

NDA 20-210 - MEDICAL OFFICER'S REVIEW - 1

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA 20-210

Propulsid™ (cisapride) Tablets

17 March 1992

Andre Dubois, M.D., Ph.D.

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MEDICAL OFFICER'S REVIEW

NDA 20-210

Name of Drug: Propulsid™ (cisapride) Tablets

Sponsor: Janssen Research Foundation

Formulation: Tablets 10 mg for oral administration.

Route of Administration: Oral

Proposed Indications: Treatment of gastroesophageal reflux disease (GERD) characterized by symptoms of heartburn, regurgitations and epigastric pain or endoscopic evidence of esophagitis.

Date of Submission: 29 August 1991

Material Submitted: Volume 1 (Cover letter, form 356H, Patent Information, Index, Annotated Package Insert, an Overall Summary), and the 42 volumes of the Clinical Data Section (Volumes 1.45 to 1.86).

Date Reviewed: 10 March 1992

Reviewer: Andre Dubois M.D., Ph.D.

I. INTRODUCTION

Gastroesophageal reflux disease (GERD) is due to multiple factors, the main one being the presence of abnormal amounts and concentrations of acid in the esophagus. Agents that suppress gastric acid secretion have been shown to be effective in patients with gastroesophageal reflux. Although effective, this approach does not appear to address the primary cause of the disease since most patients with GERD do not have gastric acid hypersecretion. Many consider GERD to be a gastrointestinal motility disorder, and abnormal motility of the esophagus, of the stomach, and of the Lower Esophageal Sphincter (LES) have been proposed as being responsible for this disease. The prokinetic agent metoclopramide has been shown to be effective in GERD without modifying gastric acid secretion, but the safety profile of this drug limits its use in GERD patients. Cisapride is different pharmacologically and structurally from metoclopramide, and it does not have CNS or prolactinemia side effects that have been associated with this compound. However, it has similar and more potent pharmacological effects in tests related to the motility defects implicated in GERD. Therefore, this NDA evaluates the efficacy and safety of cisapride in the treatment of GERD.

II. PHARMACOLOGY, PHARMACOKINETICS AND PHARMACODYNAMICS.

A. ANIMAL PHARMACOLOGY

Cisapride is a substituted piperidiny benzamide that enhances the motor activity of the esophagus, stomach, gallbladder, small intestine and large intestine both *in vivo* and *in vitro*. In addition, this compound stimulates and coordinates propulsive motility throughout the gastrointestinal tract, increasing lower esophageal sphincter pressure and esophageal clearing, enhancing antroduodenal coordination, and accelerating gastric emptying, as well as small and large bowel transit.

In strips of gastrointestinal tissue obtained from cats, dogs, opossums, rabbits, rats, and human, cisapride enhanced spontaneous rhythmic phasic activity and it stimulated contractile activity induced by electrical stimulation of the enteric nervous system. Its effective dose ranged from 5×10^{-9} to 10^{-6} M. EC_{50} values obtained from guinea pig preparations ranged from 10^{-8} to 10^{-7} M. Concentrations above 10^{-6} M produced a less pronounced stimulatory effect, or even caused inhibition, suggesting a "U-shaped" dose-response curve.

Similar to the *in vitro* data, cisapride stimulated phasic motor activity *in vivo* from the esophagus to the large intestine. Its effect was less pronounced in anesthetized animals compared to conscious animals. Cisapride stimulated motility in various animal species, including the dog, cat, rat, ferret, miniature pig, pig, opossum, rabbit and pony. Cisapride enhanced motility both in the fed and in the fasted state and remained effective after chronic administration. Relevant to the present NDA, cisapride (0.16 mg/kg IV) increased lower esophageal sphincter pressure (LESP) 90% in fed conscious dogs. It also prevented the decrease in LESP induced by intragastric lipids.

The motor-stimulating properties of cisapride resulted in an acceleration of transit throughout the gastrointestinal tract, demonstrated by an increase in gastric emptying, small intestinal and large intestinal transit. Most transit studies were performed in the dog and rat. The effective dose ranges were 0.02 to 0.03 mg/kg IV and 0.1 to 2.5 mg/kg PO in the dog and 0.31 to 5.0 mg/kg SC in the rat. Beyond having a demonstrated effect *in vitro*, the activity of cisapride was not affected by vagotomy, indicating that its action is primarily mediated by the enteric nervous system.

Cisapride primarily acts on postganglionic nerves in the myenteric plexus of gastrointestinal smooth muscle, leading to an enhanced release of acetylcholine when the tissue bath contained 10^{-6} to 10^{-5} M of the drug. It does not induce muscarinic or nicotinic receptor stimulation, lacks direct cholinergic effects, and does not inhibit acetylcholinesterase activity. It is also devoid of general body functions and central and cardiovascular effects at motility-stimulating doses except for antiserotonergic properties at 5-HT₂- and 5-HT₃-receptor sites. Its antiserotonergic properties on 5-HT_{1,2,3} receptors were not involved in enhancing motor activity of isolated strips of tissue. In the guinea pig ileum, its effect appears to be mediated via an agonistic effect on, or involving, 5-HT₄ receptors. However, these results may not be applicable to other organs and/or species, since the effects of cisapride on longitudinal strips of the canine antrum were independent

of a serotonergic mechanism. Since dopamine receptor-blocking effects were only observed at doses by far exceeding those needed to stimulate motility both in vitro and in vivo, a contribution from dopaminergic mechanisms was also excluded. The interaction of cisapride with its receptor-effector system on the enteric nerves results in a facilitation of cholinergic neurotransmission as demonstrated in the guinea pig ileum, feline esophagus and canine stomach. Enhanced release of acetylcholine, properly timed by the enteric nervous system, explains the majority of motility effects observed with cisapride in vivo, although some interactions with non-adrenergic non-cholinergic mechanisms have been reported.

B. TOXICOLOGY

Toxic levels were reached by both oral and IV routes of administration and in both species. Clinical signs of CNS depression and the deaths of one female and one male were seen in dogs at 160 mg/kg/day orally, (approximately 100x maximum adult use level (MAUL)). CNS depression was also observed in dogs at 40 mg/kg/day (approximately 25x MAUL) but not at 10 mg/kg/day (6x MAUL). Similar CNS effects were noted in a 3-month rat gavage study at 160 and 320 mg/kg/day where deaths also occurred. At 40 mg/kg (25x MAUL) no toxic effects were found. Similar CNS disturbances were noted following IV injection at lower dosage levels. No specific drug-related ophthalmic abnormalities were seen. The administration of high doses of cisapride caused reduced food consumption and body weight gain.

No carcinogenic potential was found when cisapride was studied in mice and rats (two studies per species)

C. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

1. Absorption, excretion, and metabolism

In addition to the techniques used in the studies of nonclinical pharmacokinetics, High-Performance Liquid Chromatography (HPLC) methods were developed to measure cisapride in human urine and plasma with a detection limit of 1 ng/ml. The plasma levels, metabolism and excretion of cisapride were studied in three healthy male volunteers after a single oral dose of 10 mg of ¹⁴C-cisapride in solution. Subjects had been fasted overnight and remained fasting until two hours after cisapride administration.

Absorption. Peak plasma levels of both the radioactivity and the parent drug were reached at 1 to 1.5 hours after dosing, and amounted to 127.1 and 46.7 ng equiv./ml, respectively. Elimination half-lives were 16.6 h for the radioactivity and 10.7 h for the parent drug. Cisapride accounted for 1 to 3% of the administered radioactivity in the urine and 4.4 to 6.3% in the feces, indicating extensive absorption.

Excretion. Excretion of the radioactivity was rapid and complete, with the urine and feces each accounting for approximately 50% of the radioactive dose. By 24 h after dosing, 44.3% of the administered radioactivity had already been excreted with the urine, and 35.3% was excreted with the first two stools. Excretion was complete (102.3% recovery)

96 h after dosing.

Metabolism. Norcisapride, formed by oxidative N-dealkylation, was the principal metabolite in urine, represented 65% of the urinary radioactivity (33% of the dose), and was approximately six times less effective than cisapride. The remaining portion of urinary radioactivity consisted of a large number of minor metabolites, including some glucuronides. Norcisapride was also the major metabolite in the feces, representing 22-29% of the fecal radioactivity (8-12% of the dose). Other metabolites in feces were 3-fluoro-4-hydroxy-cisapride (9% of the dose) and 4-fluoro-2-hydroxy-cisapride (7% of the dose). Both metabolites resulted from aromatic hydroxylation in combination with an NIH-shift.

A comparison between the mass balance of the metabolites of cisapride in humans, in rats and in dogs showed that the biotransformation of cisapride in humans was similar to that in dogs, and less complicated than in rats.

Cisapride represented the largest fraction of all of the compounds in plasma (30 to 45% of the plasma radioactivity at peak time). Norcisapride was the main plasma metabolite and accounted for about 10% of plasma radioactivity. Maximal plasma concentrations of norcisapride were below the 10 ng/ml detection limit. The rest of the plasma radioactivity consisted of a large number of minor metabolites. To further characterize the pharmacokinetics of norcisapride, a gas chromatographic assay was developed with a detection limit of 1 ng/ml. Six healthy volunteers were given a single 10 mg oral dose of a 1 mg/ml cisapride solution. The plasma concentration profiles of norcisapride paralleled, but were much lower than, those of cisapride, peaking at one hour. Plasma concentrations of norcisapride were below 10 ng/ml, i.e. several times lower than those of cisapride. Similarly, the C_{max} was nine-fold lower, and the $AUC_{0-\infty}$ was eightfold lower. Norcisapride had a very high renal clearance rate (347 ml/min) and exceeded the normal glomerular filtration rate of 130 ml/min. This was considered indicative of high tubular secretion of norcisapride and explained the low levels of the metabolite found in the body. Thus norcisapride is extensively excreted in the urine and feces.

2. Single-dose pharmacokinetics in healthy subjects

The intravenous pharmacokinetics of cisapride in six healthy volunteers after a single 4 mg bolus injection is illustrated in Figure 1. Plasma concentration-time curves were characterized by a sum of three exponentials with sequential half-lives of 0.11 ± 0.12 h (7 ± 7 min), 1.9 ± 1.3 h and 19.4 ± 11.3 h. The overall volume of distribution was six to seven times higher than the volume of distribution of the central compartment, indicative of tissue distribution of cisapride. Total plasma clearance was 6.7 ± 0.9 l/h.

As shown in Figure 2 and Table 1, the relative bioavailabilities of the oral solution, suspension, and tablet were similar. The absolute bioavailabilities compared to the intravenous bolus injection, and normalized for the doses, were 0.42 ± 0.11 , 0.37 ± 0.17 and 0.34 ± 0.06 for the solution, suspension and tablet, respectively. The plasma clearances after oral administration was approximately 20 l/h, which is about three times higher than the systemic plasma clearance of 6.7 l/h after intravenous drug

administration. These data are indicative of first-pass metabolism (presystemic metabolism in the gut wall and liver) of orally administered cisapride.

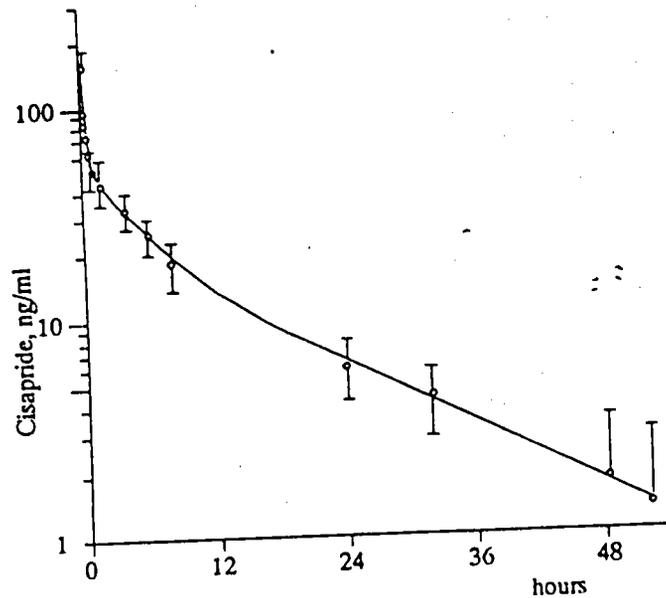


Figure 1: Time course of the mean plasma levels of cisapride (\pm SD) after intravenous bolus administration of 4 mg to six healthy male volunteers.

