CISAPRIDE (Veterinary—Systemic)

There are no human- or veterinary-labeled commercial cisapride products in the United States or Canada.

Category: Gastrointestinal emptying adjunct; peristaltic stimulant.

Indications

Note: Cisapride is not specifically approved for veterinary use. In other USP information monographs, the [EL US] and [EL CAN] designations refer to uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of commercial product availability in the countries indicated. See also the *Regulatory Considerations* section below in this monograph.

Classification as *Accepted, Potentially effective,* or *Unaccepted* is an evaluation of reasonable use that considers clinical circumstances, including the availability of other therapies. The quality of evidence reviewed for an indication is shown by the evidence rating.

Cats

Accepted

[EL US,CAN] Constipation, chronic (treatment)[EL]; or

[EL US,CAN] Megacolon, idiopathic (treatment)[EL]—Although no studies of clinical disease cases are available, cisapride may be used as part of a multifaceted regimen in the treatment of chronic constipation that has not responded to other therapies and in the treatment of idiopathic megacolon, based on *in vitro* studies of its effects on colonic tissues (Evidence rating: B-4,5).{R-1-3}

Potentially effective

[EL US,CAN] Esophageal motility dysfunction (treatment)[EL]—The action of cisapride in stimulating esophageal motility in the cat may be useful in the treatment of esophageal disorders (Evidence rating: B-4,5).{R-2; 20}

[EL US,CAN] Gastroesophageal reflux (treatment)[EL];

[EL US,CAN] Delayed gastric emptying (treatment)[EL]; or

[EL US,CAN] Small bowel motility disorders (treatment)[EL]—Although no feline studies are available, the documented effects of cisapride in healthy dogs and other animals suggest it may have efficacy in disorders that benefit from stimulation of gastric, small intestinal, or colonic motility and from shortened transit time in cats (Evidence rating: B-2).{R-2; 4-7; 21-24}

Dogs

Potentially effective

[EL US,CAN] Gastroesophageal reflux (treatment)[EL];

[EL US,CAN] Delayed gastric emptying (treatment)[EL];

[EL US,CAN] Small bowel motility disorders (treatment)[EL]; or

[EL US,CAN] Colonic motility disorders (treatment)[EL] —Although no studies of clinical disease states are available, studies of the effects of cisapride in healthy dogs suggest it may have efficacy in disorders that benefit from stimulation of gastric, small intestinal, or colonic motility and from shortened transit time (Evidence rating: B-2 [table 1][table 2][table3]).{R-4-7; 17; 21-24}

Note: There is no evidence that cisapride is effective in the treatment of megaesophagus in dogs. The canine esophagus is striated muscle, with no smooth muscle to directly respond to the medication; cisapride is not expected to aid in canine esophageal emptying.{R-25}

Horses

Accepted

[EL US,CAN] Ileus, post-operative (prophylaxis and treatment)[EL]—Based on evidence demonstrating the ability of cisapride to stimulate gastrointestinal motility and emptying in horses, as well as clinical studies suggesting it decreases the risk of post-operative ileus, cisapride may be used as part of a comprehensive regimen to prevent or treat post-operative ileus (Evidence rating: B-2,3,4,5).{R-8-16; 26}

Evidence ratings

Evidence Quality	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Insufficient evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Evidence Type	
1	Species-specific evidence from at least one large randomized and controlled trial (RCT) or multiple small RCTs
2	Species-specific evidence from a small RCT, disease models, large case studies, pharmacokinetic studies using surrogate endpoints, or evidence from well-designed trials in a different species that is considered appropriate for comparison
3	Dramatic results from either well-designed, species-specific trials without controls, controlled trials without randomization, or small case studies
4	Pharmacokinetic studies without surrogate endpoints or well designed pharmacodynamic studies in healthy animals
5	*In vitro* studies
6	Opinions of respected authorities on the basis of clinical experience or reports of expert committees

More research is needed to establish the relative efficacy of cisapride in comparison with other promotility agents and to demonstrate the types of gastrointestinal tissue injuries that are likely to benefit from prokinetic therapy.

Potentially effective

[EL][US,CAN]Gastroesophageal reflux (treatment)[EL]; [EL][US,CAN]Delayed gastric emptying (treatment)[EL]; [EL][US,CAN]Small bowel motility disorders (treatment)[EL]; or [EL][US,CAN]Colonic motility disorders (treatment)[EL]—Studies of the effects of cisapride in horses suggest it may have efficacy in disorders other than post-operative ileus that would benefit from stimulation of gastric, small intestinal, or colonic motility and from shortened transit time (Evidence rating: B-2 [table 1][table 2]).{R-10-14; 27-32}

Regulatory Considerations

U.S. and Canada—

Commercial cisapride products labeled for human use were withdrawn from the United States and Canadian markets in 2000 due to reports of adverse events.{R-34} Because there are no commercial cisapride products, medicinal or analytic grade cisapride must be purchased from an approved source and compounded for veterinary use. In the United States, refer to the Animal Medicinal Drug Use Clarification Act, Food and Drug Administration regulations pertaining to compounding (CFR 21 Part 530.13), and the current Food and Drug Administration's Compliance Policy Guide on *Compounding of Drugs for Use in Animals.*{R-35-37} In Canada, refer to the Health Canada Health Products and Food Branch's *Manufacturing and Compounding Drug Products in Canada*.{R-38}

Chemistry

Chemical group: Substituted piperidinyl benzamide.{R-40}

Chemical name: Benzamide, 4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxy-, *cis*-.{R-39}

Molecular formula: $C_{23}H_{29}ClFN_3O_4$.{R-39}

Molecular weight: 465.95.{R-39}

Description: Cisapride monohydrate—White or almost white powder.

Ionization: Weak base with a pKa_1 of 7.8 and pKa_2 of 1.7.{R-55}

Solubility: Cisapride monohydrate—Freely soluble in dimethylformamide, soluble in methylene chloride; sparingly soluble in methanol, practically insoluble in water (water solubility of 2.7 mg per liter).

Pharmacology/Pharmacokinetics

Note: See also *Tables I* and *II* at the end of this monograph.

Mechanism of action/Effect: Cisapride is a prokinetic drug; it stimulates gastrointestinal smooth muscle motility and decreases transit time of gastrointestinal contents down the length of the tract.{R-40} Cisapride acts by enhancing the release of acetylcholine from postganglionic nerve endings at the myenteric plexus. Studies have demonstrated effects at serotonin (5-hydroxytryptamine) receptors (as an agonist at 5-HT_4 and 5-HT_2; and an antagonist at 5-HT_3 and 5-HT_1); however, there appear to be differences among species in action at these receptors.{R-40-42; 49}

In the dog, cisapride increases plasma motilin concentration while stimulating motility during the interdigestive phase but during digestion, it stimulates motility without affecting plasma motilin.{R-6}

Cisapride has no central antiemetic effect and does not significantly affect secretion of gastric acid, pancreatic enzymes, or bile secretion.{R-23; 50}

Absorption:

Oral bioavailability—In cats, dogs, horses, and human beings, oral bioavailability appears to be low to moderate (30 to 60%).{R-2; 12} This is generally attributed to extensive first-pass metabolism in the intestinal wall or liver of many species but may also be affected by poor drug dissolution.{R-2; 12} In fasted rats, cisapride is almost completely absorbed.{R-18} Availability may vary among members of the same species.{R-12}

Rectal absorption—*Horses:* Absorption of rectally administered cisapride has been investigated using aqueous, propylene glycol, and dimethylsulfoxide formulations; at best, only half of horses achieved measurable plasma cisapride concentrations. Bioavailability appears to be low and extremely variable by this route.{R-10; 11; 13}

Distribution:

Dogs—Beagles given cisapride daily for a year showed no evidence of significant accumulation in tissues, even when given 40 mg/kg daily. Relative tissue drug concentrations twenty-four hours after the last dose were: colon > liver, kidney, stomach, ileum, lung, pancreas > brain, skeletal muscle.{R-17}

Rats—Cisapride is quickly absorbed and distributed, to peak in the tissues at 15 to 30 minutes, with the highest concentrations in the liver, stomach, and small intestine. Of a 10-mg/kg dose, 42% can reach the contents of the small intestine within 2 to 4

hours. Cisapride also reaches the brain, but at levels significantly less than in plasma.{R-17}

Protein binding:

Human beings—97.5 ± 0.2%.{R-19}
Dogs—95.0 ± 1.5 %.{R-19}
Rats—91.6 ± 0.3%.{R-19}
Sheep—89.0.{R-54}

Biotransformation:

Rats—Cisapride is extensively metabolized to at least 30 metabolites; *N*-dealkylation and aromatic hydroxylation are the primary pathways.{R-18} Of parent drug and metabolites measured in the plasma of male rats, only 9% was found to be parent drug; in female rats, only 29% was unmetabolized.{R-17} An extensive first-pass effect that could not be saturated was demonstrated.{R-17}

Dogs and *human beings*—The major metabolic pathways are the same as in rats, but metabolism is not as extensive, producing fewer metabolites.{R-19} The two major metabolic pathways are the oxidative *N*-dealkylation that produces norcisapride and aromatic hydroxylation at the 4-fluorophenyl ring.{R-19} An extensive first-pass effect has been demonstrated.{R-17} More of the cisapride dose is eliminated as parent drug in dogs (about 23%) than in human beings (4 to 6%); more norcisapride is eliminated in human beings (41 to 45%) than in dogs (14%).{R-19} Norcisapride has only one-sixth the pharmacological activity of cisapride but is not believed to be associated with adverse cardiac effects in human beings.{R-48}

Elimination:

