Domperidone is a benzamide molecule with primarily dopamine-2 receptor (D2R) antagonist activity. In human medicine it has been administered as an anti-emetic and prokinetic drug. In veterinary medicine it was originally investigated for use as a prokinetic in both horses and small animals. Understanding of the pharmacologic actions of domperidone has lead to its extensive use in equine reproduction and its investigation for other possible therapeutic strategies.

**Dopamine-2 Receptors (D2R)**

Dopamine receptors are wide spread throughout the mammalian body and have been linked to actions as diverse as modulation of mood and behaviour through to control of lactation. Like the dopamine-1 receptor, D2R is a G-protein-coupled trans-membrane receptor, which is linked via adenylate cyclase to the control of K⁺ and Ca²⁺ channels, arachidonic acid release and many other cytoplasmic events. However, D2R is an inhibitory receptor, and the binding of dopamine results in decreased activation of the secondary messenger systems and the subsequent decrease of cellular events controlled by these secondary messengers.

**Domperidone – Structure and Activity**

Domperidone’s antagonist effect at the D2R is believed to be responsible for the pharmacologic effects reported in horses. Domperidone is excluded from the brain by the blood brain barrier, which is possibly a function of its active efflux by P-glycoprotein[1]. This is the likely reason that it has not been implicated in inducing extrapyramidal motor effects or causing sedation - common adverse effects from other D2R antagonists like metoclopramide.

**Therapeutic Purposes**

In the horse, domperidone has been investigated and used for several different purposes.

1. Induction of Lactation
Both domperidone and another D2R antagonist, sulpiride, have been successfully used for the induction of lactation in barren mares after oestrogen and progestagen priming\[2-5\]. The induction of lactation in mares is often necessary when attempts to find lactating foster mares fail. Whilst induction of lactation may appear to be the most important component of the foster mare unit for initial survival of the foal, behavioural acceptance or adoption of the foal by the mare is often the limiting factor to success of any adoption event. It would appear that it is extremely important to also milk the mare at frequent intervals during domperidone administration to successfully induce lactation. However, as already discussed, induction of maternal behaviour is vital to getting the mare to accept an orphaned foal. Along with the priming of mares with oestrogen and progestagen administration, induction of maternal behaviour and the chance of foal acceptance appears to be increased by sedation and vaginal and cervical stimulation of the mare\[3, 6\]. Adoption success rates appear to vary between investigators; however, induction of lactation would appear to be successful in most instances where mares have previously lactated. Investigators have commented that colostrum is not always produced by mares that are induced to lactate as a foster mother, so an alternate source of colostrum should be made available to the foal. In one study, 4 of 6 mares treated with an adoption/lactation induction program including daily administration of domperidone cycled normally after lactation was induced\[3\].

2. Management of Vernal Transition (Induction of Ovulation)

Due to the mandatory establishment of the horses birthday as August 1\textsuperscript{st} (September 1\textsuperscript{st} for Standardbred horses) in the Southern Hemisphere, considerable pressure is placed on breeders to have foals born as soon after that date as possible to ensure that horses reach developmental targets with respect to sales and age related events. As mares are long day breeders, with the main regulator of reproductive activity being photoperiod, there can be significant periods at the beginning of the breeding season (when days are still relatively short) where mares will cycle in an irregular manner. The period between anoestrus and regular cyclical reproductive activity has been termed the vernal transition period and is now considered to be a result of inhibitory signals such as short day length on gonadotrophin and GnRH secretion\[7\].

Domperidone has been used in transitional mares to induce ovulation, and thereby allow earlier covering of mares. As prolactin is responsible for increasing gonadotrophin receptors in developing follicles, domperidone’s effect of increasing prolactin may explain its ability to induce ovulation. Increased sensitivity to FSH and LH results and, consequently, follicular development and ovulation are induced.

A blinded, placebo controlled, investigation of the effects of domperidone administration on 47 thoroughbred mares considered to be either in anoestrus or vernal transition has been performed in Australia\[8\]. Mares were not placed under artificial lighting. Results indicated that administration of domperidone to mares with follicles 2 cm or larger resulted in 87% ovulating within 16 days of treatment initiation. In comparison, mares treated with an altrenogest/cloprostenol regime resulted in only 73% of mares with follicle size of 2 cm or more ovulating 17 to 21 days after treatment. Ovulation appeared more likely to occur if commencement of domperidone treatment coincided with a follicle of 2 cm or greater. No
adverse effects were recognised with administration of daily doses up to 1200 mg/mare. Over 70% of mares treated with domperidone conceived. There were 15 (out of a possible 17) foals born to mares that had received domperidone. All foals were considered normal at birth and 12 hour post partum IgG levels from these foals showed no evidence of deficiency of colostral transfer.

