more foals of treated mares had ALP concentrations above the reference range than foals of control mares. There were no histopathologic findings of hepatobiliary disease in foals that died or were euthanized.
9. Mare Hormones: Treated mares had higher progesterone (with the exception of 1X mares in Cohort 2) and prolactin values than control mares from Day 2 of treatment up to foaling.
10. Rebreeding: All mares evaluated during the rebreeding phase of the study exhibited foal heat (follicle  $\geq 35$  mm) within 1 to 2 weeks after foaling, except for one 5X mare that exhibited foal heat 23 days after foaling. Of the 12 mares that were rebred in the 0X and 3X groups, 8 (4 treated and 4 controls) were reproductive successes, 4 (1 treated and 3 controls) were reproductive failures. The fertility index, calculated as the number of mares pregnant on Day 50 divided by the total number of mares bred, was 57% for the 0X and 80% for 3X group.

g. **Conclusions:**

This study supports the safety of EQUIDONE Gel when administered to periparturient mares 15 days prior to EFD and continuing up to 5 days post-foaling. Treatment with EQUIDONE Gel at the labeled dose and duration may cause dripping of milk and failure of passive transfer. Foals of mares treated with EQUIDONE Gel should be evaluated for passive transfer.

Treatment with EQUIDONE Gel beginning 45 days prior to EFD resulted in premature parturition, decreased foal body weight, increased signs of foal immaturity and morbidity, decreased foal neutrophil counts at birth, as well as dripping of milk and failure of passive transfer. EQUIDONE Gel should not be administered to mares 45 days prior to EFD, or to mares with unknown EFDs.

## B. Field Safety:

### 1. Study Title and Number: Prevention of Equine Fescue Toxicosis Using Oral Domperidone. Study #: ETIdomEFTCTE01 and CT3.

Two uncontrolled, open-label, field studies evaluating a total of 2,556 mares producing 2,723 foals over a total of 2,730 seasons were conducted between 1994 and 2001. Mares were treated with the final market formulation of EQUIDONE Gel or a bioequivalent molasses based formulation at varying doses and durations. Data were collected using a mail survey. The survey solicited information regarding: gestation length, udder development, lactation, mare and foal mortality, dystocia, placental retention, and fescue exposure. Results are summarized in Tables 8 and 9.

Table 8. Treatment Initiation Based on 2,730 Breeding Seasons

Start of Treatment	Percent*
1 to 9 days prior to EFD	18
10 to 15 days prior to EFD	26
16 to 30 days prior to EFD	9
> 30 days prior to EFD	1
After EFD, but before foaling	16
Day of foaling	10
After foaling	12

\* Adequate data was not available to determine treatment initiation relative to foaling for every mare for every breeding.

Table 9. Safety Data Based on 2,730 Breeding Seasons

Safety Variable	Percent
Premature lactation	9.6
Premature parturition	0.5
Poor quality or absent colostrum	1.4
Failure of passive transfer (n=2,723)	1.8
Retained placentas	4.3
Dystocia	1.8
Mares: died/euthanized	0.4
Foals: stillborn/died/euthanized (n=2,723)	4.4

## **Conclusions:**

These studies support the safety of EQUIDONE Gel in periparturient mares. Treatment with EQUIDONE Gel may be associated with premature lactation, failure of passive transfer, and premature parturition.

## **IV. HUMAN FOOD SAFETY:**

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

## **V. USER SAFETY:**

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

Not for use in humans. For oral use in animals only. Keep this and all drugs out of the reach of children. Pregnant and lactating women should use caution when handling EQUIDONE Gel, as systemic exposure to domperidone may affect reproductive hormones. Domperidone is not approved for any indication in humans in the United States. The safety of domperidone in lactating women and their nursing children has not been evaluated. Consult a physician in case of accidental human exposure.

## **VI. AGENCY CONCLUSIONS:**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that EQUIDONE Gel, when used according to the label, is safe and effective for the prevention of fescue toxicosis in periparturient mares.

### **A. Marketing Status:**

This product may be dispensed only by or on the lawful order of a licensed veterinarian. Adequate directions for lay use cannot be written because professional expertise is required to diagnose the condition and to monitor the safe use of the product, including treatment of any adverse reactions.

### **B. Exclusivity:**

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

**C. Patent Information:**

EQUIDONE Gel is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
5,372,818	February 1, 2013
6,534,526	July 16, 2021
6,224,895	December 18, 2016

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