Cats—There is great variation among cats in clearance of cisapride.{R-2}
Dogs—After administration of a 1-mg/kg dose, 97% of the dose is eliminated within 96 hours, with about 72% eliminated in the feces and 25% in the urine.
Human beings—Orally administered cisapride is almost completely eliminated within 96 hours, in fairly equal amounts in the feces (37%) and the urine (44%).{R-19}
Rats—Orally administered cisapride is almost completely eliminated within 98 hours, primarily via the bile into feces (75 to 85%), but also in urine (15 to 25%).{R-18} A significant amount of phenolic metabolites excreted into the bile undergoes enterohepatic circulation before final elmination in the feces.{R-18}

Precautions to Consider

Fertility

Rats: When administered at oral doses of up to 160 mg/kg a day, cisapride was found to have no effect on fertility in male rats. Female rats given oral doses of ≥ 40 mg/kg a day and the female offspring of female rats given 10 mg/kg a day were found to need a prolonged breeding interval for impregnation.{R-43}

Pregnancy

Rabbits: Rabbits given up to 40 mg/kg showed no evidence of teratogenicity. However, doses of 20 mg/kg a day or higher were shown to be embryotoxic and fetotoxic.{R-43}
Rats: Small amounts of primarily parent drug (<1% of the dose) cross the placenta in pregnant rats.{R-17} No evidence of teratogenic potential was seen when rats were given up to 160 mg/kg a day; however, embryotoxicity and fetotoxicity were seen. When cisapride was administered at a dose of 40mg/kg a day, birth weights of pups and pup survival were reduced.{R-43}
Sheep: Cisapride crossed the placenta within 5 minutes of a 0.2-mg/kg dose and was already measurable in fetal plasma. Equilibrium between maternal and fetal plasmas was reached within 20 to 30 minutes of cisapride administration. The average fetal to maternal plasma concentration ratio between twenty minutes and three hours after administration was 0.71.{R-54}

Lactation

Dogs and *rats:* Cisapride appears to be easily distributed into milk in lactating dogs and rats. In dogs, the milk to plasma ratio of cisapride is 1.7 to 2.2; metabolites cross more readily than unmetabolized cisapride, with a metabolite milk to plasma ratio of 3.2 to 5.2.{R-17}

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: There have been no reported cases of serious induced *arrhythmias* associated with cisapride administration to animals. Because of fatalities due to arrhythmias associated with cisapride in human beings, the administration of medications that prolong the QT interval, including Class IA antiarrhythmics (procainamide, quinidine), Class III antiarrhythmics (sotalol), phenothiazines; and medications that may cause a rapid decrease in plasma potassium levels, such as furosemide, are contraindicated in people receiving cisapride.{R-34;

[43] See *Side/Adverse Effects* in this monograph for more information.

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Benzodiazepines or
Cimetidine or
Ranitidine
(In human beings, the prokinetic effect of cisapride has been reported to increase the rate of absorption of these medications, possibly affecting bioavailability)[R-34; 43]

Anticholinergic compounds, including:
Aminopentamide sulfate or
Atropine or
Glycopyrrolate
(Atropine has been shown to reduce or prevent the action of cisapride on gastrointestinal motility in dogs;[R-4; 6; 23] other anticholinergics would be expected to have a similar effect in animals treated with cisapride.)

Medications that inhibit cytochrome P450 3A4 enzyme, such as:[R-25; 43]
Cimetidine or
Clarithromycin or
Erythromycin or
Fluconazole or
Itraconazole or
Ketoconazole
(In human beings, administration of these medications concurrently with cisapride inhibits metabolism and can increase the serum concentration and AUC of cisapride; other medications inhibiting metabolism may have a similar effect.)

Medications with narrow therapeutic ratios, such as:
Digoxin[R-25; 50]
(Because the rate of gastric emptying is increased, cisapride may affect the rate of drug dissolution or absorption of other medications; digoxin may have reduced absorption when cisapride is administered concurrently.)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: No significant laboratory value alterations have been reported in association with cisapride treatment.[R-2; 34]

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Note: There have been no reported cases of serious induced *arrhythmias* associated with cisapride administration to animals. Because of human fatalities due to arrhythmias associated with cisapride, administration to human patients with certain cardiac risk factors is contraindicated. These include cardiac disease (bradycardia, congestive heart failure, congenital long QT syndrome, second or third degree atrioventricular block, sinus node dysfunction, ventricular arrhythmia, or sinus node disease), hypokalemia, hypomagnesemia, or renal or respiratory failure.[R-34] See *Side/Adverse Effects* in this monograph for more information.

Except under special circumstances, this medication should not be used when the following medical problems exist:

Gastrointestinal hemorrhage or
Gastrointestinal obstruction or
Gastrointestinal perforation
(Stimulation of peristalsis may adversely affect animals with severe hemorrhage, obstruction, or perforation.)[R-34; 47; 50]

Risk-benefit should be considered when the following medical problems exist:

Hepatic dysfunction
Renal dysfunction
(Because cisapride is metabolized by the liver and eliminated in bile and urine, disruptions of organ function can affect plasma concentration; reduced dosage may be necessary.)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: There have been no reports of animals developing the *cardiac arrhythmias* reported in 270 human patients that led to 70 deaths and the withdrawal of commercial cisapride from markets. Reported human arrhythmias have included ventricular tachycardias, ventricular fibrillation, QT prolongation, and associated torsade de pointes.[R-43] In human beings, the incidence of arrhythmias in association with cisapride is believed to be very low, but potentially fatal. About 85% of human deaths occurred in patients with certain risk factors, such as disorders that predispose to arrhythmias or taking other medications that

inhibit cisapride metabolism, cause QT prolongation, or lower serum electrolytes.[R-43; 45]

Researchers were *unable to induce* arrhythmias in dogs given a single cisapride dose of 2 to 8 mg per kg of body weight (mg/kg) while under anesthesia. They did note an increased heart rate and a non-dose-dependent prolonged QT interval but considered the changes mild in relation to the dose.[R-46] A study established the presence in equine heart tissue of potassium channels that have been associated with human toxicity, and also reported sufficient cisapride concentrations in cardiac tissue to trigger arrhythmias with the recommended dosage in horses.[R-33] However, arrhythmias have not been reported in horses in association with cisapride administration.

Those indicating need for medical attention only if they continue or are bothersome

Incidence unknown

Dogs

Diarrhea*—**with an oral dose of 0.61 mg/kg;[R-47] ***licking or lip-smacking, mild—with an intravenous dose of 0.48 mg/kg[R-21]

Horses—occassionally reported in horses given 0.1 to 0.2 mg/kg intravenously

Abdominal discomfort, mild;[R-16; 26; 29; 30; 32] ***increased heart rate, slight and transient***[R-16; 30; 32]

Overdose

For more information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer**.

Lethal dose

LD_{50}—Oral administration: *Rats*—4155 mg/kg.[R-44]

The following have been reported as lethal when administered as a single oral dose—

Dogs: 640 mg/kg.[R-43]

Mice: 1280 mg/kg.[R-43]

Rats, neonatal: 160 mg/kg.[R-43]

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: There is little published information about toxic doses of cisapride in cats and horses. In research studies, cats tolerated a single intravenous dose of 1 mg/kg and an oral dose of 2 mg/kg.[R-2]

In one research study, dogs tolerated an oral dose of 40 mg/kg a day for a year, with no evidence of excessive drug accumulation.[R-17]

The following signs were reported by the National Animal Poison Control Center from 17 reports of cisapride toxicity in dogs received between 1994 and 1996:

Dogs[R-47]

With an oral dose between 5 and 18 mg/kg:

Abdominal pain; aggression; ataxia; fever; vomiting

With an oral dose of ≥ 18 mg/kg (listed in order of frequency):

Diarrhea; ataxia and incoordination; fever; muscle fasciculations and tremors; disorientation; dyspnea; hyperactivity; aggression; nystagmus; ptosis; recumbency; weakness

With an oral dose of 104 mg/kg (one dog):

Diarrhea, severe; fever; muscle fasciculations, severe; nystagmus; recumbency; tachycardia; tachypnea

Treatment of overdose

Treatment may include the following:[R-43; 47]

- Administration of 1 to 2 grams of activated charcoal can significantly reduce the bioavailability of cisapride. One gram slurries given orally at 1 and 4 hours after exposure have been reported to reduce peak plasma concentrations at least 50% in dogs.[R-17]
- Early induction of emesis (<15 minutes after consumption) may also be useful; however, high dosages of cisapride have blocked attempts to produce emesis with apomorphine.
- Supportive therapy and treatment of signs
- Cardiac monitoring
- Although atropine interferes with the clinical action of cisapride,[R-4; 6; 23] the administration of anticholinergics in the treatment of severe cisapride overdose has not been investigated and is not considered likely to be useful.

Client Consultation

In providing consultation, consider emphasizing the following selected information:

Familiarizing clients with signs of potential adverse effects in animals, including abdominal pain, diarrhea, flatulence, or vomiting. Familiarizing clients with how to know when it is necessary to contact their veterinarian.

Keeping cisapride out of the reach of children and pets. Familiarizing clients that will be handling these medications with the risk factors for human

beings.

General Dosing Information

With oral administration

Due to the necessity of compounding cisapride and concerns about dissolution, if considering treatment with an oral dosage form for which there is no dissolution data, note that bioavailability may vary among formulations.

Cats: Because of the great variation in clearance of cisapride among cats, it can be expected that some adjustment of dosage will need to be made for cats not initially responding.{R-2}

Diet

Rats—Oral absorption is significantly affected by administration with food. In rats with free access to food, the bioavailability of a single 10-mg/kg dose was only 55% of that found in fasting rats.{R-17}

Dosing and Dosage Forms

Note: Cisapride is not specifically approved for veterinary use. In other USP information monographs, the EL[US] and EL[CAN] designations refer to uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of commercial product availability in the countries indicated. See also the *Regulatory Considerations* section in this monograph.