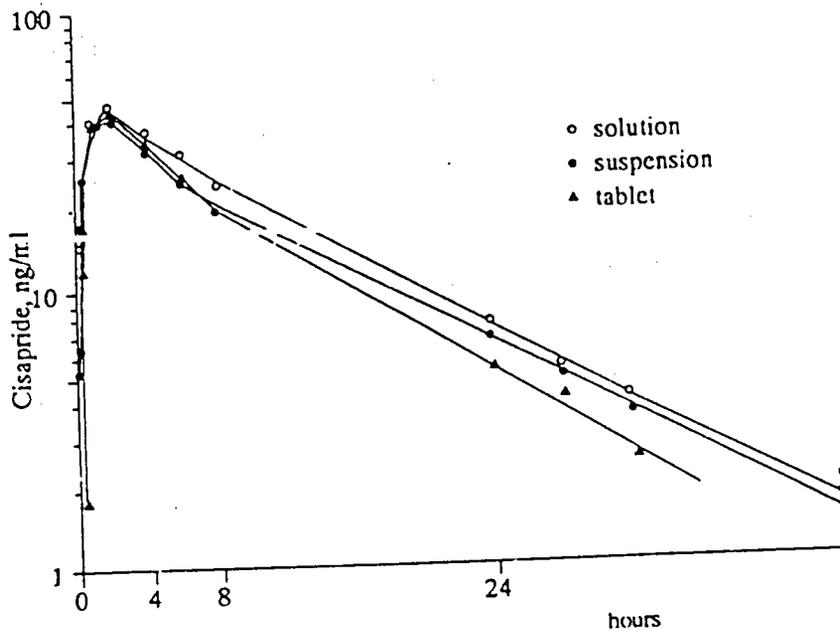


Figure 2: Time course of the mean plasma levels of cisapride after oral administration of 10 mg in solution, suspension and tablet to six healthy male volunteers.

Table 1: Pharmacokinetic parameters of 10 mg orally administered cisapride to six healthy fasting volunteers. (Mean \pm SEM)

Parameters	Solution	Suspension	Tablet
T_{max} (h)	2 ± 1	1.5 ± 0.5	1.5 ± 0.5
C_{max} (ng/ml)	48 ± 12	42 ± 12	49 ± 11
$T_{1/2, terminal}$ (h)	11.4 ± 4.5	11.0 ± 2.6	8.4 ± 2.5
$AUC_{0-\infty}$ (ng.h/ml)	641 ± 195	547 ± 210	515 ± 92
$F_{absolute}$ (%)	42 ± 11	37 ± 17	34 ± 6

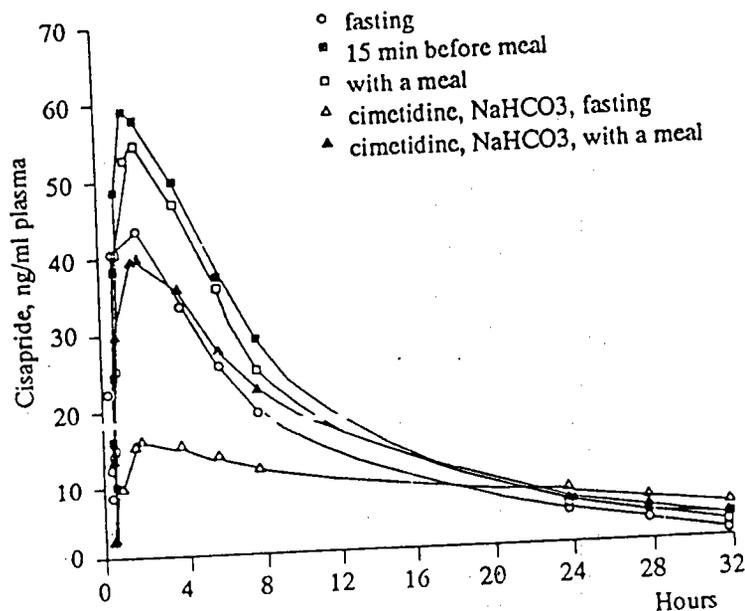


Figure 3: Mean plasma concentrations of cisapride after oral administration of a 10 mg tablet to six healthy volunteers while fasting, 15 minutes before a meal, with a meal and under experimentally reduced gastric acidity (fasting or with a meal)

Influence of Food and Experimentally Reduced Gastric Acidity. Cisapride absorption was fairly rapid when a tablet was administered with, or 15 minutes before, a meal (Figure 3).

Reduced gastric acidity in combination with fasting slowed the absorption of cisapride and lowered peak plasma levels (Table 2). However, food taken immediately after cisapride under conditions of reduced gastric acidity enhanced the rate and extent of cisapride absorption to normal. When cisapride was given with a meal or 15 minutes before a meal, peak plasma concentrations were 20 to 30% higher than in the fasting state, and the bioavailability was increased 35 to 40%. The rate of absorption was not altered by meals.

Table 2: Influence of food and reduced gastric acidity on the oral bioavailability of a 10 mg cisapride tablet.

Parameter	Fasting	With meal	15 min. before a meal	Reduced gastric acidity*	
				Fasting	With meal
T _{max} (h)	1.5 ± 0.5	2.0 ± 1.0	1.5 ± 0.4	6.9 ± 8.5	2.2 ± 0.9
C _{max} (ng/ml)	49 ± 11	60 ± 7	61 ± 7	17.6 ± 8.4	42.9 ± 13.0
T _{1/2} (h)	8.4 ± 2.5	--	7.7 ± 1.2	--	--
AUC _{0-∞} (ng.h/ml)	508 ± 99	673 ± 110	702 ± 156	540 ± 277	576 ± 122
F _{rel,0-∞} solution (%)	83 ± 20	111 ± 28	110 ± 22	84**	90**
F _{rel,0-∞} tablet (%)	100**	135 ± 19	138**	105 ± 43	115 ± 25

Mean ± SD; n=six healthy volunteers

* Volunteers were given an oral dose of 400 mg cimetidine two hours before cisapride and an oral dose of 100 ml 0.5% (w/v) NaHCO₃ solution immediately following cisapride administration.

** Based on mean AUC values

3. Pharmacokinetics in special patient groups

In patients with constipation, the observed AUC was comparable to those of control subjects, while the elimination half-life was somewhat longer than in young healthy adults (Table 3). In cirrhotic patients with liver insufficiency, absorption rate was slower and elimination half-lives were longer than in healthy volunteers (Table 3). In patients with renal insufficiency, the oral pharmacokinetics of cisapride was comparable to data in healthy subjects (Table 3), although renal excretion of norcisapride, the main urinary metabolite in healthy volunteers, was decreased in those patients. In the elderly, the rate of oral absorption of cisapride was fairly normal in most elderly (T_{max} 1 to 2 hours) but was delayed in some subjects (T_{max} 4 to 6 hours). During repeated administration, plasma concentrations and steady-state AUC's tended to be higher in the elderly than in young subjects. Finally, steady-state plasma concentrations of cisapride in adults with gastrointestinal disorders were similar to those obtained in volunteers.

Table 3: Single dose pharmacokinetics of cisapride after oral administration to various groups of patients and healthy subjects. Cisapride tablets were administered 15 minutes before a meal.

Subjects	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-∞} (ng.h/ml)	T _{1/2 terminal} (h)
<u>5 mg:</u> Healthy volunteers (n=12)	1.3 ± 0.5	16.4 ± 4.6	121 ± 51 ^a	8.8 ± 3.0
Elderly (n=12)	2.7 ± 2.6	25.1 ± 9.0	392 ± 198	12.9 ± 4.7
<u>10 mg:</u> Healthy volunteers (with meal);(n=6)	2.0 ± 1.0	59.7 ± 6.7	673 ± 110	--
Healthy volunteers (n=6)	1.5 ± 0.4	61.2 ± 7.1	702 ± 156	7.7 ± 1.2
Healthy volunteers (n=12)	1.4 ± 0.9	32.7 ± 10.1	294 ± 134 ^a	10.9 ± 3.0
Healthy volunteers (n=22)	1.7 ± 0.5	45.0 ± 15.2	325 ± 117 ^a	7.0 ± 1.6
Constipated patients: <62 years (n=5)	1.4 ± 1.0	63.3 ± 18.1	823 ± 213	14.3 ± 6.2 ^b
>76 years (n=4)	1.1 ± 0.5	47.5 ± 17.9	762 ± 127	17.5 ± 6.5 ^b
All patients (n=9)	1.4 ± 0.8	54.6 ± 18.3	794 ± 171	15.2 ± 6.5 ^b
Patients with liver cirrhosis (n=7)	3.5 ± 2.7	36.0 ± 20.9	777 ± 467	18.1 ± 10.0 ^{**}
Patients with renal insufficiency (n=5)	1.4 ± 0.6	37.4 ± 19.5	503 ± 248	15.0 ± 5.3
Elderly (n=10)	3.2 ± 1.7	69.3 ± 12.2	775 ± 240	7.8 ± 3.3
<u>20 mg:</u> Healthy volunteers (n=12)	1.0 ± 0.5	64.1 ± 15.4	569 ± 156 ^a	10.4 ± 3.4

a: AUC₀₋₄₈

b: T_{1/2β}

4. Repeated-dose pharmacokinetics in healthy subjects

a. 5 and 10 mg TID. The steady-state pharmacokinetic profile of cisapride was studied in healthy volunteers following oral administration of 5 mg TID for fifteen days and 10 mg TID for four to seven days. Table 4 lists the trough and peak concentrations measured in these studies, together with the concentrations observed in various patients and in the elderly. Steady-state was attained within one to two days. There was no unusual drug accumulation due to time-dependent non-linear changes in pharmacokinetics. After cessation of the repeated dosing, the elimination half-life was 8 to 10 hours, which is similar to the values observed after single dosing. Steady-state plasma concentrations of cisapride in adults with gastrointestinal disorders were similar

to those obtained in volunteers.

Table 4. Steady-state pharmacokinetics of cisapride (mean \pm SD) after repeated oral administration to healthy volunteers, elderly subjects and patients with renal insufficiency.

Subjects	C _{min} (morning) (ng/ml)	C _{max} (evening) (ng/ml)	AUC ₀₋₂₄ (ng.h/ml)	T _{1/2} (h)
5 mg TID: 6 healthy volunteers	15.3 \pm 6.8	---	800 \pm 187	10.6 \pm 3.2
15 patients with gastro-intestinal disorders	12.3 \pm 9.3	---	---	---
12 elderly (68-77 yrs)	25.4 \pm 14.1	59.4 \pm 33.2	1052 \pm 456	15.8 \pm 3.4
10 mg TID: 8 healthy volunteers	25.1 \pm 10.5	---	---	---
6 healthy volunteers	22.0 \pm 6.7	78.9 \pm 31.1	1244 \pm 406	---
8 healthy volunteers	26.7 \pm 16.0	---	509 \pm 289	8.1 \pm 2.5
40 patients with gastro-intestinal disorders	25.5 \pm 22.2	---	---	---
10 elderly (65-80 yrs)	47.8 \pm 21.0	---	878 \pm 315 ^a	9.9 \pm 3.7
5 patients with renal insufficiency	33.5 \pm 29.7	---	1212 \pm 687	13.0 \pm 3.0

^a: AUC_{0-12 h}

b. 10, 20 and 40 mg QID. A study was conducted to determine the steady state dose proportionality of cisapride tablets from the anticipated labelled dose range (10 to 20 mg QID) to twice the anticipated dose range (40 mg QID). The 25 healthy male volunteers enrolled in this randomized double-blind crossover study received 10, 20 or 40 mg cisapride (as 10 mg tablets, identical to that proposed in this NDA) before each meal and at bedtime for five consecutive days on three different occasions, separated by at least a nine-day washout period. This dosing regimen is the same as the one used in the U.S. GERD studies and as proposed in this NDA. C_{max} and AUC_{0-24 h} increased only 60% for a 100% increase in the dose (i.e., doubling the dose resulted in 1.6 times the expected value). For example, following the 10, 20 and 40 mg QID doses, the AUC_{0-24 h} was 1193 \pm 397 vs. 1925 \pm 656 vs. 2978 \pm 1127 ng.h/ml respectively, while the C_{max} were 76, 115 and 190 ng/ml (Figure 4). Similarly, cisapride clearance increased approximately 25% with each 100% increase in dose from 10 mg to 20 mg to 40 mg QID (612 \pm 179 vs. 758 \pm 214 vs. 995 \pm 325 ml/min). One possible explanation for this apparent increase in clearance and decrease in the expected AUC and C_{max} (bottom portion of Figure 4) may be that the plasma protein binding of cisapride was modified, resulting in a faster clearance of the drug and lowering of the expected

plasma concentrations. Subsequent analyses of the plasma samples revealed that the plasma protein binding was inversely related to the plasma drug concentration. The free drug concentrations were found to be dose-proportional at the 10 and 20 mg QID dosages.

