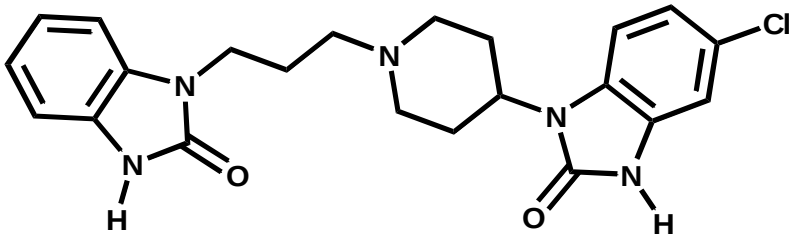
EQUIDONE® Gel
(domperidone)

CAUTION
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

For oral use in horses only.

DESCRIPTION
Domperidone is a D_2 dopamine receptor antagonist. Chemically, domperidone is 6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one.

The structural formula is:



Molecular Formula: $C_{22}H_{24}ClN_5O_2$ Molecular Weight: 425.91

INDICATION
For prevention of fescue toxicosis in periparturient mares.

DOSAGE AND ADMINISTRATION
Orally administer 0.5 mg/lb (1.1 mg/kg) once daily starting 10 to15 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.

DIRECTIONS FOR ADMINISTRATION
1. Determine the appropriate dose for the body weight of the mare based on the dosing table below. One cc will treat 220 lb (100 kg) of body weight.

Table 1. Dosing Table

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

2. Turn the dial ring until the edge of the ring nearest the tip of the syringe lines up with the dose to be delivered.
3. Remove the syringe cap.
4. Make sure the horse's mouth is free of food or other obstructions.
5. Insert the nozzle of the syringe through the interdental space of the horse's mouth and deposit the gel on the back of the tongue by depressing the plunger.
6. Recap the syringe.

This is a 25 cc multi-dose syringe. Please note that for subsequent doses, it will be necessary to adjust for previous doses. For example, if the intended dose for a horse is 5 cc, then the dial ring is set at 5 cc for the first dose, at 10 cc for the second dose, at 15 cc for the third dose, at 20 cc for the fourth dose, and at 25 cc for the fifth dose.

CONTRAINDICATION
Horses with hypersensitivity to domperidone should not receive EQUIDONE Gel.

WARNINGS
Failure of passive transfer of immunoglobulins (IgG) may occur when using EQUIDONE Gel even in the absence of leakage of colostrum or milk. All foals born to mares treated with EQUIDONE Gel should be tested for serum IgG concentrations.

Do not use in horses intended for human consumption.

HUMAN WARNINGS
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 US. The safety of domperidone in lactating women and their

nursing children has not been evaluated. Consult a physician in case of accidental human exposure.

PRECAUTIONS

EQUIDONE Gel may lead to premature birth, low birth weight foals or foal morbidity if administered >15 days prior to the expected foaling date. Accurate breeding date(s) and an expected foaling date are needed for the safe use of EQUIDONE Gel.

The safety of EQUIDONE Gel has not been evaluated in breeding, pregnant and lactating mares other than in the last 45 days of pregnancy and the first 15 days of lactation (see Animal Safety). The safety in stallions has not been evaluated. The long term effects on foals born to mares treated with EQUIDONE Gel have not been evaluated.

Do not use in horses with suspected or confirmed gastrointestinal blockage, as domperidone is a prokinetic drug (it stimulates gut motility).

Use of EQUIDONE Gel may cause a false positive on the milk calcium test used to predict foaling.

Domperidone is a known P-glycoprotein substrate[1] and its main metabolic pathway in humans is through CYP3A4. Significant inhibition of domperidone metabolism may occur when co-administered with drugs such as erythromycin[2] and ketoconazole[3]. This could result in significantly greater domperidone drug exposure (multi-fold increase) when used with these drugs.

ADVERSE REACTIONS

The most common adverse reactions associated with treatment with EQUIDONE Gel are premature lactation (dripping of milk prior to foaling) and failure of passive transfer.

In a laboratory effectiveness study with 32 periparturient mares (17 treated with EQUIDONE Gel and 15 treated with vehicle control) 3/17 (18%) mares treated with EQUIDONE Gel experienced premature lactation. In the 25 foals (16 foals of mares treated with EQUIDONE Gel and 9 foals of vehicle control mares) evaluated for passive transfer, failure of passive transfer occurred in 13/16 (81%) foals of mares treated with EQUIDONE Gel and 8/9 (89%) foals of control mares. 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.

In a field study with 279 periparturient mares treated with EQUIDONE Gel, premature lactation was reported in 3 mares (1%) and failure of passive transfer was reported in 3 foals (1%).

In two additional field studies, a total of 2,556 mares were treated with EQUIDONE Gel or a bioequivalent formulation for 2,730 breeding seasons. Horses in these studies were treated with EQUIDONE Gel for varying durations. Of the 2,730 breeding seasons evaluated, premature lactation was reported in 262 mares (9.6%), failure of passive transfer was reported in 50 foals (1.8%), and premature parturition (gestation length ≤ 320 days) occurred in 13 mares (<0.5%).