Until dosing studies are performed using cisapride prepared by an accepted, standard compounding formula, the most effective dose may depend on how the drug preparation is compounded. Ranges are given based on the information available at this time.

DOSAGES

EL[US,CAN] ***Cats***—

For *Cisapride Oral Suspension, Veterinary*

Constipation, chronic; or

Megacolon, idiopathic; or

Gastrointestinal motility dysfunction, other: Oral, 2.5 to 5 mg as a *total* dose *per cat,* every eight to twelve hours up to a maximum dose of 1 mg per kg of body weight every eight hours.{R-2; 56} Each dose should be administered thirty minutes before feeding.{R-50}EL

Note: Because there are no clinical efficacy studies for the use of cisapride in cats, the above dose is based on a pharmacokinetic study that used serum concentrations achieved with clinically effective dosages in human beings as initial target concentrations.{R-2}

EL[US,CAN] ***Dogs***—

For *Cisapride Oral Suspension, Veterinary*

Note: Gastrointestinal motility dysfunction—Although the safety and efficacy have not been established, an oral dose of 0.1 to 0.5 mg per kg of body weight every eight to twelve hours, up to a maximum dose of 0.5 to 1 mg per kg of body weight every twelve hours, has been recommended.{R-4; 21-23; 56} Each dose should be administered thirty minutes before feeding.{R-50}EL

Note: Because there are no clinical efficacy studies available, the above dose is based on limited studies of drug effects in healthy dogs.

EL[US,CAN] ***Horses***—

For *Cisapride Oral Suspension, Veterinary*

Note: Cecal or colonic impaction—There is very limited information on which to base an oral dose of cisapride in horses with gastrointestinal compromise. Based on case reports and disease models, an oral dose of 0.1 to 0.4 mg per kg of body weight every eight hours may be used; however, it should be considered that absorption may be adversely affected in horses with motility disorders.{R-12; 30}

For *Cisapride Injection, Veterinary*

Gastrointestinal motility dysfunction, including post-operative ileus: Intravenous, 0.1 mg per kg of body weight every eight hours.{R-14-16; 26; 27; 30-32}EL

DOSAGE FORMS

Oral

CISAPRIDE ORAL SUSPENSION, VETERINARY

Strength(s) usually available: Cisapride oral suspension is not available as a commercial product in the United States or Canada. Therefore, it must be compounded for veterinary use. Utilizing the services of a qualified compounding pharmacist to formulate this dosage form is recommended.

Caution: Keep out of the reach of children.

Packaging and storage: Pending.

USP requirements: Proposal pending.

Parenteral

CISAPRIDE INJECTION, VETERINARY

Note: A maximum intravenous dose of 0.1 mg of cisapride per kg of body weight is being used to set *USP NF* endotoxin limits for this dosage form.

Strength(s) usually available: Cisapride injection is not available as a commercial product in the United States or Canada. Therefore, it must be compounded for veterinary use. Utilizing the services of a qualified compounding pharmacist to formulate this dosage form is recommended.

Caution: Keep out of the reach of children.

Packaging and storage: Pending.

USP requirements: Proposal pending.

Table I. Pharmacology/Pharmacokinetics—Intravenous Administration

Species	Dose (mg/kg)	Elimination half-life (hours)	Vd_{SS} (L/kg)	Clearance (mL/min/kg)	$AUC_{0-\infty}$ (mcg/mL·hr)	C_0* (mcg/mL)
Cats[R-2]	1.0	5.19 ± 3.77 (range, 3.03 to 15.14)	4.50 ± 1.36	15 ± 0.67 (range, 0.73 to 25)		0.421 ± 0.155
Cattle[R-53]	0.1	1.90 ± 0.18	2.95 ± 0.45	23.17 ± 1.05		
Dogs[R-17]†	0.63	Single dose: 4.8 Multiple (daily for 30 days): 5.4	Single dose: 1.0 Multiple: 0.64	Single dose: 5.3 Multiple: 3.0	Single dose: 2.1 Multiple (AUC_{0-24hr}): 3.9	(From graph) Single dose: 0.8 Multiple: 1.5
Horses[R-12] [R-13] *Horses* with POI[R-33]§	0.1 0.1 0.1	2.12 ± 0.66 1.90‡	1.47 ± 0.58 0.82 ± 0.34	8.23 ± 0.72 4.30 ± 1.80	0.20 ± 0.19 0.44 ± 0.18	0.151 ± 0.062 0.221 ± 0.192 H1 = 0.097 H2 = 0.231 H3 = 0.550
Rats[R-17]	5	1.0	4.7	91	0.91	
Ewes, pregnant[R-54] *Lambs*[R-54]	0.2	1.54	4.3	36	0.09	
Fed		1.39	3.7	33.3	0.10	
Fasted		1.83	5.2	34	0.10	

*All initial samples were taken at 15 minutes postadministration, with the exception of *horses*[R-12], taken at 5 minutes and canine data from a graph[R-17] with an unreported initial sample time.

†In this study of Beagles, results from cisapride administered as a single dose were mostly comparable to those found when it was administered once daily for 30 days. Median plasma concentration for single and multiple dosing was 0.63 mg/kg/day.

‡Harmonic mean

§Three horses (H1, H2, and H3) with post-operative ileus (POI). It is not clear if these samples were taken after the initial dose or after repeated doses administered every six hours.

Table II. Pharmacology/Pharmacokinetics—Other Routes of Administration

Species	Dose (mg/kg) /Route	C_{max} (mcg/mL)	T_{max} (hours)	Elimination half-life (hours)	Mean residence time (hours)	$AUC_{0-\infty}$ (mcg/mL·hr)	F (Bioavail-ability; %)
Cats[R-2]	2/PO	0.073 ± 0.016	1.25 ± 0.84	5.27 ± 3.16	8.32 ± 4.47		29 ± 22.6
Dogs[R-17]	0.31/IG 1.25/IG 10/IG	0.22 1.0 4.6 ± 1.0	1.2 0.75 3.4 ± 1.9	7.2 7.0 8.1 ± 1.7		1.6 6.6 47 ± 19	53
Horses[R-12]	0.1/IG 0.2/IG 0.4/IG	0.024 ± 0.020 0.048 ± 0.021 0.101 ± 0.029	2.0 1.0 1.0	1.50 ± 0.890 2.44 ± 0.997 2.24 ± 0.512	3.31 ± 0.82 4.29 ± 1.46 4.06 ± 0.63	0.087 ± 0.088 0.191 ± 0.111 0.453 ± 0.162	
Rabbits[R-17]	5/IG	0.061	≤ 0.5	13			
Rats[R-17]	10/IG	Males: 0.87 ± 0.28 Females: 0.96 ± 0.18	≤ 0.25	Males: 0.8 Females: 2.2		Males: 0.76 Females: 2.44	23 (males)

IG = Intragastric, PO = Oral

Developed: 03/12/08

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Cisapride for the treatment of chronic constipation or idiopathic megacolon in cats.

Revision date: October 10, 2007

Back to the indication

The following tables are not intended to be in-depth reviews of each article. Instead, they are brief overviews/reviews of the studies, assuming reviewers are already familiar with the cited references. If you would like additional information about these studies, please contact veterinary@usp.org.

Study 1 of 3: Hasler AH, Washabau RJ. Cisapride stimulates contraction of idiopathic megacolonic smooth muscle in cats. Journal of Veterinary Internal Medicine 1997 Nov/Dec; 11(6): 313-8.

Design	**Goal:** To investigate the *in vitro* effects of cisapride on colonic muscle samples taken from cats with megacolon	**Limitations:**
• *In vitro* study of drug responses in diseased feline muscle tissue N = 8 cats	**Methods:** • Strips of colonic smooth muscle were taken from cats with idiopathic megacolon diagnosed by history, physical exam, and radiographs at the Veterinary Hospital of the University of Pennsylvania between 1992 and 1994. Inclusion criteria: history of megacolon for one year, a lack of response to medical therapy, and no evidence of endocrine or metabolic disease. Healthy colon samples were obtained from age-matched cats. • Samples were taken during exploratory laparotomy and suspended on isometric force transducers. Contractions were measured after treatment with acetylcholine, substance P, and cisapride. • The muscle contraction response to cisapride was measured after pretreatment of muscle strips with a) tetrodotoxin, b) atropine, and c) with lowered calcium concentration. **Results:** • The potency of tested substances in stimulating contractions in ascending and descending longitudinal megacolonic smooth muscle was substance P > cisapride > acetylcholine. • In ascending muscle, the maximum response to cisapride was of similar magnitude to other test substances, but in descending muscle, the responses were of significantly lower magnitude than to the other two substances. • Contractions induced by cisapride were only partially inhibited by tetrodotoxin and atropine. • Contractions induced by cisapride were significantly inhibited by removing extracellular calcium. **Conclusions:** • Cisapride induces contractions of feline megacolonic smooth muscle *in vitro*. • The magnitude of response to cisapride in tissue from cats with megacolon was less than that reported for colonic smooth muscle from healthy cats in a previous study (study 3 in this table; Washabau, et al.).	• Tissue from cats with less severe megacolon might be more responsive to cisapride.

Study 2 of 3: LeGrange SN, Boothe DM, Herndon S, et al. Pharmacokinetics and suggested oral dosing regimen of cisapride: a study in healthy cats. Journal of the American Animal Hospital Association 1997; 33: 517-23.