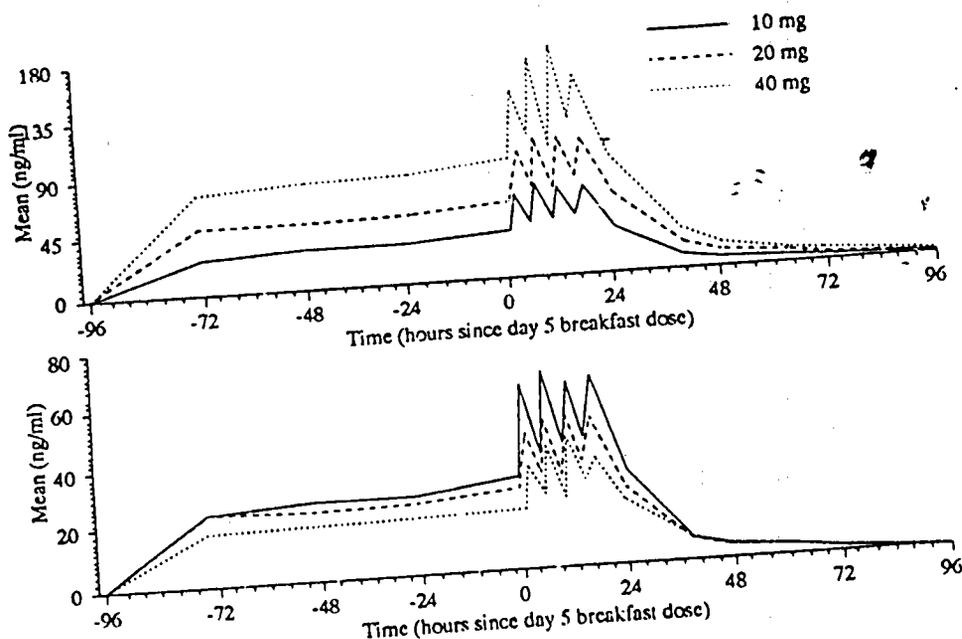


Figure 4. Cisapride plasma levels after five days of 10, 20 and 40 mg QID dosing in healthy, male subjects. The top graph represents unadjusted levels, the bottom graph plasma levels adjusted to the 10 mg standard.

D. PHARMACODYNAMICS OF CISAPRIDE

1. Distal Esophageal Motor Activity.

i. Manometric studies: In healthy subjects and symptomatic patients, single doses of cisapride (4 to 10 mg IV) significantly increased the lower esophageal sphincter pressure (LES) and lower esophageal peristalsis compared to placebo and/or metoclopramide. The LES increase in normal volunteers paralleled the pressure during phases I to III of the interdigestive motor complex. In patients with a LES of <10 mm Hg, cisapride significantly and dose-dependently increased peristaltic strength and more than doubled the LES, raising it to normal values. The increase in LES in patients was partially reversed by atropine, suggesting a mechanism of action that is primarily, but not exclusively, cholinergically-mediated. Similarly, 20 mg cisapride PO given once significantly increased LES, but lower doses were ineffective. TID administration of 10 mg cisapride for 4 days or more resulted in a significant increase in LES.

ii. Distal Esophageal pH Measurements: In adult volunteers, esophageal acid clearance

was faster after a one-day oral dosage of 10 mg cisapride TID compared to basal conditions. The duration of nocturnal reflux was decreased after the administration of cisapride 10 mg TID for one month to patients with symptoms and endoscopic evidence of gastroesophageal reflux. Acid clearance was enhanced in adult patients with reflux symptoms after a three-day dosage of 10 mg cisapride TID.

2. Stomach.

i. Gastric Emptying: This effect is relevant to GERD since increased gastric emptying may reduce the volume of gastric contents available for reflux. In patients with idiopathic gastroparesis, gastric stasis associated with diabetes, anorexia nervosa, progressive systemic sclerosis or myotonic dystrophy, as well as in groups of mixed patients with gastrointestinal disorders, cisapride (single 10 mg doses IV or PO or 10 mg PO administered TID up to six weeks) significantly accelerated gastric emptying of both liquids and solids. Acceleration of gastric emptying was greatest when a dose of 10 mg was given both in the morning and at lunch, intermediate when 20 mg was given in the morning and least when only 10 mg was taken in the morning. These increases were mirrored by the plasma levels measured following the different regimens. Therefore, even though cisapride has a relatively long half-life, the results suggest that a TID or QID dosage regimen may have an optimum effect on gastric emptying. Also, it was determined that once a threshold plasma concentration of 50 to 70 ng/ml of cisapride was reached, there was a predictable relationship between plasma concentrations of cisapride and gastric emptying.

3. Conclusions.

In an overall comparison across studies, and especially in studies where there were multiple cisapride dosages, there was a positive dose-response relationship. Intravenously administered doses of 8 or 10 mg cisapride were more effective than 2.5, 4 or 5 mg cisapride or 10 mg metoclopramide in increasing LESP. Orally administered doses of 20 and 10 mg cisapride were more effective than 5 mg cisapride and were also more effective, or comparable to, metoclopramide 10 mg. Additionally, a positive dose-response relationship was seen between plasma concentrations of cisapride and an objective measurement (gastric emptying). Once a threshold concentration of 50 to 70 ng/ml of cisapride was reached, there was a predictable relationship between plasma concentrations and gastric emptying.

III. EFFICACY OF CISAPRIDE IN GERD

The studies included in the present submission were performed to investigate whether cisapride is an effective agent in patients with gastroesophageal reflux disease. Based on the previously demonstrated prokinetic effect of cisapride, and its absence of effect on acid output, the sponsor presumed that this medication exerts its effect by its action on the motility aspect of the disease, not as an antisecretory agent.

Three multicenter trials, two conducted in the United States, MC 1201 and MC

1203, and a joint United States/Canada multicenter study, MC 121-125;851 fulfill the statutory requirements for adequate and well-controlled studies. Two non-US studies, MC Martin-Abreu 096 and MC Lepoutre 056 also support the proposed indication.

All protocols were satisfactorily randomized and placebo-control was adequate. Intent-to-treat analysis was performed using all patients that were randomized. Compliance was evaluated by reconciling diary and tablet count. All computations were two-tailed. Those resulting in p-values less than or equal to 0.05 were considered significant; those resulting in p-values between 0.05 and 0.10 were considered marginally significant.

A. MULTICENTER STUDY MC 121-125;851

1. Description of the study.

This study was performed in five centers in the US and two in Canada. To be included in the study, patients had to have at least Grade 1 esophagitis at the baseline endoscopy, a positive Bernstein test, at least a moderate (≥ 2 on a 0 to 3 point scale) severity of daytime or nighttime heartburn and to have had symptoms for at least three months. Patients with infectious esophagitis, active gastro-duodenal ulcer disease or anatomic obstruction were excluded.

After a two-week single-blind placebo run-in designed to exclude placebo-responders, patients were randomized to receive double-blind placebo or cisapride 10 mg QID for eight weeks. Symptoms were assessed every two weeks. Endoscopy, endoscopic biopsy, Bernstein test and manometry were performed prior to entry and at the end of the study (Table 5).

Table 5: Schedule of evaluations

Assessment	Pre-Baseline	Selection Wk 0	Single-Blind Placebo Phase Baseline (2 wks)	Double-Blind Phase			
				Wk 4	Wk 6	Wk 8	Wk 10
-Symptoms (Investigator)		X	X	X	X	X	X
-Endoscopy		X					X
-Bernstein test		X					X
-Biopsy		X					X
-Manometry	X						X
-ECG			X				X
-pH probe*			X		X		X
-Lab tests		X	X	X	X	X	X
-Diary completion							X
-Global evaluation							X

*Optional

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Patients rated the severity of symptoms based on a 100 mm analog scale where 0 was 'none' and 100 was 'most severe'. Investigators rated symptom severity on a 0 to 3 scale, where 0=none, 1=mild, 2=moderate and 3=severe. Investigators also rated the frequency of symptoms on a 4-point scale, where 0=none, 1=occasional, 2=often and 3=frequent. Endoscopies were rated as Grade 0=normal, Grade 1=erythema and/or friability, Grade 2=esophageal erosions without ulcerations and Grade 3=esophageal ulcerations with or without erosions. In addition, the numbers of erosions and/or ulcerations were noted, the longest diameter of the largest lesion was measured and a pinch biopsy specimen was obtained at the selection and end of treatment endoscopies.

A total of 147 patients were randomized to double-blind treatment using computer-generated blocks of 10 in the U.S. and of 4 in Canada. As shown in table 6, the groups were comparable in the demographic variables. In addition, their background, vital signs and subjective variables were similar, although there were marginally significant differences in number of symptom episodes of nighttime heartburn (least square means 0.8 for placebo and 1.3 for cisapride, $P < 0.10$) and of daily eructation (least square means 5.2 for placebo and 4.2 for cisapride, $P < 0.10$). However, baseline nighttime heartburn and eructation intensities were almost identical. The median number of days on drug was 56 for both groups. The distribution of days on drug was very similar for the two groups. The groups were also comparable in all objective variables except that among patients without ulcers and with erosions at baseline the cisapride group had a significantly ($P = 0.04$) longer value for the longest diameter of the largest erosion. The cisapride group had a significantly higher percentage of normal swallows than the placebo group ($P = 0.02$) in the baseline manometry; a significantly longer mean duration of waves as measured at 3 cm above the LES; and a marginally greater mean duration and mean amplitude of waves as measured at 8 cm above the LES ($0.05 \leq p \leq 0.10$).

Table 6: Demographics

		Plac	Cis	Total
Randomized		71	76	147
Sex	M	54	58	112
	F	17	18	35
Age (yrs)	Mean	46.3	48.4	47.4
	Min.	19.0	22.0	19.0
	Max.	73.0	75.0	75.0
Weight (kg)	Mean	81.2	79.4	80.3
	Min.	50.9	50.0	50.0
	Max.	130.9	135.4	135.4
GERD symptom dur. (yrs)	Mean	8.2	9.7	9.0
	Min.	0.3	0.5	0.3
	Max.	50.0	41.0	50.0

There were no significant differences between the groups in regards to baseline biopsies which were read by the multicenter pathologists or by Dr. Madara, the pathologist who reevaluated all of the biopsies on a post hoc basis. A higher proportion of patients were found to have normal biopsies by Dr. Madara than by the multicenter pathologists. The multicenter pathologists were not restricted by protocol in their determinations. However, Dr. Madara defined abnormality as only the presence of one of the following: 1) acute inflammatory infiltrate (neutrophils), 2) erosion or ulcer, or 3) Barrett's-type mucosa. Because the post-hoc analysis had not been planned in the initial protocol, only the initial reading of the biopsies was considered in this review.

2. Sponsor's analysis.

The results were similar among the investigators. Except for the investigator's assessment of eructation severity at Week 4, no significant (or marginally significant) between-treatment differences were accompanied by any significant (or marginal) treatment-by-investigator interactions.

a. Symptom assessment.

i. Investigator assessments:

The investigator symptom severity assessments improved significantly in the placebo and cisapride groups during treatment compared to baseline in both daytime and nighttime heartburn intensity, as well as combined heartburn ($P \leq 0.02$). The improvements were about the same in the two groups for daytime heartburn (Figure 5), but improvement was significantly greater for cisapride than for placebo in nighttime heartburn at Week 6, when it decreased from 1.8 to 1.1 vs 1.8 to 1.4 respectively (difference of 0.4; $P = 0.03$) (Figure 6). A similar difference was observed at Week 8 ($P = 0.05$). Values at endpoint may reflect data obtained at the time of discontinuation, and are therefore less interesting.