In a separate communication there is reference to the use of artificial lighting for 14 days followed by daily sulpiride administration resulting in mares ovulating approximately 16 days earlier than mares only under artificial lighting[7]. Whilst this has not been investigated with domperidone, the common mechanism of action would suggest that similar results should occur.

3. Prokinetic Activity

Whilst there are references to the use of domperidone as a prokinetic treatment in horses with gastrointestinal disturbances such as ileus[9, 10], there appears to be no published review of its efficacy in equine patients. A preliminary study using an experimental model of post operative ileus in ponies showed encouraging results when domperidone was administered at 0.2 mg/kg intravenously[11]. Gastrointestinal transit time, electromechanical activity and coordination of gastric and intestinal cycles were restored after administration.

The commonly proposed mechanism of action of domperidone in the gut is through its D2R antagonism, resulting in reduction of the inhibitory effects of dopamine on motility. Several studies in humans and laboratory species have demonstrated excessive gastrointestinal dopaminergic and adrenergic activity in post-operative ileus. Laboratory models showed domperidone successfully antagonises the inhibitory effects of dopamine on gastric motility[12]. However recent work in people indicated that domperidone was responsible for an increase in circulating motilin and somatostatin, possibly as a result of an effect at muscarinic receptors[13]. These two peptides play important roles in gastrointestinal contractility. Whether direct effects at D2R or the release of motilin and somatostatin as a result of a putative muscarinic receptor effect is responsible for changes in motility is unknown.

Though nausea and vomiting are not recognised in equine practice, domperidone can be expected to have an anti-emetic effect through its D2R activity at the chemoreceptor trigger zone. It appears that there is little effect on colonic motility related with domperidone administration[14]. There are no reports of increased GI motility from administration to mares for reproductive of lactation management (Jurox APVMA Pharmacovigilance Reports 2003-2006). Unfortunately, the currently available formulation of domperidone in Australia is an oral paste, which may make it unsuitable for treatment of animals suffering from gastric reflux and ileus. Direct or retrospective studies into the efficacy of domperidone for management of ileus may be warranted.

4. Diagnostic Tool for Diagnosis of Equine Cushing’s Disease
Cushing’s disease in the horse is almost always associated with functional adenoma development in the pars intermedia region of the pituitary gland. Along with characteristic clinical signs such as hirsutism and polyuria/polydypsia, pre-mortem diagnosis relies on laboratory investigation. Diagnostic tests for Cushing’s disease in the horse include evaluation of baseline plasma cortisol and ACTH levels and dexamethasone suppression tests. Some horses with histologically confirmed tumours of the pars intermedia may exhibit normal baseline cortisol and ACTH levels and interpretation of dexamethasone suppression tests can sometimes be misleading.

Recent work performed at Purdue University investigated the effect of domperidone on plasma ACTH levels in horses with pars intermedia tumours\(^1\)\(^5\). Whilst only a limited number of cases were investigated, horses that had histologically-confirmed tumours of the pars intermedia had plasma ACTH levels above reference ranges 4 hours post dosing and horses that did not have tumours had levels within the reference range. Exaggerated responses to domperidone administration were exhibited in horses with pars intermedia tumours, most likely as a result of antagonism of the inhibitory effects of hypothalamic dopamine binding to D2Rs. Interestingly, this is in contrast to a placebo controlled study performed in normal humans, which indicated that administration of domperidone resulted in blunted secretion of ACTH and cortisol in response to the stress of venipuncture\(^1\)\(^3\). A full understanding of the effects of domperidone on the hypothalamic-pituitary-adrenal axis may develop with future research.