Design	**Goal:** To investigate the pharmacokinetics of cisapride after oral and intravenous administration.	**Limitations:**
• Pharmaco-kinetic study N = 7	**Methods:** • Healthy, 1-year-old, male, specific-pathogen-free cats at Texas A&M College of Veterinary Medicine. • Randomized, cross-over design with a one-week washout period. Food was withheld in preparation for catheter placement and cats were also fasted through drug administration and sample collection the next day. • Capsules were formulated with dextrose as excipient. Intravenous injection was formulated by dissolving crystalline cisapride in 100% ethanol. • Cisapride analysis was performed by HPLC; limit of the assay was 5 nanograms per mL (ng/mL). **Dose:** • Oral cisapride, 2 mg per kg of body weight (mg/kg) • Intravenous cisapride, 1 mg/kg **Results:** • After intravenous dosing, 3 cats defecated within 33 minutes and 2 cats had anal contractions; however, this response could not be correlated with plasma drug concentrations. • Intravenous administration: Elimination half-life ($T_{1/2}$) = 5.19 ± 3.77 hours, Volume of distribution (Vd_{SS}) = 4.50 ± 1.36 L/kg, Clearance = 15 ± 0.67 mL/kg/min, Mean Residence Time (MRT) = 6.36 ± 4.21 hours • Oral administration: Bioavailability = 29 ± 22.6%, C_{max} = 73.32 ± 16.59 ng/mL, T_{max} = 1.25 ± 0.84 hours, Elimination $T_{1/2}$ = 5.27 ± 3.16 hours, MRT = 8.32 ± 4.47 hours • Cats did not show significant side effects with plasma concentrations up to 589 ng/mL. **Conclusions:** • The highest oral bioavailability in any cat was 33%; it is possible an oral solution would be more available. • Based on these results, an oral dose of 1 mg/kg every eight hours or 1.5 mg/kg every twelve hours should produce a plasma concentration within the human therapeutic range of from 20 to 40 ng/mL to 60 to 80 ng/mL. However, the wide variation in half-life may mean that response to dosage will be variable as well. Higher dosing (doubled) may be necessary and is expected to be tolerated.	• Ethanol may have affected metabolism of the intravenous dosage form; however, similarity of intravenous data ($T_{1/2}$) to oral data suggests minimal effect.

Study 3 of 3: Washabau RJ, Sammarco J. Effects of cisapride on feline colonic smooth muscle function. American Journal of Veterinary Research 1996 Apr; 57(4): 541-6.

Design • *In vitro* study of drug responses in feline colon tissue	**Goal:** To investigate the effects of cisapride on normal feline colonic smooth muscle function. **Methods:** • Colons were removed from cats being euthanised during another study at the University of Pennsylvania School of Veterinary Medicine. Muscle samples were prepared from proximal and distal colon and attached to isometric force transducers. • Tissues were exposed to test substances, then the bath was rinsed before subsequent test exposures. • Control muscle responses were measured with acetylcholine, substance P, neurotensin, and then cisapride. • Muscles responses were measured for the following: -Tetrodotoxin pretreatment, then cisapride treatment -Atropine pretreatment, then cisapride -Extracellular calcium-free solution rinses, followed by cisapride -Nifedipine pretreatment, then cisapride • Some tissues were stimulated with electrical field stimulation. **Results:** • Cisapride evoked isometric stress responses of proximal and distal colonic tissue that were about 32 to 53% of acetylcholine responses and 88 to 91% of substance P and neurotonin responses. • Tetrodotoxin and atropine prevented tissue response to acetylcholine and almost completely prevented contractile response to electrical field stimulation. Tissue response to cisapride was only partically inhibited (10% reduction). • Nifedipine, a preventer of calcium influx, inhibited the tissue response to cisapride by 80%. Pretreatment removal of extracellular calcium had the same effect. **Conclusions:** • Responses to cisapride in feline colon is similar to that in guinea pig colon. Responses appear to be primarily mediated by direct smooth muscle effects. Cisapride effects appear to be dependent on calcium influx through L-type voltage-dependent calcium channels. • Feline idiopathic megacolon is believed to be a dysfunction of proximal and distal colon smooth muscle. Because of the demonstrated action on these tissues *in vitro*, cisapride may be effective in the treatment of this disorder.	

Cisapride for the treatment of esophageal motility dysfunction in cats.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 1: Schuurkes JA, Van Bergen PJ, Van Neuten J. Cholinergic innervation of the feline esophagus [abstract]. British Journal of Pharmacology 1989; 96: 50.

Design • *In vitro* study of effects on feline esophageal tissue samples	**Goal:** To investigate the relative importance of the cholinergic innervation of the feline esophagus and lower esophageal sphincter. **Methods:** • The contraction of circular feline esophageal strips and lower eosphageal sphincter strips in response to electrical stimulation was recorded. Tissue response during exposure to other substances was then tested. **Results:** • Esophageal muscle contraction response to electrical stimulation was abolished by tetrodotoxin or atropine. Cisapride enhanced the contraction response to 126 ± 9% of baseline. • For lower esophageal sphincter strips, the response to electrical stimulation was relaxation followed by small contraction. This response was blocked by tetrodotoxin but was not affected by atropine or cisapride. • Continuous electrical stimulation caused esophageal strips to have contractions that were sensitive to atropine and tetrodotoxin. The lower esophageal sphincter responded with weak contractions. Cisapride enhanced the esophageal contraction to 190 ± 34% of baseline but did not significantly effect the lower esophageal contractions. **Conclusions:** • The feline esophagus has primarily cholinergic innervation but the lower esophageal sphincter has non-cholinergic innervation. • The results provide an explanation for the enhancement by cisapride of esophageal motility in the cat.	

The effect of cisapride on gastric motility and gastric emptying in dogs.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 5: Burger DM, Wiestner T, Hubler M, et al. Effect of anticholinergics (atropine, glycopyrrolate) and prokinetics (metoclopramide, cisapride) on gastric motility in Beagles and Labrador Retrievers. Journal of Veterinary Medicine Series A 2006; 53(2): 97-107.

Design	**Goal:** To investigate the effects of atropine, cisapride, glycopyrrolate, and metoclopramide on motility of the gastric antrum in healthy dogs. **Methods:** • Four healthy three-year-old Labradors and four beagles aged 1 to 6 years were surgically implanted with an instrument that continously measured intraluminal pressure and electromyogram (EMG) activity, with a few breaks, between 8:30 am and 4 pm for a total of 21 study days for each dog. The study began with 5 days of measurement when no medication was administered. • Medications were administered at 9:29 am (intramuscular administration) or 9:00 am (oral administration). Dogs were fed half their daily food at 9:30 and the remainder after 4 pm. Each medication dose was administered to every dog on two days (16 total treatment days); the order in which medication doses were administered was randomized separately for each dog. **Dose:** • Intramuscular atropine, 0.02 mg per kg of body weight (mg/kg) and 0.04 mg/kg • Intramuscular glycopyrrolate, 0.005 mg/kg and 0.01 mg/kg • Oral metoclopramide, 0.3 mg/kg and 0.6 mg/kg • Oral cisapride, 0.2 mg/kg and 0.5 mg/kg **Results:** • Atropine and glycopyrrolate caused a large reduction in the intensity and peak frequency of antral stomach contractions for up to three hours. The effect was clearly dose-related in Beagles, but less so in Labradors. • Metoclopramide and cisapride increased the intensity of antral contractions in all dogs. With cisapride, there was no increase in frequency of contractions. • In Labradors, the lower doses of metoclopramide and cisapride had little and no effect, respectively; the higher doses for these drugs increased contraction amplitude. In Beagles, the lower doses increased antral contraction amplitude, while the higher doses gave a less distinct response. **Conclusions:** • This study demonstrates the effect of prokinetic drugs at different doses on antral motility in dogs, but not how the changes affect gastric emptying.	**Limitations:** • It's unclear if the apparent breed differences were related to differences in body weight: 9.6 kg vs 25.2 kg for Beagles and Labradors, respectively.
• Random-ized, active controlled study of drug effects in healthy subjects N = 8		

Study 2 of 5: Tanaka T, Mizumoto A, Mochiki E, et al. Effects of EM574 and cisapride on gastric contractile and emptying activity in normal and drug-induced gastroparesis in dogs. Journal of Pharmacology and Experimental Therapeutics 1998 Nov; 287(2): 712-9.

Design • Study of healthy and disease-model dogs, with active control, nonrandom-ized N = 6	**Goal:** To investigate the activity of EM574 (an erythromycin derivative) and cisapride on gastric motor activity and gastric emptying in normal dogs and dogs with induced gastroparesis. **Methods:** • Healthy, mixed-breed dogs, weighing 8 to 13 kg. Tubes were implanted from ports in the skin to the proximal duodenum for infusion of phenosulfonphthalein marker and to the distal duodenum, 20 cm from the proximal tube, for aspiration of contents and administration of test materials. A force transducer was implanted on the gastric antrum to continuously measure circular muscle contractions during study periods. • EM574 or cisapride was administered at the beginning of feeding a solid (freeze dried dog food) or liquid meal. Then, these tests were repeated during induced gastroparesis, produced by administering clonidine 15 minutes before feeding and drug administration. • Gastric emptying rate was measured at 15 minute intervals, based on three consecutive duodenal samples. **Dose:** • Intraduodenal EM574, administered at a dose of 3, 10, and 30 micrograms per kg of body weight (mcg/kg) • Intraduodenal cisapride, 0.3, 1, and 3 milligrams mg/kg • Subcutaneous clonidine, 3, 10, and 30 mcg/kg **Results:** • Cisapride caused a significant dose-dependent increase in antral motor activity with the 1- and 3-mg/kg doses. EM574 also increased activity, but the change was not measured as significant. • Only the 1-mg/kg dose of cisapride significantly shortened the half-life of solid food removal from the stomach. The 0.3- and 1-mg/kg doses did not affect gastric emptying of liquid and the 3-mg/kg dose actually lengthened the half-life of liquid emptying from the stomach. • Clonidine decreased postprandial muscle contractions and significantly delayed gastric emptying of liquids and solids. • In clonidine-treated dogs, cisapride (1 mg/kg) restored contractile activity in the gastric antrum and increased the speed of gastric emptying of solids and liquids, but only the change in liquid emptying was shown to be statistically significant. EM574 (30 mcg/kg) significantly increased gastric motor activity and returned gastric emptying to the normal rate. **Conclusions:** • Both EM574 and cisapride increase postprandial gastric antral motor activity and accelerate gastric emptying in normal dogs. Gastric motor activity does not always increase the rate of gastric emptying. • EM574 completely restored gastric motor activity and emptying after clonidine treatment. Cisapride only partially restored them.	