Table 7 illustrates the other investigator symptom severity assessments for which there was significant or close to significant differences between the two treatment groups. Overall nighttime heartburn tended to improve more with cisapride than with placebo, but the difference was not significant ($P = 0.08$). Combined daytime and nighttime heartburn tended to be reduced to a greater extent in the cisapride group than in the placebo group at Week 6 but the difference was not significant ($P = 0.07$). In addition, the combined heartburn/regurgitation scores significantly favored cisapride at Week 6 ($P = 0.04$). Cisapride patients also had significant improvement in both eructation and nausea from Week 4 on ($P < 0.01$), while no significant improvement occurred on placebo. Eructation decreased significantly more in the cisapride group than in the placebo group at Week 8 ($P = 0.03$) and marginally at Week 4 and Endpoint. Not shown in Table 7, is the observation that there was no difference between the two groups in daytime heartburn, daytime and nighttime regurgitation, combined regurgitation, abdominal pain, bloating/distension, or combined non-reflux symptom severity.

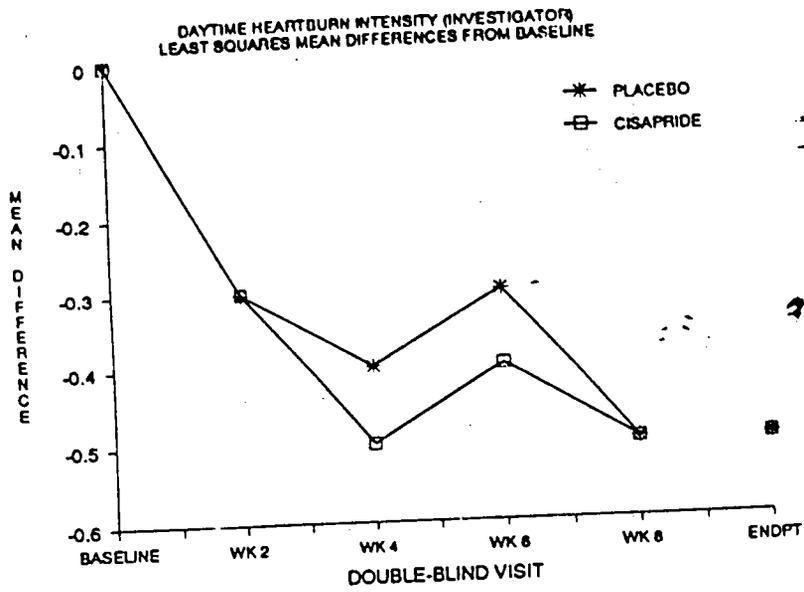


Figure 5. Investigators' assessments of daytime heartburn.

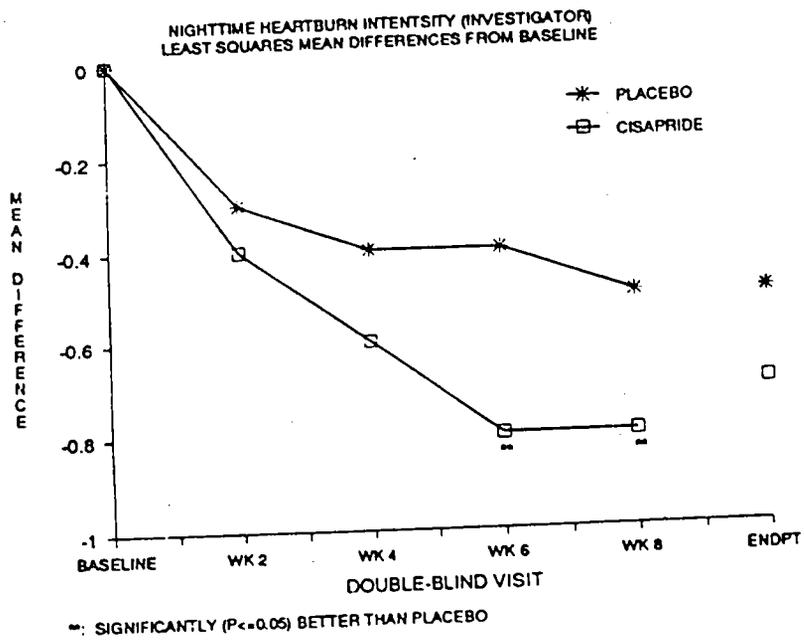


Figure 6. Investigators' assessments of nighttime heartburn.

Table 7. Investigator symptom intensity assessments
Scale 0=none, 1=mild, 2=moderate, 3=severe

		PLAC	CIS 10 mg
Heartburn Combined Severity	Baseline	3.8	3.9
	Week 2	-0.7	-0.7
	Week 4	-0.8	-1.1
	Week 6	-0.7	-1.2
	Week 8	-1.0	-1.3
	Endpoint	-1.0	-1.1
Total Reflux Symptom Severity	Baseline	6.0	6.0
	Week 2	-0.8	-0.9
	Week 4	-1.2	-1.5
	Week 6	-1.0	-1.8**
	Week 8	-1.5	-2.0
	Endpoint	-1.4	-1.6
Eructation (# of episodes)	Baseline	1.8	1.6
	Week 2	0.0	-0.3
	Week 4	-0.1	-0.3
	Week 6	-0.1	-0.3
	Week 8	-0.1	-0.4**
	Endpoint	-0.1	-0.3
Vomiting (# of episodes)	Baseline	0.4	0.4
	Week 2	-0.1	0.1
	Week 4	0.0	-0.1
	Week 6	0.1	-0.2
	Week 8	0.0	-0.2
	Endpoint	0.0	-0.1
Total Symptom Severity	Baseline	11.0	11.0
	Week 2	-1.4	-1.1
	Week 4	-1.8	-2.3
	Week 6	-1.4	-3.0
	Week 8	-2.3	-3.5
	Endpoint	-2.3	-3.0

**P \leq 0.05 vs. other group; baseline values are LSMs, all other values are the LSM differences from baseline.

ii. Patient assessments: Table 8 presents the results for symptom severity assessments and for numbers of episodes of symptoms. With cisapride, mean reductions in nighttime heartburn severity ranged from approximately 7 to 13 points and were significantly greater throughout than those on placebo, which never exceeded 3.6 (P \leq 0.02). Although there were no significant differences between treatments in daytime heartburn, cisapride was marginally favored for combined heartburn severity at Weeks 6 (P = 0.06) and 8 (P = 0.10).

Table 8. Patient diary assessments. Severity Scale
 0=none....100=most severe; Frequency = # per day

		PLAC	CIS 10 mg
Heartburn Severity Night	Baseline	22.0	27.6
	Week 2	-2.6	-6.7**
	Week 4	-3.6	-8.9**
	Week 6	-2.0	-11.6**
	Week 8	-3.2	-13.0**
	Endpoint	-3.2	-11.6**
Heartburn Severity Combined	Baseline	60.1	64.6
	Week 2	-6.9	-11.8
	Week 4	-11.6	-16.8
	Week 6	-10.0	-20.9
	Week 8	-14.3	-25.2
	Endpoint	-13.6	-22.8
Nighttime Heartburn (# of episodes)	Baseline	0.8	1.3
	Week 2	-0.1	-0.2
	Week 4	-0.1	-0.2
	Week 6	0.0	-0.4**
	Week 8	0.1	-0.4**
	Endpoint	0.1	-0.4**
Abdominal Pain Episodes	Baseline	0.6	0.9
	Week 2	0.1	-0.2
	Week 4	-0.1	-0.4
	Week 6	-0.1	-0.3
	Week 8	-0.1	-0.3
	Endpoint	-0.1	-0.3
Eructation Episodes	Baseline	5.2	4.2
	Week 2	0.0	-0.4
	Week 4	-0.1	-0.2
	Week 6	-0.3	-0.7
	Week 8	-0.4	-0.7
	Endpoint	-0.3	-0.7
Number of Antacid Tablets	Baseline	3.6	3.6
	Week 2	-0.1	-0.2
	Week 4	-0.1	-0.3
	Week 6	0.1	-0.3
	Week 8	0.0	-0.5
	Endpoint	0.0	-0.5

** P ≤ 0.05 vs. other group; baseline values are LSMs, all other values are the LSM differences from baseline.

As shown in Table 8, the frequency of nighttime heartburn also improved significantly in both groups, with the exception of placebo at Week 6. In addition, although the cisapride group had more episodes at baseline, improvement was significantly greater with cisapride at Weeks 6 and 8 and at endpoint (P = 0.05). Abdominal pain tended to

improve more with cisapride than with placebo, but the difference was not statistically significant. Finally, the patient diaries showed that, although there was no significant differences between the two groups, the cisapride group took significantly fewer antacid tablets at Week 8 and at endpoint and overall compared to pretreatment intake ($P \leq 0.04$) while the placebo group's antacid intake remained unchanged (Table 8 and Figure 7).

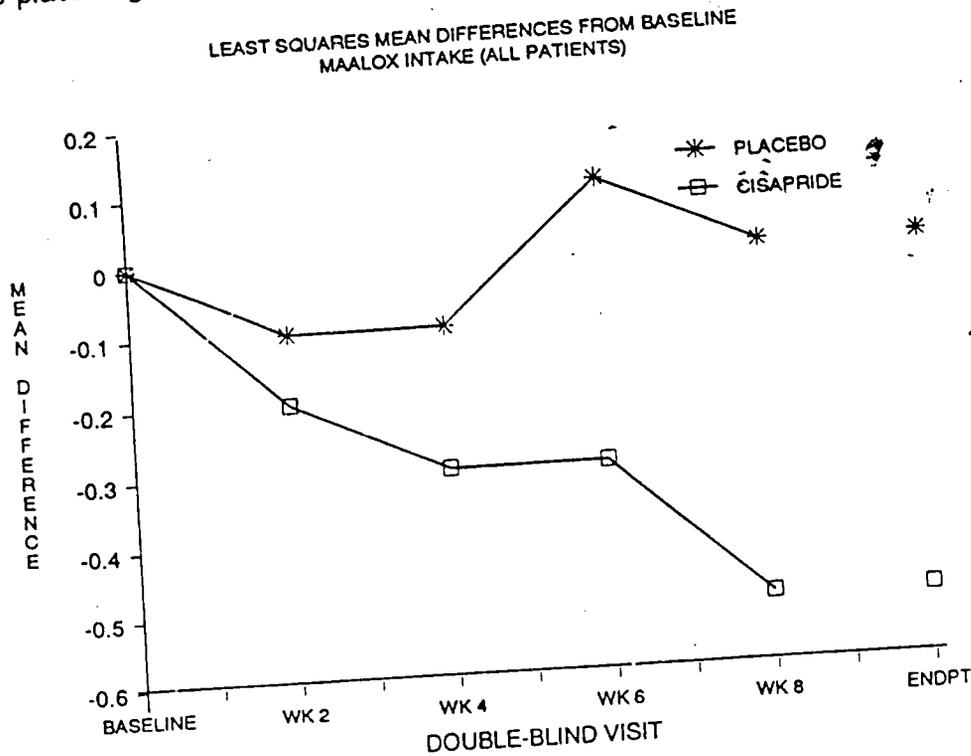


Figure 7. Antacid intake as determined based on patients' diaries.

Both the cisapride and the placebo groups improved significantly in daytime, nighttime and combined heartburn severity throughout the study, at endpoint and overall ($P \leq 0.03$), with the exception that improvement on placebo was not statistically significant for nighttime heartburn at Week 6 ($P = 0.07$). However, there was no statistically significant differences between the two groups.

Nausea was significantly improved at Weeks 4 through 8 only in the cisapride group ($P \leq 0.03$), though not significantly more than in the placebo patients.

The number of daytime heartburn episodes dropped significantly in both groups throughout double-blind treatment, except that the reduction was not significant for cisapride at Week 4. Between-treatment differences were not significant.

Cisapride patients had significant improvement in the incidence of all eight other symptom parameters for at least Week 8, except for diarrhea. For abdominal pain, significant

improvement started at Week 2. The placebo group improved significantly in three symptoms: daytime bitter/sour taste throughout treatment, nighttime bitter/sour taste at Week 4 and overall, and abdominal pain at Weeks 6 and 8 and endpoint. Mean changes in both groups were generally small and none of the differences between groups was significant.

b. Global assessments. The cisapride group responded significantly better ($P = 0.02$) than the placebo group according to the investigator's assessment (Figure 8 and Table 9). Fifty-percent of the cisapride patients had at least a "good" response versus only 35% of the placebo patients, a marginally significant difference. The cisapride group also tended to have better responses than placebo in the patient's global assessment, but not the difference was not statistically significant.