5. Laminitis

There is currently no published peer-reviewed information about the use of domperidone for treatment or management of laminitis in the horse. However, a patent search revealed that there is an application lodged for the use of domperidone in the treatment and management of laminitis in the horse and other hoofed species\(^1\)\(^6\). It is proposed by the patent applicant that by virtue of an α-adrenergic antagonist action, domperidone can prevent lamellar detachment. The application claims that trials have indicated long term elimination of the signs of laminitis and 6 case examples indicating resolution of clinical signs of laminitis have been sited. Whether there is any scientific merit to the use of domperidone for laminitis will no doubt be clarified in the future by the presence (or lack of) peer-reviewed publications on this subject.

6. Prevention and Treatment of Fescue Toxicosis in Pregnant Mares

Though it is minor concern for horse studs in Australia and New Zealand, certain regions of the US have recognised for many years a syndrome of gestational and post-parturient problems in mares and foals that have been exposed to endophyte infected fescue grass. After exposure, pregnant mares exhibit a range of symptoms including prolonged gestation, agalactia, thickened and retained placentas and will often give birth to dysmature and weak foals. Death of the mare and foal may also occur.

Endocrine related findings in mares and foals exposed to endophyte infected fescue included decreased maternal plasma progesterone and prolactin concentrations and higher plasma oestradiol-17β concentrations than normal mares at similar stages of their gestation\(^1\)\(^7\).
The ergot alkaloid, ergovaline, is considered one of the major contributors to the syndrome of fescue toxicosis, and has been shown to be directly responsible for decreased prolactin production through its D2R agonist activity. The mechanisms of activity involved in the other components of the toxicosis have not yet been fully elucidated.

Domperidone has been used successfully to treat and prevent the signs of fescue toxicosis, most likely as a result of its D2R antagonist activity and prevention of the effects of ergovaline. However, this only clearly defines the role of domperidone in reversing the effect of ergot exposure on maternal prolactin secretion by the pars distalis. The mechanism/s associated with increasing maternal and neonatal progestagen, maternal ACTH and cortisol levels are not yet fully understood, but are possibly associated with neuro-endocrine feedback loops between the hypothalamus, pituitary gland, gonad, placenta and adrenal gland.

The efficacy of domperidone in preventing and treating fescue toxicosis has been reported in two studies previously presented at AAEP conferences. The first study[^18^], looked at the comparative effects of domperidone administration in four groups of mares: 1. not exposed to endophyte infected fescue; 2. exposed to endophyte infected fescue; 3. exposed to endophyte infected fescue and treated with domperidone up to parturition; and 4. exposed to endophyte infected fescue and treated with domperidone past parturition. Whilst their was no difference in gestational length amongst all four groups there were statistically significant improvements in mammary scores and prepartum progestagen and prolactin concentrations for mares receiving domperidone up to and past parturition compared to mares exposed to endophyte infected fescue and not receiving domperidone. There were no differences in milk composition noted amongst treatment groups. All foals from non-exposed mares and mares exposed and treated with domperidone survived up to 10 days post partum whilst only 50% of foals survived up to 10 days from endophyte exposed untreated mares.

In the second study by the same research group[^19^], the clinical effect of domperidone on fescue toxicosis in pregnant mares was investigated. Clinical observations from 1423 pregnancies considered at risk of fescue toxicosis were reviewed. Two main sub-populations of mares were identified with respect to time of initiation of treatment with domperidone: 1. a preventative mode group, where domperidone treatment was initiated around 10 to 15 days prior to due date and 2. a treatment mode group, where mares started treatment less than 10 days before due date of foaling. A third small population of mares that started treatment greater than 16 days prior to expected due date was also evaluated. When compared to historical positive controls, mares receiving treatment had 1. normal gestational lengths and udder development, 2. much lower incidence of agalactia, 3. better live foal delivery rates and, 4. a lower rate of placental retention. Owners and vets administering domperidone felt it was an effective therapy.

**Conclusion**

Domperidone is a benzamide molecule that is proposed to have antagonistic pharmacologic activity at the dopamine-2 receptor. Currently in Australia, domperidone is primarily used for management of the vernal transition period and in the induction of lactation in foster mares.
There are, however, several potential expansions of use for domperidone in horses, which may develop in coming years. It should be noted that use of domperidone in horses for laminitis, treatment of fescue toxicosis, promotion of ovulation, parturition and lactation are all protected by patent, therefore only the licensed registered equine product (Jurox Domperidone Paste for Horses) can legally be used for these indications, even though some are off-label uses.