Study 3 of 5: Song CW, Lee KY, Kim CD, et al. Effect of cisapride and renzapride on gastrointestinal motility and plasma motilin concentration in dogs. Journal of Pharmacology and Experimental Therapeutics 1997; 281(3): 1312-6.

Design • Study of drug effects in healthy dogs, with active control, nonrandom-ized N = 7	**Goal:** To investigate the effects of cisapride and renzapride on plasma motilin concentration and gastroduodenal motility. **Methods:** • A gastric cannula and three strain gauges (two proximal to the pylorus and one on the duodenum) were implanted in each dog. • Motor activity was recorded for a period of time before cisapride or renzapride was administered intravenously, then for at least 2 hours after treatment. Blood samples for motilin determination were taken at 5- to 10-minute intervals after drug administration. This cycle was repeated while treating concurrently with atropine and repeated again during a period when the dogs were fed. **Dosage:** • Intravenous cisapride, 5 mg total dose (0.23 to 0.33 mg/kg) • Intravenous renzapride, 5 mg total dose • Intravenous atropine, 5 mcg/kg, followed by continuous infusion at 20 mcg/kg/hour **Results:** • During the initial (nonfed) period, cisapride and renzapride both caused rapid marked increases in gastroduodenal motility that lasted at least 2 hours. During this time, significant increases in plasma motilin occurred. • Atropine treatment completely suppressed stimulation of motility by cisapride and renzapride. • The meal caused a digestive motility pattern that was increased by cisapride or renzapride administration, but the medications did not affect plasma motilin concentrations. **Conclusions:** • Cisapride and renzapride have similar effects on plasma motilin and gastroduodenal motility.	

Study 4 of 5: Orihata M, Sarna S. Contractile mechanisms of action of gastroprokinetic agents: cisapride, metoclopramide, and domperidone. American Journal of Physiology 1994; 266: G665-G676.

Design • Study of drug effects in heathy dogs, with active controls, nonrandom-ized N = 6	**Goal:** To investigate the effects of cisapride, domperidone, and metoclopramide on gastroduodenal emptying of solid meals. **Methods:** • In each dog, strain-gauge transducers were attached to the seromuscular layer of the stomach, pylorus, and duodenum, a catheter was implanted into the duodenum to perfuse poyethylene glycol (PEG) to measure liquid flow rate, and a cannula was implanted further down the intestine to collect chyme. • Nonabsorbable [^{3}H]PEG solution was perfused into the catheter starting 60 minutes before feeding. Dogs were fed a solid meal labeled with ^{99m}Tc sulfur colloid. Chyme samples were collected at 10- and 20-minute intervals until no solid particles were detected for several samples. Transducer recording was continous throughout the procedure. • Chyme samples were centrifuged.: H^{3} and ^{99m}TC counts were performed on the liquid portion and ^{99m}TC counts were performed on the solid portion. **Dosage:** • Medications were administered beginning one hour after ingestion of the meal and were infused for one hour. • Cisapride infusion, 0.3 mg/kg/hour • Domperidone infusion, 0.5 mg/kg/hour • Metoclopramide infusion, 0.5 mg/kg/hour **Results:** • Cisapride significantly shortened gastroduodenal emptying time. Metoclopramide had no effect and domperidone significantly lengthened gastroduodenal emptying time. • Cisapride significantly enhanced pyloric and duodenal motor activity. Metoclopramide had some effect on motor activity but also aided in antropyloroduodenal coordination. Domperidone decreased the frequency of some contractions and weakened antropyloroduodenal coordination. **Conclusions:** • Cisapride is more effective than metoclopramide or domperidone in increasing the rate of gastric emptying (12% decrease in total duration).	

Study 5 of 5: Michiels M, Monbaliu J, Hendriks R, et al. Pharmacokinetics and tissue distribution of the new gastrokinetic agent cisapride in rat, rabbit, and dog. Arzneimittelforschung 1987 Oct; 37(10): 1159-67.

Design
• Pharmaco-kinetic study

N = 8

Goal: To investigate the pharmacokinetics of cisapride after intravenous and oral administration.

Methods:
• Six healthy Beagle dogs (3 male and 3 female). Studies included:
-Pharmacokinetics of intravenous cisapride after single and multiple dosing
-Bioavailability study in a cross-over design of single intravenous and intragastric doses
-Daily oral dosing by capsule for 12 months followed by euthanasia and autopsy
-The effects of activated charcoal on oral cisapride (tablet) pharmacokinetics
• Two lactating Laborador retrievers, 5 and 7 weeks after delivery. This study looked at distribution of cisapride into milk after a single oral administration.

Dose:
• Intravenous cisapride, 0.63 mg/kg as a single dose or once daily for 30 days
• Intragastric cisapride, 0.31, 1.25, and 10 mg/kg
• Oral cisapride (capsule), 2.5, 10, and 40 mg/kg
• Oral cisapride (tablet), 10 mg/kg
• Intragastric activated charcoal slurry, 1 gram per kg

Results:
• Intravenous administration to dogs

Dose (mg/kg)	Elimination half-life (hours)	Vd_{SS} (L/kg)	Clearance (mL/min/kg)
0.63	4.8	1.0	5.3

• Oral administration

Dose (mg/kg)	C_{max} (mcg/mL)	T_{max} (hours)	Elimination half-life (hours)	$AUC_{0-\infty}$ (mcg/mL·hr)	F (%)
0.31	0.22	1.2	7.2	1.6	53
1.25	1.0	0.75	7.0	6.6	
10	4.6 ± 1.0	3.4 ± 1.9	8.1 ± 1.7	47 ± 19	

• Cisapride appears to be easily distributed into milk in lactating dogs. The milk to plasma ratio of cisapride is 1.7 to 2.2; metabolites cross a little easier than unmetabolized cisapride, with a ratio of 3.2 to 5.2.
• Activated charcoal given 1 and 4 hours after cisapride administration significantly reduced the systemic availability of the drug.

Comments:
• The authors did not note whether any adverse effects were seen in dogs administered oral cisapride for 12 months.

The effect of cisapride on intestinal motility in dogs.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 2: Summers RW, Flatt AJ. A comparative study of the effects of four motor-stimulating agents on canine jejunal spike bursts. Scandinavian Journal of Gastroenterology 1988 Dec; 23(10): 1173-81.

Design • Study of drug effects in healthy dogs with active and negative controls, nonran-domized N = 16	**Goal:** To study the effects of cisapride on transit time by linking increased contractions with movement of intestinal contents in conscious dogs. **Methods:** • Study 1—Ten healthy mixed breed dogs with seven electrodes implanted 3 centimeters (cm) apart in the intestinal serosa. Myoelectric activity was continuously monitored. • Study 2—Six healthy mixed breed dogs with two cannulas from the intestine out through the skin; one placed 10 cm proximal to the electrodes, as described, and one 10 cm distal. **Dose:** • Study 1 measured myoelectrical activity during the following treatments: -Intravenous cisapride or metoclopramide, 0.16 mg per kg of body weight (mg/kg), given as a bolus over five minutes, followed thirty minutes later by a 0.32-mg/kg bolus. -Intravenous bethanechol infusion at a rate of 1.5, 3.0, and 6.0 mg/kg/min for twenty minutes. Thirty minute intervals of no treatment between dosages. -Intravenous cholecystokinin infusion of 0.2, 0.4, and 0.8 IDU/kg/min for twenty minutes. Thirty minute intervals of no treatment between dosages. • Study 2 measured travel of a phenol red bolus from proximal cannula to the distal cannula during: -Intravenous saline control administration -Intravenous cisapride, 0.16 mg/kg and 0.48 mg/kg **Results:** • A dose-related agitation was noted in dogs that received metoclopramide. Both bethanechol and cholecystokinin caused loose stools in half the studies and, with the highest dosages, bethanecol caused salivation and lacrimation. Some lip-smacking was reported with the highest dosage of cisapride. • Cisapride caused the greatest response in terms of the length of jejunal spike burst spread along the bowel; thereby causing increased propulsive efficiency. • Bethanechol and cholecystokinin produced a higher spike burst frequency and duration. Metoclopramide had little myoelectric effect. **Conclusions:** • The results confirm cisapride's prokinetic activity and demonstrate a link between contractile activity and intestinal content transit rate.	

Study 2 of 2: Schemann M, Ehrlein HJ. 5-Hydroxytryptophan and cisapride stimulate propulsive jejunal motility and transit of chyme in dogs. Digestion 1986; 34(4): 229-35.