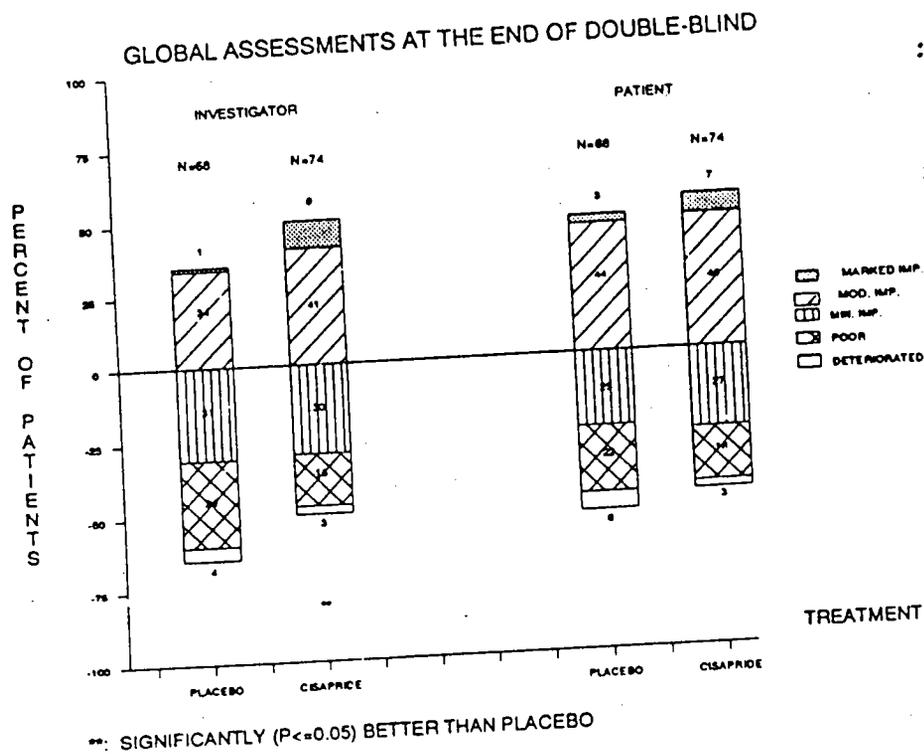


Figure 8. Investigators' and patients' global assessments.

Table 9. Global evaluation at the end of double-blind (% of patients).

	Investigators' Assessments		Patients' Assessments	
	PLAC	CIS 10 mg	PLAC	CIS 10 mg
	n=68	n=74	n=68	n=74
Excellent	1.5	9.5	2.9	6.8
Good	33.8	40.5	44.1	45.9
Fair	30.9	29.7	25.0	27.0
Poor	29.4	17.6	22.1	17.6
Deteriorated	4.4	2.7	5.9	2.7

** : P <0.05 compared to placebo.

c. Objective Assessments

i. Endoscopy: Endoscopic grade improved significantly from baseline to the end of double-blind treatment for both treatment groups (P <0.01), but differences between the groups were not significant. Among the other parameters, the cisapride group and not the placebo group had significant reductions from baseline for the longest diameter of the largest ulcer, distance of erosion between extent, and longest diameter of the largest erosion. Only the placebo group had a significant decrease in the number of erosions. There were no significant or marginally significant differences between the groups, however, except that the cisapride group had a marginally greater reduction in the longest diameter of the largest erosion than the placebo group.

The endoscopic grade was further analyzed by examining the number of patients improved from baseline. Again, there were no significant differences (Table 10).

Table 10. Endoscopy scores

	PLAC	CIS 10 mg
Grade:		
Baseline	2.2	2.1
Double-blind	-0.4	-0.5
Number of patients:		
Improved	21	26
Not improved	44	42

Additionally, the ulceration variables were analyzed using only patients with ulcers at pretreatment, and the erosion variables were analyzed using only patients with erosions and without ulcers at pretreatment. The only significant difference was that the cisapride group had a significantly (P <0.01) larger reduction in the longest diameter of the longest erosion than placebo. Although the cisapride group did have a significantly longer

diameter to begin with, its reduction far exceeded the placebo group's. Also of interest here is that although only the placebo group had a significant reduction in the number of erosions when all patients were considered, when those starting out with ulcers were excluded, the cisapride group had a greater mean reduction than the placebo group.

ii. Biopsies: In the original biopsy readings, 32% of the cisapride patients with abnormal baseline biopsies were normalized, while only 8% of the placebo patients were, a highly significant difference ($P < 0.01$). However, as stated before, the biopsies were re-read by a single pathologist. In this *a posteriori* evaluation using different criteria, there was no difference between the two groups regarding the percentage of normal biopsies at the end of double-blind trial (cisapride group: 53% and placebo group: 51%).

iii. Manometry: There was no assessment in which the groups significantly differed.

Also examined was the ratio of patients with reduced lower esophageal pressures at pretreatment to the number at the end of double-blind. Two measurements were considered: LES values less than or equal to 18 mm Hg and mean amplitude values less than 40 mm (examined separately at the three measured sites). There were no significant between-group differences.

iv. 24-hour pH-probe: Only about half the patients had data to be analyzed in this optional test. There were no significant differences between the groups.

v. Bernstein test: This test lasted for no more than 15 minutes. Any patient with a negative result (no heartburn during the test) was considered to have symptoms first appearing at 16 minutes. In the cisapride group, the mean time until symptoms appeared increased by 1.3 minutes from baseline to the end of double-blind treatment; this was significantly better than the corresponding increase of 0.4 minutes in the placebo group ($P < 0.05$). There was no significant difference between the groups in the percentages having negative results at the end of double-blind.

d. Joint improvement analyses.

Joint improvement analyses were performed in order to examine the effects of cisapride on two or more assessments jointly. The first set of analyses examined three subjective assessments; the second set examined pairs of subjective and objective (or antacid intake) assessments:

i. Combinations of daytime heartburn, nighttime heartburn, and antacid intake: The sponsor felt that any patient who experienced a reduction in daytime and nighttime heartburn and who used less antacids would be considered a clinical success. Three analyses were therefore performed: the first used investigator-assessed heartburn severity, the second used patient-assessed severity, and the third used patient-assessed numbers of heartburn episodes.

The cisapride group had significantly better response patterns for all three analyses (Table 11). For the investigator assessments, the cisapride group had a 4:1 ratio of

responders to failures, while the placebo group had about the same number of responders and failures. For the patient assessments, the ratios of responders to failures were 10:1 in the cisapride group and 3:1 in the placebo group. More than half the cisapride patients improved on all three of the assessments when heartburn was patient-assessed.

Table 11. Joint improvement analysis of daytime and nighttime heartburn severity and antacid intake in patients without ulcer at pretreatment.

	Investigators' Assessments		Patients' Assessments	
	PLAC (N=60)	CIS 10 mg (N=63)	PLAC (N=60)	CIS 10 mg (N=61)
% Failure	23	8*	13	5**
Partial responders	55	57	50	43
Responders	22	35	37	52

*: P <0.04 compared to placebo; **: P <0.02 compared to placebo.

ii. Objective assessments (or antacid intake) paired with subjective assessments: The combinations of nighttime heartburn severity assessments (patient and investigator) with endoscopic grade, LESP, and antacid intake all showed significantly better response to cisapride than to placebo ($P \leq 0.04$), with the exception of investigator heartburn assessment/antacid intake, which did not reach statistical significance ($P = 0.06$). Those based on patient episodes were also favorable to cisapride, but the difference did not reach statistical significance ($0.05 \leq P \leq 0.07$). None of the combinations of daytime heartburn assessments with objective parameters showed significant differences between treatments.

When global assessments made were combined with objective parameters, the combination with LESP showed significantly better response on cisapride ($P < 0.01$) and those with endoscopic grade and antacid intake tended to show better response with cisapride, although the difference did not reach statistical significance ($0.06 \leq P \leq 0.08$). Combinations based on patient global assessments showed no significant differences, although that with LESP showed that cisapride tended to be superior to placebo ($P = 0.06$).

e. Conclusions

The results of this trial were consistent with the hypothesis that the activity of a drug would be most apparent when comparing the most severe symptoms or the most severely affected patients. Cisapride produced significant relief of eructation and heartburn at night, the most severe symptoms before treatment. Antacid use remained unchanged in the placebo group and decreased significantly with cisapride. Cisapride patients responded better overall than those on placebo according to investigator global

assessments. Cisapride increased time to appearance of symptoms in the Bernstein test significantly more than placebo.

Patients with a lower LESF benefitted the most symptomatically from cisapride, while those without esophageal ulcers at baseline showed the greatest objective improvement. Cisapride significantly improved both subjective and objective parameters among those with more severe heartburn at pretreatment.

Based on the results of this trial, the sponsor concluded that additional studies should: 1) focus on reflux symptoms, antacid intake, global assessments and endoscopic evaluations, 2) have a longer double-blind duration to determine if effectiveness parameters continued to improve, 3) include 20 mg QID dosage to determine if patients not responding to 10 mg QID would respond better to a higher dose, and 4) require patients to have moderate to severe daytime and nighttime heartburn at entry.

3. Reviewer's evaluation.

This double blind placebo-controlled study randomized 147 patients with symptoms of GERD for at least three months, and with at least moderately severe day- and nighttime heartburn (i.e. ≥ 2 on a scale of 0-3). They also had to have at least a grade 1 of esophagitis at endoscopy, and a positive Bernstein test. After a two week single blind placebo run-in, 71 patients were given placebo and 76 patients were given cisapride 10 mg QID for 8 weeks. Symptoms were assessed every 2 weeks and endoscopy was performed before and after the study.

Intent-to-treat analysis demonstrated that daytime heartburn improved significantly in both groups, but cisapride was not significantly better than placebo. Nighttime heartburn improved significantly more after cisapride than after placebo, and, in the opinion of this reviewer, this change is clinically important. Patients in the cisapride group took significantly less antacids than before treatment whereas there was no difference in the placebo group. Joint analysis of heartburn (day and night) and antacid consumption also significantly favored cisapride according to both patients' and investigators' assessments. Global assessment by investigator was significantly better in the cisapride group ($P = 0.02$), but only a non significant trend was observed when the assessment was made by the patients. Endoscopy showed a significant improvement compared to baseline in both groups ($P < 0.01$), and there was no difference between the two groups. However, the cisapride, but not the placebo group, had a significant reduction of the longest diameter of the largest ulcer. As a result, although the cisapride group had a significantly longer diameter to begin with, it had a significantly greater reduction of the longest diameter of the largest ulcer than placebo ($P < 0.01$). Only the placebo group had a significant decrease of the number of erosions. When patients starting out with an ulcer were excluded from analysis, the cisapride group had a greater mean reduction in the number of erosions than the placebo group. In the original biopsy reading, 32 % of the cisapride patients with abnormal baseline biopsies were normalized vs only 8% of the placebo patients. Although this difference was not observed when all biopsies were reread by one pathologist with different criteria, this second *a posteriori* analysis cannot be used as it was not planned in the original protocol. No differences were observed

between the two groups regarding manometry or proportion of patients with baseline LESF <18 mm Hg and mean amplitude <40 mm Hg. Similarly, there was no difference in 24 hr pH monitoring between placebo- and cisapride-treated patients. Bernstein test performed at the end of the trial showed that the time to symptom increased by 1.3 min in the cisapride group, which was significantly better than 0.4 min for placebo. Subgroup analysis (i.e. (1) At least moderate heartburn; (2) esophageal ulcers at pretreatment; and (3) LESF <18 mm Hg) also demonstrated a significant improvement of nighttime heartburn and significantly better overall investigator global assessment (same finding in all subgroups as when all patients analyzed). Finally, joint improvement analyses significantly favored cisapride compared to placebo.

B. MULTICENTER STUDY 1201

1. Description of the study.

This randomized, double-blind study was conducted in 14 U.S. centers, randomizing a total of 182 patients to double-blind treatment with one of two doses (10 and 20 mg QID) of cisapride or placebo. The study design is summarized in Table 12.

Table 12: STUDY DESIGN.