INFORMATION FOR HORSE OWNERS

Owners should be aware that treatment with EQUIDONE Gel may result in failure of passive transfer of immunoglobulins to the foal and that this may occur even when the mare does not drip milk. Owners should be advised that all foals born to mares treated with EQUIDONE Gel should be tested for serum immunoglobulin (IgG) concentrations. Owners should be informed that EQUIDONE Gel causes false positives on the milk calcium test used to predict foaling. Owners should be directed on the proper use of the multi-dose dosing syringe, including how to set the dial ring for accurate dosing after the first dose.

CLINICAL PHARMACOLOGY

Domperidone is a D_2 dopamine receptor antagonist that blocks the agonistic action of fescue alkaloids at the cellular level. Unlike other D_2 antagonist drugs, domperidone does not readily cross the blood-brain barrier[4]. Distribution studies with radio-labeled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of the drug cross the placenta in rats[5]. In humans, domperidone is 91-93% bound to plasma proteins. Domperidone in humans undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation[1]. Urinary and fecal excretions of domperidone in humans amount to 31 and 66% of the oral dose, respectively. The proportion of the drug excreted unchanged in humans is small (10% of fecal excretion and approximately 1% of urinary excretion). The average terminal plasma half-life of domperidone administered orally to horses is approximately 6 hours with very low systemic bioavailability.

EFFECTIVENESS

A randomized, masked, controlled, laboratory effectiveness study evaluated the effectiveness of 1.1 mg/kg EQUIDONE Gel administered once daily beginning 10 to 15 days prior to the expected foaling date (EFD - defined as 340 days after the median breeding) and continuing up to 5 days after foaling for the prevention of fescue toxicosis. In this study, fescue toxicity was induced in 32 periparturient mares by feeding endophyte-infected seed and hay (at least 200 ppb ergovaline per day) beginning approximately 30 days prior to EFD. A total of 17 mares were treated with EQUIDONE Gel and 15 mares were treated with a vehicle control. Twenty-seven mares (13 EQUIDONE Gel and 14 vehicle control) were included in the statistical analysis. Overall treatment success was determined by an actual foaling date within 14 days of EFD, adequate lactation at foaling, mammary gland development and adequate postpartum lactation. EQUIDONE Gel was superior to the vehicle control.

Table 2. Treatment Success

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

Table 3. 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)[1]	30% (3 / 10) [2]
EQUIDONE Gel (13)	337	100% (13 / 13)	100% (13 / 13)
Test Statistic	t statistic = 3.754 p=0.0014	Pearson χ2 = 8.793 p=0.0030	Pearson χ2 = 9.984 p=0.0016

[1]Three mares rescued prior to foaling for exceeding EFD by ≥15 days, 1 euthanized after foaling, 1 missing observation
[2]Three mares rescued prior to foaling for exceeding EFD by ≥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 either stillborn, died or were euthanized within 5 days of birth. Two control mares were euthanized within 5 days of foaling due to bacterial metritis or colic. Dystocia occurred in 1 mare treated with EQUIDONE Gel and 4 control mares.

One mare treated with EQUIDONE Gel and three control mares experienced retained placentas.

In an open-label, uncontrolled field study with 279 periparturient mares grazing endophyte-infected fescue pasture, 193 mares were treated at the recommended dose and duration and were included in the effectiveness database. Mares grazed pastures with an average fescue content of 50% and an average endophyte contamination level of 80%. The mares had an average gestation length of 340 days. Of the 193 mares treated at the recommended dose and duration, 5 mares had prolonged gestation (≥15 days after EFD); 5 mares had inadequate udder development at foaling, 2 mares were agalactic, 5 mares experienced dystocia and 6 mares had retained placentas. Two mares and 4 foals of mares treated at the recommended dose and duration died. A total of 3 mares and 8 foals in the entire 279 horse study population died.

ANIMAL SAFETY

In a target animal safety study EQUIDONE Gel was administered orally to 32 healthy periparturient mares once daily at 0X, 1X, 3X or 5X the maximum exposure dose estimated for a 550 lb mare. Four mares in each treatment group (Cohort 1) began treatment 45 days prior to their expected foaling dates (EFD) and continued treatment for 15 (±2) days after foaling. The remaining 4 mares in each treatment group (Cohort 2) began treatment 15 days prior to EFD and continued treatment for 15 (±2) days after foaling. Mares in the 0X and 3X groups were rebred and the mares and their foals were followed to 50 days of gestation. EFD was calculated as 340 days after the median breeding date.

Table 4. 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.