Design • Active controlled, randomized study of drug effects in healthy dogs N = 4	**Goal:** To investigate the effect of 5-HTP and cisapride on postprandial jejunal motor activity in conscious dogs. **Methods:** • Beagle dogs, weighing 10 to 15 kg, with 6 strain gauge transducers implanted 4 cm apart on the serosal surface of the jejunum. Contractions were continuosly monitored. A Teflon catheter was implanted 10 cm proximal to the most proximal transducer. Two mL boluses of contrast were administered through the intestinal catheter and fluoroscopy performed to calculate transit time. • Control measurements were taken for a period of time with no medication administered. • 5-hydroxytryptophan (5-HTP) was administered before a caloric-free meal and after a nutrient meal (protein, fat and carbohydrate). Cisapride was administered after a nutrient meal. **Dose:** • Intravenous 5-HTP, 200 mcg/kg/min for 30 minutes. • Intravenous cisapride, 0.32 mg/kg as a bolus, followed by a thirty-minute infusion of 0.04 mg/kg/hr. **Results:** • 5-HTP increased the incidence and length of spread of contractile waves, enhancing propulsion. It also increased the frequency of contractions after the nutrient meal. • Cisapride increased the length of spread of contractile waves, but not the frequency. • Both agents accelerated the transit rates of intestinal contents. Effects continued at least through the monitoring period of 15 minutes after infusions ended. **Conclusions:** • Cisapride might be useful when intestinal propulsion is decreased or stopped. • 5-HTP stimulates intestinal motility, decreasing transit time.	

The effect of cisapride on gastrointestinal, including colonic, motility in dogs.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 2: Fujii K, Okajima M, Kawahori K. Effect of cisapride on the cholinergic control mechanisms of gastrointestinal motility in dogs. Nippon Heikatsukin Gakkai Zasshi 1988 Jan; 24(1): 1-12.

Design • Study of drug effects in healthy dogs and in dogs with induced dysfunction N = 11	**Goal:** To study the effects of cisapride on gastrointestinal motor function and on function during induced pseudo-obstruction. **Methods:** • Healthy dogs were implanted with force transducers on the serosal surface of the gastric body and antrum, duodenum, ileum, and colon. Studies performed were— 1&2. Cisapride doses were given during interdigestive and post-prandial states in conscious dogs, each time followed by the administration of atropine. 3. In one dog, a Thiry loop was constructed 15 cm proximal to the ileocecal junction to create a pseudo-obstruction. Domperidone, metoclopramide, cisapride and trimebutine maleate were each administered separately. 4. Dogs anesthetized with pentobarbital were given either cisapride or tetrodotoxin followed by cisapride. 5. The effect of cisapride on gastric acid secretion, pancreatic secretion, and bile production was measured in conscious dogs with fistulas. **Dose:** • Intravenous cisapride, 0.5, 0.75, or 1 mg/kg, infused over five minutes • Intravenous atropine, 0.05 to 0.1 mg/kg • Intravenous trimebutine, 3 mg/kg • Intravenous tetrodotoxin, 10 mcg/kg, infused over thirty minutes **Results:** • Cisapride induced or increased motility in the gastrointestinal tract from gastric body to distal colon during interdigestive quiescence or digestion. The motility migrated from the proximal ileum to the distal ileum. Intestinal contents were evacuated during pseudo-obstruction. • Trimebutine maleate produced effects similar to cisapride, but metoclopramide and domperidone did not produce the migration of motility. • Both atropine and tetrodotoxin prevented the effects of cisapride on gastrointestinal motility. **Conclusions:** • Results suggest cisapride acts on the cholinergic neurones in the gastrointestinal wall to stimulate acetylcholine release and stimulate motility. Cisapride does not induce any significant amount of gastric acid, pancreatic enzyme, or bile secretion.	

Study 2 of 2: Lee KY, Chey WY, You CH, et al. Effect of cisapride on the motility of gut in dogs and colonic transit time in dogs and humans [abstract]. Gastroenterology 1984; 86: 1157.

Design • 1) Study of drug effects in healthy dogs, with negative control; and 2) human placebo-controlled, double-blind, randomized study N = 11 dogs, 9 human beings	**Goal:** To investigate the effect of cisapride on canine gastrointestinal motility and on colonic transit time in dogs and human beings **Methods:** • Animal study—Effects of medication were noted in fasting dogs: 8 dogs with gastric cannulas and electrodes in the antrum, duodenum, jejunum, ileum, and colon. 3 dogs with additional cannulas in the cecum. Barium pills administered through the cecal cannula were counted in hourly stool checks. • Human study—Fluroscopy recorded transit time for barium-containing pellets from the proximal right colon to the rectum: 4 human patients with idiopathic constipation 5 healthy human subjects **Dose:** • Animal study— -Intravenous cisapride, 5 mg total dose -Intravenous saline • Human study— -Oral cisapride, 20 mg total dose every 8 hours for one day -Placebo **Results:** Animal study— • During phase I digestion, cisapride caused migrating motor complex-like (MMC-like) activity in the ileum and colon, followed by continuous phase II-like activity. The upper intestine responded with phase II activity only. In 2 dogs, defecation occurred within an hour of drug administration. • Atropine blocked the MMC-like activity, but not the phase II activity. • When medications were given hourly, cumulative bowel emptyings changed from a baseline of 0, 14, 34.3, and 45.7% at 1, 6, 12 and 24 hours to 22.9, 28.6, 48.6, and 91.4%, respectively. Human study— • There was a statistically significant decrease in transit time in patients given cisapride, rather than placebo. **Conclusions:** • Cisapride might be useful for ileal or colonic motor dysfunction.	

Cisapride in the treatment of post-operative ileus in horses.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 7: Smith MA, Edwards GB, Dallap BL, et al. Evaluation of the clinical efficacy of prokinetic drugs in the management of post-operative ileus: can retrospective data help us? The Veterinary Journal 2005; 170(2): 230-6.

Design		**Comment(s):**
• Retrospect-ive clinical case series N = 55	**Goal:** To determine whether retrospective clinical data is useful in evaluating efficacy of prokinetic drugs in the treatment of post-operative ileus (POI). **Methods:** • Cases at 2 large equine referrals centers over 10- and 15-year periods. Inclusion limited to horses with pedunculated lipoma obstruction (PLO); horses with PLO are considered 3 times more likely to suffer POI than with other intestinal disorders. • Variables evaluated included signalment, heart rate, packed cell volume, duration of colic prior to presentation, length of intestine resected, anastomosis type performed, outcome, time to first feed, duration of hospitalization, occurrence of ileus, duration of post-operative reflux, and the use of one or more prokinetic agents. • Duration of the study was three days after surgery. **Dose:** • All horses received intravenous lignocaine/lidocaine at a loading dose of 1.3 mg per kg of body weight (mg/kg) over fifteen minutes, followed by maintenance of 0.05 mg/kg/min. Of the following prokinetics, the clinician selected which would be administered in each case: • Per rectum, cisapride in dimethyl sulfoxide 100 to 200 mg every six hours • Intravenous metoclopramide, 0.06 mg per kg of body weight infused over one hour, given every six hours • Intravenous erythromycin, 1000 mg total dose, infused over one hour, given every six hours **Results:** • The statistical power of the study was low; odds ratio of > 5 with 95% confidence and 80% power. Univariate analysis suggested that the two hospital populations were not similar. • There was no significant association between prokinetic administration and outcome. **Conclusions:** • The authors felt interpretation of the results was limited by the low statistical power.	• This study grouped outcomes from all three medications. • In the pharmacokine-tic studies compiled for this ballot, cisapride in DMSO administered rectally was successfully retained in only 1 horse (see "Study 3" in this table). The impact of rectal administration on this study is unclear.

Study 2 of 7: Nieto JE, Van Hoogmoed L, Spier SJ, et al. Use of an extracorporeal circuit to evaluate effects of intraluminal distention and decompression on the equine jejunum. American Journal of Veterinary Research 2002 Feb; 63(2): 267-75.

Design • *In vitro* study of healthy equine jejunum	**Goal:** To create an *in vitro* model to investigate intestinal distension and decompression in horses and its effect on vascular resistance, mucosal permeability, histomorphologic abnormalities, and response to prokinetic drugs. **Methods:** • Jejunal segments and blood from 5 euthanized horses were studied in an extracorporeal circuit; control and distended segments were studied simultaneously. • The effects of intraluminal distention and decompression on vascular resistance, mucosal permeability, and histological samples were evaluated. Contractile response of circular smooth muscle to prokinetic drug exposure was measured. **Results:** • Vascular resistance increased with 10 and 30 minutes of distension and returned to baseline during decompression. • Edema, hemorrhage, shortened villi and reduction of mucosal surface area were seen after distension and decompression of segments. Mucosal permeability increased after distension ended. • Distension and decompression reduced the response of smooth muscle to cisapride, erythromycin, and metoclopramide. **Conclusions:** • Intraluminal distension may explain the inconsistent response of horses with postoperative ileus to prokinetic drugs.	

Study 3 of 7: Summarized equine pharmacokinetic studies, including—

*10. Steel CM, Bolton, JR, Preechagoon, et al. Unreliable rectal absorption of cisapride in horses. Equine Veterinary Journal 1999; 31(1): 82-84.
11. Cable CS, Ball MA, Schwark WS, et al. Preparation of a parenteral formulation of cisapride from Propulsid tablets and pharmacokinetic analysis after its intravenous administration. Journal of Equine Veterinary Science 1998; 18(10): 616-21.
12. Steel CM, Bolton JR, Preechagoon Y, et al. Pharmacokinetics of cisapride in the horse. Journal of Veterinary Pharmacology and Therapeutics 1998; 21: 433-36.
13. Cook G, Papich MG, Roberts MC, et al. Pharmacokinetics of cisapride in horses after intravenous and rectal administration. Amerian Journal of Veterinary Research 1997 Dec; 58(12): 1427-96.