Treatment period	Single-blind	Double-blind		
		Placebo	Cisapride 10 mg	Cisapride 20 mg
Medication:	Placebo	Cisapride 10 mg	Cisapride 20 mg	Placebo
Box A Box B	Placebo Placebo	Cisapride 10 mg Placebo	Cisapride 10 mg Cisapride 10 mg	Placebo Placebo
Dosage	Two tablets (one tablet from each box) QID 30 minutes before each meal and at bedtime			
Duration	Two weeks	Twelve weeks		
Assessments	Selection. Weeks 0 (end of s-b phase), 4, 8 and 12			

A two-week, single-blind placebo phase preceded the twelve-week double-blind treatment to assess patient compliance and eligibility. Symptoms were then evaluated at monthly visits. Endoscopy, endoscopic biopsy, Bernstein test and LESF measurements were performed within seven days prior to entry and during Week 12 while the patient was still receiving study medication. The schedule of evaluations is described in Table 13.

Demographic data in the three groups were not significantly different (Table 14), although the ages were marginally (P =0.06) different. Medical background and baseline vital signs were also similar.

Table 13: Schedule of evaluations.

	Visit 1 (Week -2)	Visit 2 (Week 0)	Visit 3 (Week 4)	Visit 4 (Week 8)	Visit 5 (Week 12)
Assessments	Selection	End of s-b placebo phase	Double-blind treatment phase		
Symptoms (Investigator)	X	X	X	X	X
Diary (Patient)		X	X	X	X
Global Assessment					X
Endoscopy	within 7 days				X
Endoscopic Biopsy	within 7 days				within 5 days
Barnstein test	within 7 days				within 5 days
LESP	within 7 days		X	X	X
Laboratory	X	X			
determinations					X
Physical examination	X				X
EKG	X				

Table 14: Demographics

		PLAC	CIS 10 mg	CIS 20 mg	Total
Entered d-b		60	63	59	182
Sex	M	41	44	33	118
	F	19	19	26	64
Age (yrs)	Mean	44.4	41.3	47.5	44.4
	Min.	21.0	21.0	22.0	21.0
	Max.	73.0	69.0	75.0	75.0
Weight (kg)	Mean	83.4	88.2	86.7	86.1
	Min.	54.1	47.7	50.0	47.7
	Max.	139.1	159.1	135.0	159.1
GERD symptom dur. (yrs)	Mean	8.5	8.7	8.0	8.4
	Min.	0.3	0.7	0.3	0.3
	Max.	30.0	26.0	40.0	40.0

The groups were also comparable for the baseline heartburn assessments with the treatment group mean daytime intensities between 5.7 and 6.2 (on the 0-10 scale) and the mean nighttime intensities between 5.8 and 6.4. However, the placebo group had less intense regurgitation than the cisapride groups, marginally less than the 10 mg group at nighttime ($P = 0.06$) and daytime and nighttime combined ($P = 0.06$), and significantly ($P \leq 0.05$) less than the 20 mg group at daytime, nighttime and combined. The placebo group's mean total symptom intensity was marginally less than the cisapride 10 mg group's ($P = 0.09$) and the cisapride 20 mg group's ($P = 0.10$). The groups' mean overall assessments of symptoms were comparable.

Table 13: Schedule of evaluations.

	Visit 1 (Week -2)	Visit 2 (Week 0)	Visit 3 (Week 4)	Visit 4 (Week 8)	Visit 5 (Week 12)
Assessments	Selection	End of s-b placebo phase	Double-blind treatment phase		
Symptoms (Investigator)	X	X	X	X	X
Diary (Patient)		X	X	X	X
Global Assessment					X
Endoscopy	within 7 days				X
Endoscopic Biopsy	within 7 days				X
Bernstein test	within 7 days				X
LESP	within 7 days		X	X	X
Laboratory determinations	X	X			X
Physical examination	X				X
EKG	X				X

Table 14: Demographics

		PLAC	CIS 10 mg	CIS 20 mg	Total
Entered d-b		60	63	59	182
Sex	M	41	44	33	118
	F	19	19	26	64
Age (yrs)	Mean	44.4	41.3	47.5	44.4
	Min.	21.0	21.0	22.0	21.0
	Max.	73.0	69.0	75.0	75.0
Weight (kg)	Mean	83.4	88.2	86.7	86.1
	Min.	54.1	47.7	50.0	47.7
	Max.	139.1	159.1	135.0	159.1
GERD symptom dur. (yrs)	Mean	8.5	8.7	8.0	8.4
	Min.	0.3	0.7	0.3	0.3
	Max.	30.0	26.0	40.0	40.0

The groups were also comparable for the baseline heartburn assessments with the treatment group mean daytime intensities between 5.7 and 6.2 (on the 0-10 scale) and the mean nighttime intensities between 5.8 and 6.4. However, the placebo group had less intense regurgitation than the cisapride groups, marginally less than the 10 mg group at nighttime (P =0.06) and daytime and nighttime combined (P =0.06), and significantly (P ≤0.05) less than the 20 mg group at daytime, nighttime and combined. The placebo group's mean total symptom intensity was marginally less than the cisapride 10 mg group's (P =0.09) and the cisapride 20 mg group's (P =0.10). The groups' mean overall assessments of symptoms were comparable.

Male or female ambulatory patients 18 to 75 years old and with at least a three-month history of GERD symptoms were eligible for inclusion in the studies. The subjects also had to have an endoscopic evaluation of Grade 1 esophagitis or higher, a positive Bernstein test, and moderate to severe daytime and nighttime heartburn. Patients with active ulcer disease, anatomic obstruction, intestinal infections or inflammations or other severe gastrointestinal diseases were not eligible. Patients with infectious esophagitis, esophagitis caused by exogenous substances, Barrett's esophagus, peptic stenosis, history of gastric surgery (except appendectomy or cholecystectomy), history of seizures, or patients who had significant laboratory abnormalities were also excluded, as were females who were pregnant or who were not using adequate contraception.

The primary effectiveness variables were the daytime and nighttime heartburn assessments, global evaluations and daytime and nighttime antacid (Maalox[®]) consumption.

2. Sponsor's analysis.

a. Symptom assessment

i. Investigators assessment.

During double-blind treatment, all three groups showed significant (usually at the P <0.001 level) improvements from baseline at all of time points; these improvements generally increased with treatment duration. The improvements were generally largest in the cisapride 10 mg group and about the same in the placebo and cisapride 20 mg groups. Results at week 4 (the first visit during the double-blind phase), week 12 (the last scheduled visit during the double-blind phase) and endpoint are summarized in Table 15.

Table 15: Investigators' symptom assessments.

Assessment	Reductions from Baseline (LSM's)								
	Week 4			Week 12			Endpoint		
	Plac.	10 mg	20 mg	Plac.	10 mg	20 mg	Plac.	10 mg	20 mg
Heartburn:									
Daytime	1.2	1.8**	1.1	2.0	3.0	1.9	1.9	2.7**	1.4
Nighttime	1.4	2.4**	1.5	2.4	3.8**	2.8	2.0	3.4****	2.1
Combined	2.6	4.2****	2.5	4.3	6.7**	4.7	3.9	6.2****	3.5
Regurgitation:									
Daytime	1.2	1.3	1.1	1.4	2.3	2.0	1.4	2.0	1.5
Nighttime	1.0	1.5	1.0	1.4	2.4	1.7	1.2	2.2**	1.5
Combined	2.1	2.8	2.1	2.8	4.7	3.8	2.6	4.2	3.0
Total	4.7	7.1	4.6	7.1	11.5**	8.5	6.4	10.4****	6.5
Overall	0.8	1.5**	0.8	1.4	2.4	1.4	1.3	2.1**	0.9

** : P ≤0.05 compared to placebo; ** : P ≤0.05 compared to the cisapride 20 mg group.

Daytime heartburn was not significantly reduced in the cisapride groups compared to placebo (Table 15). In contrast, both nighttime heartburn (Figure 9) and combined daytime and nighttime heartburn (Table 15) were significantly reduced in the cisapride 10 mg groups compared to placebo at Weeks 4 and 12. In addition, nighttime regurgitation was significantly reduced at endpoint in the cisapride 10 mg group compared to placebo. (Table 15). Similarly, the total of the daytime and nighttime heartburn and regurgitation assessments was significantly reduced in the cisapride 10 mg group compared to the placebo group at Week 12 ($P = 0.02$) and Endpoint ($P = 0.02$).

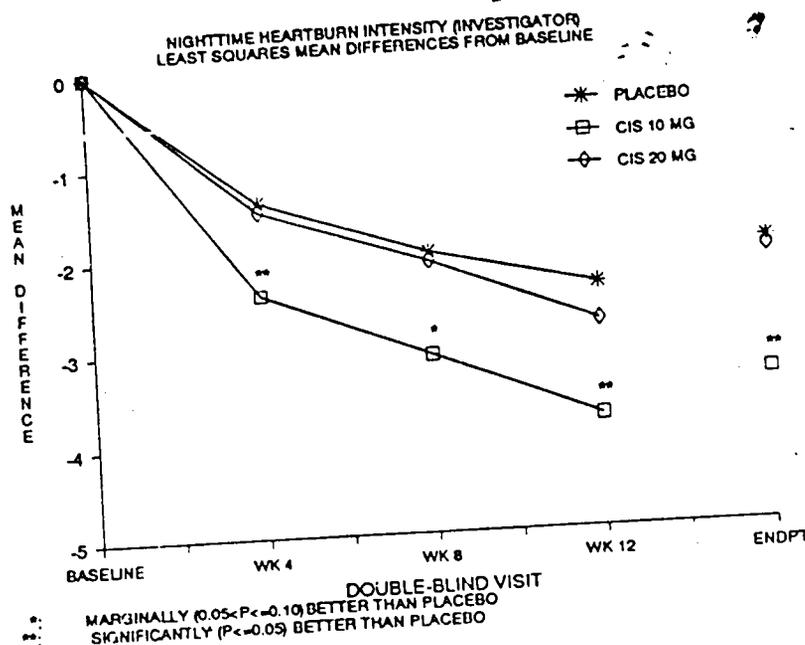


Figure 9. Investigators' assessments of nighttime heartburn.

ii. Patient (diary) symptom assessments.

During double-blind treatment, all three groups had significant (usually with $P < 0.001$) improvements from baseline for all of the assessments at all of the time points. As with the investigator assessments, the improvements increased with duration of treatment and were generally largest in the cisapride 10 mg group and about the same in the cisapride 20 mg and placebo groups.

Daytime heartburn: The mean reductions from baseline ranged from 10.6 (Week 4) to 22.6 (Week 12) in the placebo group, from 19.1 (Week 4) to 31.0 (Week 12) in the cisapride 10 mg group, and from 10.8 (Week 4) to 21.2 (Week 12) in the cisapride 20 mg group. At Week 4, the mean intensity in the cisapride 10 mg group was reduced significantly ($P = 0.02$) more than in the placebo group and at Week 12 it tended to be reduced to a greater extent, although not significantly ($P = 0.06$). At all weeks, the mean

intensities in the cisapride 10 mg group were reduced significantly ($P \leq 0.05$) more than in the cisapride 20 mg group.

Nighttime heartburn: The mean reductions ranged from 10.2 (Week 4) to 22.4 (Week 12) in the placebo group, from 18.0 (Week 4) to 27.6 (Week 12) in the cisapride 10 mg group, and from 13.3 (Week 4) to 20.7 (Week 12) in the cisapride 20 mg group. The mean reduction was significantly ($P = 0.04$) greater in the cisapride 10 mg group than in the placebo group at Week 4 and marginally ($P = 0.09$) greater than in the cisapride 20 mg group at Week 8.

Combined daytime and nighttime heartburn: The cisapride 10 mg group improved significantly ($P = 0.03$) more than the placebo group at Week 4, and at least marginally ($P \leq 0.09$) more than the cisapride 20 mg group at all analyzed time points.

Regurgitation: There were no significant differences between the groups for any of the regurgitation assessments.

Total symptoms: No significant differences between the groups were observed for the total of the daytime and nighttime heartburn and regurgitation assessments.

Maalox[®] tablet intake: During the single-blind baseline period, the mean number of tablets taken daily during the daytime were comparable among the groups and ranged from 1.9 in the placebo group to 2.8 in the cisapride 20 mg group. However, at nighttime the cisapride 20 mg group took an average of 2.1 tablets, significantly ($P = 0.01$) more than the 1.3 tablets taken by patients in the placebo group and marginally ($P = 0.05$) more than the 1.6 tablets taken by patients in the cisapride 10 mg group. Again, the mean total number of Maalox[®] tablets taken at night during the baseline period was significantly ($P = 0.04$) higher in the cisapride 20 mg group than in the placebo group and marginally ($P = 0.07$) higher than in the cisapride 10 mg group.