Mares treated with EQUIDONE Gel had a higher incidence of premature parturition. There was a significant decrease in gestation length, with corresponding lower birth weights of foals, in mares treated with EQUIDONE Gel beginning 45 days prior to EFD (Cohort 1). Mares treated with EQUIDONE Gel

beginning 45 days prior to EFD foaled an average of 27 days early (range 12 to 40 days early). Mares treated with EQUIDONE Gel beginning 15 days prior to EFD foaled an average of 5 days early (range 12 days early to 5 days late). (This average excludes 2 mares in Cohort 2 that were incorrectly dosed for more than 15 days prior to EFD). Control mares (both cohorts combined) foaled an average of 2 days early (range 30 days early to 10 days late).

Premature parturition resulted in low foal birth weights and may have contributed to morbidity and mortality in foals (both treated and control) in Cohort 1. Four out of 12 foals born to mares treated with EQUIDONE Gel in Cohort 1 died or were euthanized within 11 days of birth. These foals were born 12 to 40 days early. One control foal in Cohort 2 (born 30 days early) died at 14 days. Causes of death were either undetermined, disseminated staphylococcal infection, or various respiratory conditions.

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 the likelihood that mares would drip milk.

Table 5. Number of Mares Dripping Milk for 3 or More Days Prior to Foaling

Cohort	0X	1X	3X	5X
1	0	3	3	4
2	0	2	2	4

Failure of passive transfer occurred in all groups; however, there was a greater incidence of IgG concentrations <400 mg/dL in foals of mares treated with EQUIDONE Gel. 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 6. Serum IgG Concentrations of Foals

		# Foals (percentage)			
Treatment group	# Foals	<400 mg/dL	400-800 mg/dL	≥800 mg/dL	Overall incidence of <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

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

Table 7. 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%)

Mares treated with EQUIDONE Gel generally had higher white blood cell counts (WBC) and/or granulocyte counts and gamma glutamyl transferase (GGT) and/or alkaline phosphatase (ALP) concentrations than control mares. GGT and ALP elevations occurred mostly at time points surrounding foaling, and demonstrated a declining trend post-foaling; however, the concentrations had not returned to normal in all mares by 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 histologic findings indicative of hepatobiliary disease and no clinical abnormalities were noted.

More foals of mares treated with EQUIDONE Gel had granulocyte and/or neutrophil counts below the reference range on the day of foaling than foals born to control mares. The decreased neutrophil counts in foals of mares treated with EQUIDONE Gel occurred more commonly 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. Foals of mares treated with EQUIDONE Gel had higher ALP concentrations than foals of control mares. Additionally, several foals of mares treated with EQUIDONE Gel also had elevations in GGT.

All mares that were examined ultrasonographically exhibited foal heat (follicle ≥35 mm) within 1 to 2 weeks after foaling with the exception of a 5X mare which

exhibited foal heat 23 days after foaling. Of the 12 mares that were rebred in the 0X and 3X groups, 8 (4 in the 3X group and 4 controls) were reproductive successes, and 4 (1 in the 3X group and 3 controls) were reproductive failures.

Table 8. Rebreeding Success Rates

Treatment group	# Mares bred	Pregnant at Day 50 (percentage)
0X	7	4 (57%)
3X	5	4 (80%)

STORAGE INFORMATION
Store at controlled room temperature 25ºC (77ºF) with excursions between 15º-30ºC (59º-86ºF) permitted. Recap after each use.

HOW SUPPLIED
EQUIDONE Gel is supplied in disposable, multi-dose, 25 cc syringes, each containing 2.75 g of domperidone suspended in an oral gel. Each cc of gel contains 110 mg of domperidone. The net weight of each syringe is approximately 26 g. Syringes are packed six per carton.

NADA 141-314, Approved by FDA.
NDC: 17033-326-06

Distributed by:
Dechra Veterinary Products
7015 College Boulevard
Suite 525
Overland Park, KS 66211

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Dechra Veterinary Products at (866) 933-2472.

US Patents 5,372,818; 6,534,526; 6,224,895

REFERENCES

[1] Pal D and Mitra AK. MDR- and CYP3A4-Mediated Drug–Drug Interactions. *Journal of Neuroimmune Pharmacology* 1: 323-339; 2006.

[2] Ung D, Parkman HP, and Nagar S. Metabolic Interactions Between Prokinetic Agents Domperidone and Erythromycin: an in vitro Analysis. *Xenobiotica* 39(10): 749–756; 2009

[3] Medicines Control Council. Interaction Between Ketoconazole and Domperidone and the Risk of QT Prolongation--Important Safety Information. *South African Medical Journal* 96(7): 596; 2006.

[4] The European Agency for the Evaluation of Medicinal Products. Motilium and Associated Names (London, 2002).

[5] Heykants J, Knaeps A, Meuldermans W, and Michiels M. On the Pharmacokinetics of Domperidone in Animals and Man. I. Plasma Levels of Domperidone in Rats and Dogs. Age Related Absorption and Passage through the Blood Brain Barrier in Rats. *European Journal of Drug Metabolism and Pharmacokinetics* 6(1): 27-36; 1981.