Intravenous Administration

Dose (mg/kg)	$T_{1/2}$ (hours)	Vd_{SS} (L/kg)	Cl_S (mL/min/kg)	AUC (ng/mL·hr)	References
0.1	2.12 ± 0.66	1.47 ± 0.58	8.23 ± 0.72	204 ± 19.5	12.
0.1	1.90†	0.82 ± 0.34	4.3 ± 1.8	442.3 ± 180.5	13.

†Harmonic mean

Rectal Administration

Formulation	Notes	References
Aqueous	Dose: 0.4 mg/kg Number of animals achieving measurable plasma drug concentrations: 3 of 5 C_{max} = 35 to 118 nanograms/mL, T_{max} = 1 to 10 hours Note: Cisapride is minimally soluble in water.	10.
DMSO	Dose: 1 mg/kg Number of animals achieving measurable plasma drug concentrations: 1 of 4 (3 horses expelled the dose within 20 minutes) Plasma cisapride for the one horse was 35, 75, and 80 ng/mL at 90, 150, and 240 minutes after administration, respectively.	11.
Propylene glycol	Dose: 1 mg/kg At any one sampling time in the first 5 hours after administration, only 1 to 3 horses of 5 studied had measurable plasma drug concentrations. C_{max} = 13.48 ± 7.17 ng/mL, AUC = 46.49 ± 30.16 ng·hr/mL, F (systemic availability) = 1.23%	13.

Intragastric Administration

Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (hours)	Mean residence time (hours)	$AUC_{0-\infty}$ (ng/mL·hr)	References
0.1	24.8 ± 20.2	2.0	3.31 ± 0.82	87.1 ± 88.2	12.
0.2	48.4 ± 21.6	1.0	4.29 ± 1.46	191 ± 111	12.
0.4	101 ± 29.7	1.0	4.06 ± 0.63	453 ± 162	12.

* Numbering (11-13) corresponds to the *Cisapride* monograph reference list.

Study 4 of 7: van der Velden MA, Klein WR. The effects of cisapride on the restoration of gut motility after surgery of the small intestine in horses; a clinical trial. Veterinary Quarterly 1993; 15: 175-9.

Design • Placebo-controlled, randomized, blinded clinical study N = 70	**Goal:** To investigate the effects of cisapride on gut motility after surgery of the small intestine. **Methods:** • Horses treated surgically for colic caused by small intestinal disorders between April 1990 and March 1991 at the State University of Utrecht. A standard protocol was used for presurgical history and evaluation, blood tests, celiotomy and anesthesia, antibiotic treatment, and postoperative evaluation. No drugs had previously been given to stimulate bowel motility. **Dosage:** • Intramuscular cisapride, 0.1 mg/kg, administered one hour after surgery and again nine hours later. Additional doses were administered, as needed, every eight hours. • Placebo was identical in appearance to the cisapride, and administered in the same way. **Results:** • Eight horses died or were euthanized within 24 hours of surgery. Fourteen died or were euthanized between 24 hours and 1 month after surgery. Four horses had a second laparotomy to resolve the ileus, successfully in three. Recoveries without complications were reported for 44 horses. • Sixty percent (18) of the placebo-treated animals and 73% (22) of the cisapride-treated animals recovered bowel motility uneventfully ($p < 0.01$) and did not develop signs of ileus; however, 7 of these 40 animals eventually died or were euthanized. • In horses that did develop ileus, fewer cisapride injections than placebo injections ($p < 0.01$) were required to restore motility in horses that susequently responded to treatment. **Conclusions:** • Cisapride decreases the risk of post-operative ileus and speeds the restoration of bowel motility after small intestinal surgery. Cisapride does not reliably prevent ileus or fatal consequences.	

Study 5 of 7: De Geest J, Vlaminck K, Muylle E, et al. A clinical study of cisapride in horses after colic surgery. Equine Veterinary Education 1991; 3(3): 138-42.

Design • Prospective uncontrol-led clinical study, cohort comparison N = 42 treated	**Goal:** To investigate the clinical efficacy of cisapride in the treatment of post-operative ileus after abdominal surgery. **Methods:** • Horses were presented for colic surgery at the University of Ghent with pathology in the small intestine (group 1, N = 17), large intestine (group 2, N = 16), or other area (group 3, N = 9). Supportive therapy, treatment for shock, and post-operative monitoring were standardized. **Dosage:** • Intramuscular or intravenous cisapride, 0.1 mg/kg, administered after surgery and followed by the same dose every eight hours, until sponteanous defecation occurred. **Results:** • Cisapride-treated horses—Group 1: 76.5% survived, Group 2: 68.8% survived, Group 3: 33.3% survived • Deaths due to ileus in treated horses—Group 1: 1 horse, Group 2: 3 horses, Group 3: 1 horse. Other deaths were due to surgical complications, infection, or other causes. • No statistical differences were noted between intramuscular or intravenous administration of cisapride or between Group 1 and Group 2 outcomes. For all animals, average time to first defecation was less than 24 hours after surgery. • Typical survival rates for this clinic (no cisapride) have been 45.9% for small intestinal pathology and 65% for large intestinal pathology. **Conclusions:** • Recovery rates were high when cisapride was administered and there was a significant reduction in death due to ileus compared to historical data. Results suggest that cisapride is promising for the treatment of postoperative ileus.	

Study 6 of 7: Gerring EL, King JN. A multicentre trial of cisapride in the prophylaxis of equine post operative ileus. Equine Veterinary Education 1991; 3(3): 143-5.

Design	**Goal:** To investigate the usefulness of cisapride in the treatment of post-operative ileus after abdominal surgery.	**Comment(s):**
• Prospective uncontrol-led clinical study N = 81 treated	**Methods:** • Horses were presented to one of five equine surgery centers in the United Kingdom and had laparotomy for decompression and/or stomach or small intestinal surgery. **Dosage:** • Intramuscular cisapride, 0.1 mg/kg, administered three, nine, and nineteen hours after surgery. Additional doses were administered, if needed, at eight-hour intervals. **Results:** • Cases included strangulation obstruction (43), simple obstruction (25), and miscellaneous (13). • Seventy percent of cases treated with cisapride did not develop post-operative ileus. Seventeen percent of cases had already developed gut sounds by the time cisapride was administered, 5% had an equivocal response to treatment, and 7% died of endotoxemia or peritonitis. • Three of the four equivocal cases were later diagnosed with grass sickness. • Two cases showed signs of abdominal discomfort after cisapride administration. One horse collapsed 3 minutes after cisapride, recovered within a few minutes, but died the next day of endotoxic shock. **Conclusions:** • The authors conclude that cisapride contributes to successful management of post-operative colic.	• Although study cases were chosen as being at high risk of developing ileus, no data were presented to evaluate outcomes.

Study 7 of 7: Gerring EL, King JN. Cisapride in the prophylaxis of equine post operative ileus. Equine Veterinary Journal 1989 Jun; 7: 52-5.

Design • a) Study of drug effects in induced disease b) Prospective uncontrolled clinical study, with retrospective cohort comparison N = 3 disease model, 22 clinical cases	**Goal:** To investigate the effects of cisapride in a model of disease and in prevention of post-operative ileus in clinical cases. **Methods:** • Experimental model—Three ponies had strain gauges and bipolar electrodes implanted onto the distal gastric antrum, jejunum, ileum, left dorsal colon, and small colon. Ileus was induced by local irritation and drying of the distal jejunum during laparotomy. Medications were administered and activity recorded. Resolution of ileus was determined by instrumentation and by the progress of spheres administered intragastrically. • Clinical study—Cases were limited to those requiring surgery for gastroenterotomy, bowel resection, or extensive intensive decompression; large colon cases were excluded. Except for the initial two cases, handled individually, each case had a standard treatment protocol. **Dosage:** • Experimental model— - Intramuscular cisapride, 0.1 mg/kg at 3 and 15 hours after surgery - Intravenous domperidone, 0.2 mg/kg at 3, 9, and 15 hours after surgery - Control group given no prokinetic treatment • Clinical study—Intramuscular cisapride, 0.1 mg/kg at 3, 11, and 19 hours after surgery. Additional doses were given every 8 hours, as needed. **Results:** • Experimental model—In untreated ponies, surgical manipulation caused prolonged ileus. Both drugs effectively restored transit time, electromechanical activity, and coordination of digestive cycles. • Clinical study—Cisapride appeared to increase survival rate from 51 to 68% and decreased post-operative ileus from 16 to 9%, when compared to typical rates for this clinic (historical data, N = 259 over 14 years). Slight discomfort was the only side effect noted. **Conclusions:** • Experimental model—Both cisapride and domperidone were effective in speeding the return to normal activity after induced post-operative ileus. • Clinical study—Cisapride appears to be highly effective in preventing idiopathic post-operative ileus, but ineffective in cases with devitalised bowel or infection.	

The effect of cisapride on gastric motility in horses.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 3: Valk N, Doherty TJ, Blackford JT, et al. Effect of cisapride on gastric emptying in horses following endotoxin treatment. Equine Veterinary Journal 1998; 30(4): 344-8.