During double-blind treatment, the patients in all three groups reduced their intake of Maalox[®] tablets, both daytime and nighttime, except for the placebo group's nighttime intake at Endpoint. The reductions in the placebo group were significant ($P \leq 0.03$) at Weeks 8 and 12 for the number of daytime and total tablets taken. The reductions were significant in the cisapride 10 mg group at all of the time points for the number of daytime, nighttime and total tablets taken, and were significant in the cisapride 20 mg group at about half of the analyzed time points for the number of daytime and nighttime tablets taken and at all of the time points for the number of total tablets taken. The reductions were smallest in the placebo group. The results at week 4 (the first visit during the double-blind phase), week 12 (the last scheduled visit during the double-blind phase) and Endpoint are summarized in Table 16. During daytime, there were no significant differences between the placebo group and either cisapride group. The cisapride 10 mg group's mean intake was significantly more reduced than the cisapride 20 mg group's at week 4 ($P = 0.03$), endpoint ($P = 0.02$) and overall ($P = 0.03$). During nighttime, both the cisapride 10 mg ($P = 0.02$) and cisapride 20 mg ($P = 0.05$) groups' mean intakes were reduced significantly more than the placebo group's at Week 4. The comparison to the cisapride 20 mg group should be cautiously interpreted due to the significant difference

at baseline. The cisapride 10 mg group had a significantly larger reduction in total number of tablets than the placebo group at Week 4 ($P = 0.02$) and marginally larger reductions at Endpoint ($P = 0.07$) and overall ($P = 0.06$). In addition, the cisapride 10 mg group had a significantly larger reduction than the cisapride 20 mg group at endpoint ($P = 0.04$) and a marginally larger reduction in the overall analysis ($P = 0.07$). Significant ($P \leq 0.01$) treatment-by-investigator interactions, however, occurred at endpoint and in the overall analysis.

Table 16: Maalox® tablet intake.

Tablets	Reductions from Baseline (see above for baseline values)								
	Week 4			Week 12			Endpoint		
	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg
Daytime	0.4	0.7**	0.5	0.6	1.0	0.8	0.3	0.9**	0.5
Nighttime	0.1	0.4**	0.6**	0.2	0.6	0.4	0.0	0.5	0.5
Total	0.6	1.2**	1.1	0.8	1.6	1.2	0.3	1.4**	1.0

** : $P \leq 0.05$ compared to the placebo group; ** : $P \leq 0.05$ compared to the cisapride 20 mg group.

b. Global assessments.

The results of the investigator and patient global assessments are shown in Figure 10. The percentages of patients rated as having marked or moderate improvement by the investigator were 52%, 62% and 59% for the placebo, cisapride 10 mg and cisapride 20 mg groups, respectively. The cisapride 10 mg group's results tended to be better than the placebo group's, although the difference was not significant ($P = 0.15$). The percentages of patients rated as having marked or moderate improvement by the patients were 52%, 70% and 65% in the placebo, cisapride 10 mg and cisapride 20 mg groups, respectively. There was a non-significant trend indicating that the results of the cisapride 10 mg group were better than the placebo group's ($P = 0.06$) and the cisapride 20 mg group's ($P = 0.07$) according to the patient assessment.

c. Objective evaluation.

i. Endoscopy results: The placebo group had significantly ($P = 0.05$) lower grades at pretreatment than the cisapride 10 mg group and also lower grades than the cisapride 20 mg group, although not significantly ($P = 0.13$). Forty-four percent of the patients in the placebo group versus 24% and 30% in the cisapride 10 mg and 20 mg groups, respectively, entered the study with the minimal allowed esophagitis, Grade 1. Only 4% of the patients in the placebo group versus 14% and 19% in the cisapride 10 mg and 20 mg groups, respectively, entered the study with the most severe esophagitis, Grade 4.

After adjusting for differences in the baseline grade, the mean endoscopic grade was reduced by 0.6 in the placebo group, 0.8 in the cisapride 10 mg group and 1.0 in the cisapride 20 mg group during double-blind. These reductions were all significant (P

≤ 0.02), and the reduction in the cisapride 20 mg group tended to be more important than in the placebo group, although the difference was not significant ($P = 0.08$).

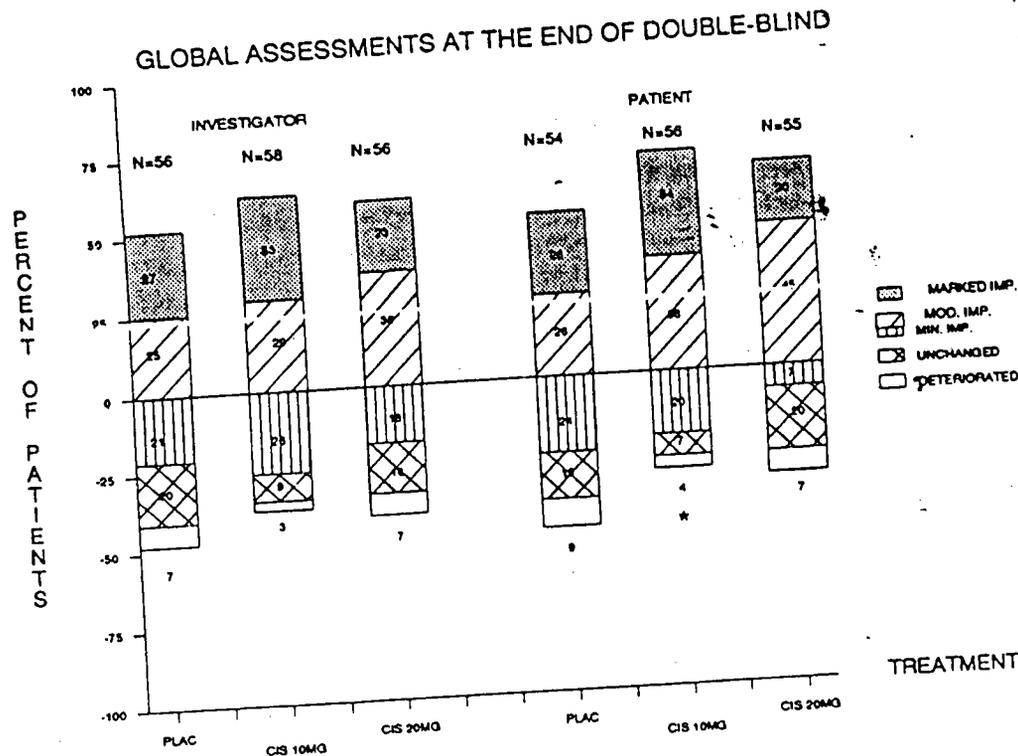


Figure 10. Investigators' and patients' global assessments.

ii. Biopsy results: The percentages of patients with normal biopsies at baseline 5 cm above the lower esophageal sphincter were 33%, 45% and 49% in the placebo, cisapride 10 mg and cisapride 20 mg groups, respectively, with the difference between the placebo and cisapride 20 mg group being marginally significant ($P = 0.06$). The percentage of patients with normal biopsies at the most severe areas were 2%, 4% and 19% in the placebo, cisapride 10 mg and cisapride 20 mg groups respectively, with the difference between the cisapride 20 mg group and each of the other two groups being significant ($P < 0.01$).

At the end of double-blind treatment, for the measurement at 5 cm above the LES, the ratios of the number of patients with abnormal biopsies at baseline (pre-treatment) only to those with abnormal biopsies at the end of double-blind treatment only were 12/6 in the placebo group, 8/5 in the cisapride 10 mg group and 5/7 in the cisapride 20 mg group. For the measurement at the most severe areas, the ratios were 6/1 in the placebo group, 4/2 in the cisapride 10 mg group and 6/1 in the cisapride 20 mg group. There were no significant differences between the groups for either site.

iii. Lower esophageal sphincter pressure: The groups were comparable at baseline with the group mean LESPs ranging between 12.6 and 14.5 mmHg. At the end of double-blind treatment, the mean LESPs declined slightly in the placebo and cisapride 20 mg groups and increased significantly ($P = 0.03$) by 1.1 mm Hg in the cisapride 10 mg group. There were no significant differences between the groups.

iv. Bernstein test: The mean time until symptoms appeared within each group at baseline were comparable and ranged between 3.0 and 3.8 minutes. The mean time until symptoms appeared at the end of double-blind treatment was longer than at baseline within each group, but not significantly so. There were no significant between-group differences. Nine percent of the patients in the placebo group, 16% in the cisapride 10 mg group and 27% in the cisapride 20 mg group tested negative at the end of double-blind treatment. However, these differences were not statistically significant.

d. Subgroups of patients according to pre-treatment endoscopic grade (Table 17).

In the following sections, the subgroups are compared using the differences from placebo. Because of the differences in sample sizes, comparisons of P-values are inappropriate.

Table 17: Distribution of patients.

Subgroup	Placebo	Cis. 10 mg	Cis. 20 mg	Total
Grade 1	27	18	20	65
Grades 2, 3 or 4	30	42	37	109
Grade 4	2	10	12	24

i. Investigator symptom assessments: In the grade 1 group, the group taking 10 mg QID improved significantly ($P \leq 0.04$) more than the placebo group only at Week 12 for heartburn (daytime, nighttime, and combined) and total symptoms. The same improvement was observed only at endpoint for the grade 2, 3 and 4 combined and, in addition, regurgitation (daytime, nighttime, and combined) and overall assessment improved significantly ($P \leq 0.04$) in this group also at endpoint. Interestingly, some of these differences also existed in the grade 4, although only two placebo patients were in that subgroup.

ii. Patient symptom assessment: No significant differences were observed in groups 1 and combined 2,3 and 4. In the grade 1 group, in contrast, heartburn (daytime, nighttime, and combined) and total symptoms improved significantly ($P \leq 0.04$) more in the two cisapride groups than in the placebo group at least overall and, in many cases also at 8 and 12 Weeks and at Endpoint. However, as previously noted, there were only two placebo patients were in that subgroup.

iii. Global assessments: No significant differences were observed between the cisapride groups compared to the placebo group.

iv. Endoscopic grade and Biopsy results: No significant differences were observed

between the cisapride groups compared to the placebo group.

v. Lower esophageal sphincter pressure: Among the patients with Grade 1 esophagitis, the cisapride 10 mg group's mean LESP, although the highest at baseline, was the only one among the three treatment groups that increased (from 17.4 mm Hg to 20.8 mm Hg). This increase was significantly different from the mean LESP changes in both the placebo ($P = 0.02$) and cisapride 20 mg ($P = 0.01$) groups, which were both decreased. In other grades groups, there were no significant differences between the treatment groups.

vi. Bernstein test: Among the patients with Grade 1 esophagitis, the mean time until symptoms appeared increased significantly ($P = 0.02$) more in cisapride 10 mg group than in the placebo group. Likewise, the percentage of patients with negative tests at the end of double-blind treatment in the cisapride 10 mg group was significantly ($P = 0.01$) higher than in the placebo group. In other grades groups, there were no significant differences between the treatment groups. However, the percentage of patients with negative tests at the end of double-blind treatment in the cisapride 20 mg group was significantly higher than in the placebo ($P = 0.05$) and cisapride 10 mg ($P = 0.02$) groups.

e. Conclusions.

The cisapride 10 mg group had consistently better results than the placebo group for the investigator symptom intensity assessments. At week 12 (the final scheduled week of treatment) and endpoint (i.e. including patients whose last visit was 4, 8 or 12), cisapride 10 mg was at least marginally superior to placebo in every assessment (except at endpoint for daytime heartburn and daytime regurgitation). The cisapride 10 mg group again had consistently better results than the placebo group for the patient symptom intensity assessments, although a few results were only marginally better. The effectiveness of cisapride 10 mg was further demonstrated by the reduction in mean nighttime and total Maalox[®] intake, and also by the patients' global assessments. According to the investigator and patient symptom assessments (excluding regurgitation), Maalox[®] intake and the global assessments, cisapride 10 mg was more effective than cisapride 20 mg.

Cisapride 20 mg was not significantly different from placebo, although both groups improved significantly from baseline. The sponsor suggests that one possible reason for this lack of effect is that cisapride stimulates the motility of the entire gastrointestinal system and that a 20 mg dose may be more likely to induce GI-related side effects that may mask the perception of the improvement of the specific symptoms being tested.