Design	**Goal:** To investigate the effect of oral cisapride on gastric emptying in healthy horses and in horses after endotoxin treatment **Methods:** • Study 1—No endotoxin: Six mares were given saline or cisapride, followed 60 minutes later by intragastric acetaminophen, an indicator of gastric emptying previously used in human studies. • Study 2—Sixteen horses randomly assigned to receive one of three treatment protocols, followed by intragastric acetaminophen 30 minutes after the last treatment. One- to three-week washouts for endotoxin-treated horses. • Blood samples for acetaminophen assay were taken at intervals for 240 minutes after the indicator was given. **Dose:** • Intragastric acetaminophen, 20 mg per kg of body weight (mg/kg), in both studies • Study 1— -Control: Intragastric water, 0.5 liter (L) -Intragastric cisapride, 0.1, 0.2, or 0.4 mg/kg in 0.5 L water • Study 2— -Control group: Intragastric water, 0.5 L and, sixty minutes later, intravenous saline -Intragastric water, 0.5 L and, sixty minutes later, intravenous endotoxin, 0.2 mcg/kg in 1 L saline solution, infused over 15 minutes -Intragastric cisapride, 0.4 mg/kg in 0.5 L water and, sixty minutes later, intravenous endotoxin, 0.2 mcg/kg in 1 L saline solution, infused over 15 minutes **Results:** • Cisapride did not significantly change acetaminophen pharmacokinetics in healthy horses. • Endotoxin slowed gastric emptying significantly, although the effect varied among horses. Clinical signs of endotoxemia were produced but resolved within 4 hours. • Cisapride (0.4 mg/kg) significantly counteracted the slowing of gastric emptying caused by endotoxin. **Conclusions:** • Pretreatment with cisapride attenuates the slowed gastric emptying caused by administration of endotoxin.	**Comment(s):** • The value of administering oral acetamino-phen to assess gastric emptying was demonstrated in a study published in the same issue—Doherty, et al. Equine Veterinary Journal 1998; 30(4): 349-51.
• Negative-controlled, randomized study of cisapride effects in healthy horses and in endotoxin-treated horses N = 22		

Study 2 of 3: Baker SJ, Gerring EL. Gastric emptying of four liquid meals in pony foals. Research in Veterinary Science 1994; 56: 164-9.

Design	**Goal:** To investigate in foals the effect of cisapride on gastric empyting of an isotonic meal with lipid concentration similar to equine milk.	**Comment(s):**
• Study of drug effects in healthy foals N = 4	**Methods:** • Welsh Mountain cross pony foals were given one of several test meals containing phenol red. Test meals were water, 0.9% saline, saline and commercial Intralipid (1.25% lipid), and mare's milk. Stomach samples before and after each meal were taken intermittently by nasogastric sampling tube. Dye concentration and gastric volumes were calculated. • The lipid meal test was performed again, after cisapride administration. **Dose:** • Intravenous cisapride, 0.1 mg/kg, given 10 minutes before the meal **Results:** • Water, saline, and lipid solution were all emptied from the stomach at similar rates; all more rapidly than reported in human studies. Milk was emptied significantly more slowly than the other three. • Cisapride did not accelerate the emptying of lipid solution from the stomach. **Conclusions:** • This study may have been unable to show the effect of cisapride on gastric emptying because of the already rapid pace of lipid solution leaving the stomach.	• It is unfortunate cisapride was not tested with other meal types.

Study 3 of 3: King JN, Gerring EL. Cisapride does not modify equine gastrointestinal motility disrupted by *E. coli* endotoxin or prostaglandin E_2. Journal of Gastrointestinal Motility 1992; 4: 261-9.

Design • Negative-controlled study of cisapride effects in healthy ponies and in ponies treated with endotoxin or prosta-glandin E_2 N = 4	**Goal:** To investigate whether cisapride would affect the changes in gastrointestinal motility induced by endotoxin or prostaglandin **Methods:** • Welsh Mountain ponies weighing 90 to 180 kg were implanted with strain gauge transducers in the gastric antrum and proximal jejunum. All treatments were administered 30 minutes after a period of transient gastric inactivity. Washout periods were 48 hours, with the exception of a 3-week period after endotoxin administration. • a) Control saline, b) prostaglandin, c) endotoxin, and d) cisapride were each administered alone to monitor effects. Cisapride was also administered e) 15 minutes after the start of a prostaglandin infusion and f) 15 minutes after the onset of motility seen after endotoxin administration. **Dose:** • Saline solution • Intravenous prostaglandin E_2, infused over 60 minutes to deliver a total dose of 10 mcg/kg • Intravenous endotoxin, 0.1 mcg/kg, administered over 15 minutes • Intravenous cisapride, 0.2 mg/kg, administered over 5 minutes **Results:** • Cisapride alone increased gastric motility, by increasing contraction amplitude. • Administration of cisapride did not affect the decreases in gastric or jejunal motility caused by prostaglandin E_2 or endotoxin, even though the effects were due to decreased contraction amplitude. • Cisapride increased heart rate but the effect was not cumulative, in that heart rates did not increase above that seen in response to endotoxin or prostaglandin. Cisapride produced mild discomfort in one pony and, when administered with endotoxin or prostaglandin, increased the frequency of passing feces. **Conclusions:** • It is possible cisapride is not effective in the presence of endotoxemia.	

The effect of cisapride on gastrointestinal, including colonic, motility in horses.

Revision date: October 10, 2007

Back to the indication.

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Study 1 of 3: Steinebach MA, Cole D. Cisapride in the resolution of pelvic flexure impaction in a horse. Canadian Veterinary Journal 1995 Oct; 36: 624-5.

Design • Single case report	**Signalment/History:** • 21-year-old, Appaloosa stallion presented to the Western College of Medicine, Saskatoon, Saskatchewan with colic. Diagnosis of nonstrangulating obstruction due to feed impaction of the pelvic flexure. **Treatment:** • Enteral fluid therapy by nasogastric tube (warm water and mineral oil on days 1, 3, and 5; warm water and dioctyl sodium sulphosuccinate in glycerine on days 2, 4, and 6) and intravenous fluids. The horse had access to water and was given bran mashes 2 to 4 times a day. • After no response to 6 days of fluid therapy, oral cisapride was administered at a dose of 0.1 mg/kg every eight hours for three days. **Results:** • Increased borborygmi were noted in all abdominal quadrants within 5 hours of the initial cisapride dose. Three hours later, the horse showed signs of discomfort and intravenous flunixin meglumine, 1.1 mg/kg, was given. Thirty-six hours after the initial cisapride dose, the horse began passing feces. Eight hours later, the pelvic flexure was empty and normal small colon feces were noted. **Conclusions:** • Results suggest oral cisapride is useful when colonic motility is slowed. • Further study is necessary to establish the best dose with fewest adverse effects.	

Study 2 of 3: Ruckebusch Y, Roger T. Prokinetic effects of cisapride, naloxone and parasympathetic stimulation at the equine ileo-caeco-colonic junction. Journal of Veterinary Pharmacology and Therapeutics 1988; 11: 322-9.

Design • Study of drug effects in healthy ponies, with active and negative controls N = 3	**Goal:** To investigate the effect of prokinetic agents on motility of the ileo-ceco-colonic junction in ponies **Methods:** • Ponies, 2 to 6 years of age, were implanted with electrodes in the terminal ileum, the cecum, and colon. In one pony, strain-gauge force transducers were placed next to the electrodes. • The pony with transducers was used initially to monitor the effects of each medication and choose equiactive doses. Then medications and saline control were administered and responses recorded in all three ponies, with at least 48 hours between each study. **Dose:** • Intravenous sodium chloride solution • Intravenous cisapride, 0.05 and 0.1 mg/kg • Intravenous pilocarpine, 0.05 and 0.1 mg/kg • Intravenous naloxone, 0.01 and 0.05 mg/kg • Intravenous carbachol, 0.002 and 0.01 mg/kg • Intravenous metoclopramide, 1, 2, and 4 mg/kg **Results:** • The electrical spiking activity was correlated with the strength of the contractions recorded from the strain gauges in one pony. • Cisapride caused cecal contraction followed by ileal and colonic motor activity. Metoclopramide produced weak responses that did not specifically stimulate ceco-colonic motility. Pilocarpine stimulated the ileum only. Carbachol enhanced motility of the ileum, cecum, and colon. Naloxone increased cecal and colonic motility. • The duration, but not the magnitude, of contractions in the colon caused by cisapride were dose-dependent. • Defecation was seen after administration of cisapride, carbachol, and naloxone. **Conclusions:** • The activity of cisapride may involve both cholinergic effects and an action at the 5-hydroxytryptamine (5-HT) receptors.	

Study 3 of 3: King JN, Gerring EL. Actions of the novel gastrointestinal prokinetic agent cisapride on equine bowel motility. Journal of Veterinary Pharmacology and Therapeutics 1988; 11: 314-21.

Design • Negative controlled, randomized study of drug effects in healthy ponies N = 4	**Goal:** To investigate the effect of cisapride on motility of the gastrointestinal tract in fasting ponies **Methods:** • Ponies, 12 to 24 months of age, were implanted with electrodes in the stomach jejunum, left dorsal colon, and small colon. Strain gauge transducers were sutured to the stomach, jejunum, ileum, and left dorsal colon to measure circular muscle activity. • Ponies were fasted for 18 hours before recording began. Test dosage given during each test was chosen by randomization. Recording began after a 90-minute control reading and ended 120 minutes after dosage administration. **Dose:** • Intravenous 0.9% saline solution infusion, 4 mL per minute (control readings) • Intravenous cisapride (dissolved in 0.9% saline), 0.05, 0.1, or 0.25 mg/kg total dose infused over sixty minutes **Results:** • All ponies responded to cisapride with significant and prolonged increase in the motility of the whole gastrointestinal tract, primarily through increased contraction amplitude rather than rate. Strength of the response and time to onset varied somewhat among ponies. • Heart rate increased mildly and transient signs of abdominal discomfort appeared after the 0.1- and 0.25-mg/kg doses. There was an increase in frequency of passing feces. **Conclusions:** • Cisapride is a potent equine gastrointestinal prokinetic agent. The 0.1-mg/kg dose appeared to produce the most consistent and prolonged response.	