All three groups had significant improvements from baseline in esophagitis. In both cisapride groups, mean reductions in endoscopic grade were marginally ($P = 0.09$ and $P = 0.08$ for cisapride 10 mg and 20 mg, respectively) greater than in the placebo group. Little difference in healing rates was apparent. These findings, however, may be due to the milder severity of the placebo patients at entry into the study. No significant between-treatment differences were observed for any of the other objective measurements (i.e., biopsies, Bernstein test and LESP).

Among patients with esophagitis sufficiently severe to have erosions (Grades 2, 3 and 4), symptom relief and Maalox[®] intake were improved slightly more in both cisapride groups than in the placebo group, but this non significant trend was not observed among patients who had only red streaks (Grade 1). Among the patients with circumferential defects or ulcers (Grade 4), both cisapride groups improved strikingly more than the placebo group, but these results are tentative because there were only two placebo patients in that subgroup. Among patients with Grade 1 esophagitis, the LESP and Bernstein test demonstrated that cisapride 10 mg was more effective than placebo and cisapride 20 mg.

Therefore, this trial indicates that cisapride 10 mg QID was significantly superior to placebo in improving the symptoms of patients with chronic, documented GERD. Cisapride 20 mg was not significantly different from placebo or from cisapride 10 mg, although both groups significantly improved from baseline.

In general, patients with more severe baseline values tended to have greater improvement during double-blind treatment, and cisapride tended to be more strongly superior to placebo in these cases. Cisapride 20 mg showed increased effectiveness in improving esophagitis scores and symptoms and reducing Maalox[®] intake when the patients with Grade 1 esophagitis were excluded.

3. Reviewer's evaluation.

In this randomized double blind trial of 147 patients with at least grade 1 esophagitis, daytime heartburn as assessed by the investigators improved significantly in all three groups and cisapride 10 mg (but not 20 mg) QID was significantly better than placebo at week 4 and at endpoint. Nighttime heartburn improved significantly more in the cisapride 10 mg group than in the placebo group at week 4, 12, and endpoint. Improvement assessed by the patients was significantly better in the cisapride 10 mg QID group than in the placebo group only at week 4. The reduction of antacid consumption was significantly greater in the cisapride 10 mg group than in the placebo group only at week 4. Global assessment by investigator and by the patients was not significantly better in the cisapride groups ($P = 0.15$ and 0.06 , respectively). Endoscopy showed a significant improvement compared to baseline in all groups ($P < 0.01$), but there was no significant difference between the two groups. No significant difference were observed regarding the normalization of biopsy scores at the level of most severe esophagitis. No differences were observed between the two groups regarding LESP manometry, but LESP increased significantly compared to baseline only after cisapride 10 mg QID ($P < 0.03$). Bernstein test performed at the end of the trial showed that the time to symptom was not significantly different in the three groups. Concordance analysis showed some significant superiority in favor of cisapride 10 mg QID.

The observation that 20 mg QID is less effective than the 10 mg QID dose is puzzling. It could result from a number of differences that were observed between the groups. First, the population in the 20 mg dosed group tended to be older. In addition, the 20 mg group had significantly ($P \leq 0.05$) more intense regurgitation than the placebo group at daytime, nighttime and combined, whereas the 10 mg group had only marginally more intense regurgitation than the placebo group at nighttime ($P = 0.06$) and daytime and

nighttime combined ($P = 0.06$). Furthermore, they took an average of 2.1 tablets of antacids, significantly ($P = 0.01$) more than the 1.3 tablets taken by patients in the placebo group and marginally ($P = 0.05$) more than the 1.6 tablets taken by patients in the cisapride 10 mg group. These two latter observations suggest that the 20 mg group were more symptomatic than the other groups, and may have responded differently to cisapride treatment. On the other hand, the cisapride 10 mg group had significantly ($P = 0.05$) higher endoscopy grades at pretreatment than the placebo group, whereas the cisapride 20 mg group only had a not significant trend ($P = 0.13$) towards higher endoscopy grades at pretreatment than the placebo group. This observation does not support the hypothesis that the cisapride 20 mg group had a more aggressive disease than the 10 mg group. Because the placebo group appears to have had a somewhat milder disease than the cisapride groups, greater improvement in these latter groups could be due maximum effect already achieved in the placebo group. However, this is unlikely as the grade of subjective symptoms was still clinically significant in all groups at 12 weeks and endpoint. This suggests that the sponsor should evaluate the possibility of extending cisapride beyond the 12 week requested in the present NDA, and to consider maintenance therapy.

C. MULTICENTER STUDY 1203

1. Description of the study.

The design of this study was identical to that of MC 1201 and of MC 121-125;851 regarding the primary effectiveness parameters but, contrary to those studies, there was no biopsies, LES measurements or Bernstein tests. A total of 177 patients from 12 U.S. centers were randomized to received double-blind medication (placebo, 10 mg cisapride and 20 mg cisapride, QID). The demography, background, vital signs and subjective variables of the groups were similar (Table 18).

Table 18: Demographics

		PLAC	CIS 10 mg	CIS 20 mg	Total
Entered d-b		60	56	61	177
Sex	M	34	30	34	98
	F	26	26	27	79
Age (yrs)	Mean	45.4	48.1	48.6	47.4
	Min.	25.0	18.0	21.0	18.0
	Max.	77.0	76.0	70.0	77.0
Weight (kg)	Mean	84.8	83.4	83.9	84.1
	Min.	49.1	50.0	56.8	49.1
	Max.	130.9	129.1	128.9	130.9
GERD symptom dur. (yrs)	Mean	9.4	6.6	8.2	8.1
	Min.	0.3	0.3	0.3	0.3
	Max.	40.0	20.0	50.0	50.0

2. Sponsor's analysis.

a. Symptom assessments.

i. Investigator assessment:

Heartburn: During double-blind treatment, all three groups showed significant (usually at the $P < 0.001$ level) improvements from baseline at all of the time points; these improvements increased with treatment duration. As shown in table 19, daytime heartburn was reduced significantly ($P = 0.01$) more in the cisapride 10 mg group than in the placebo group at Week 4, and it was reduced significantly ($P < 0.03$) more in the cisapride 20 mg group than in the placebo group's at all times. The mean differences from baseline are also illustrated in Figure 11. At Week 12, the mean reduction in the cisapride 20 mg group's nighttime heartburn was significantly ($P = 0.01$) greater than in the placebo group. The mean differences from baseline are also shown in Figure 12. Combined daytime and nighttime heartburn was reduced significantly more in the 20 mg cisapride than in the placebo group at 4 and 12 weeks, but not at endpoint.

Table 19: Investigators' symptom assessments

Assessment	Reductions from Baseline (LSM's)								
	Week 4			Week 12			Endpoint		
	Plac.	10 mg	20 mg	Plac.	10 mg	20 mg	Plac.	10 mg	20 mg
Heartburn:									
Daytime	0.8	1.8**	2.0**	2.1	2.2	3.3****	1.9	2.2	2.9**
Nighttime	1.6	1.9	2.1	2.5	2.7	3.7****	2.5	2.7	3.1
Combined	2.4	3.7	4.1**	4.6	4.9	7.0****	4.4	4.9	6.0
Regurgit.:									
Daytime	0.6	1.5**	1.6**	1.2	1.9	2.5**	1.2	1.8	2.2**
Nighttime	1.0	1.5	1.3	1.5	2.0	2.4**	1.6	2.0	2.0
Combined	1.6	3.0	2.8	2.8	3.9	4.9**	2.8	3.7	4.2
Total	4.0	6.7**	7.1**	7.4	8.7	11.8**	7.2	8.6	10.2
Overall	1.3	1.8	1.9	2.1	2.5	3.2**	2.0	2.4	2.8*

** : $P \leq 0.05$ compared to the placebo group; ** : $P \leq 0.05$ compared to the cisapride 10 mg group.

Regurgitation: Mean improvements in daytime regurgitation were significantly ($P = 0.02$) greater in the cisapride 10 mg group than in the placebo group at Week 4, and in the cisapride 20 mg group ($P \leq 0.04$) than in the placebo group's at all of the time points. The cisapride 20 mg group improved significantly ($P = 0.03$) more in nighttime regurgitation than the placebo group at Week 12. For the combined daytime and nighttime assessments of regurgitation, mean improvements were significantly greater in the cisapride 20 mg group at Week 12 ($P = 0.01$).

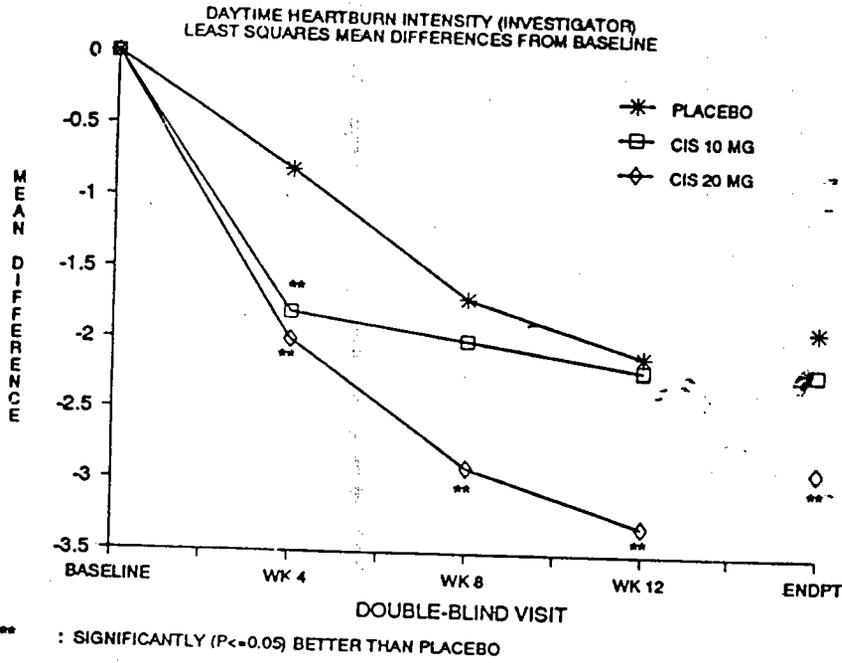


Figure 11. Investigators' assessments of daytime heartburn.

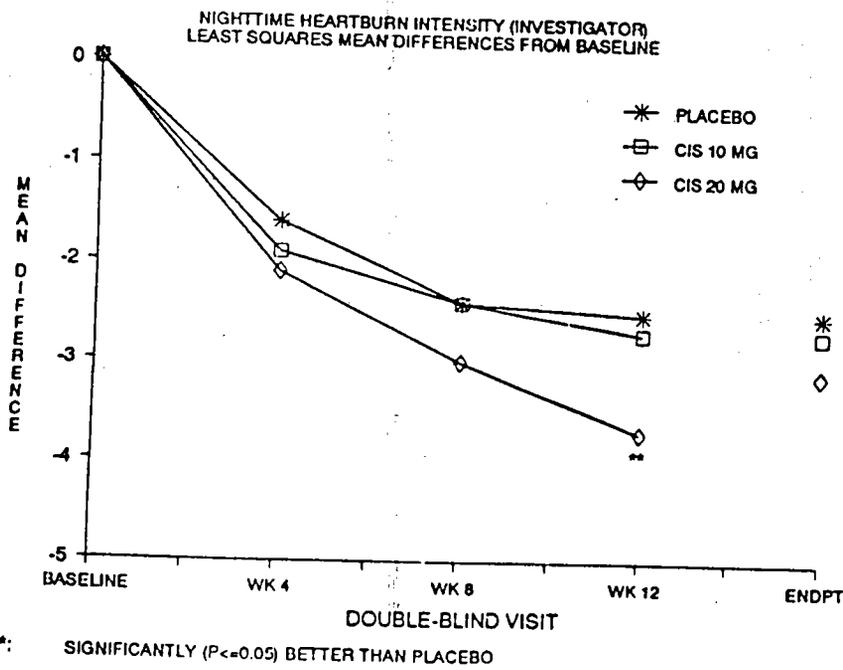


Figure 12. Investigators' assessments of nighttime heartburn.

Total symptoms: The cisapride 10 mg group had significantly ($P = 0.04$) greater reduction of total of daytime and nighttime heartburn and regurgitation assessments than the placebo group at week 4; the cisapride 20 mg group had significantly greater reductions than the placebo group at week 4 ($P = 0.01$), week 12 ($P = 0.004$), and overall ($P = 0.04$).

Overall assessment: The cisapride 20 mg group improved significantly ($P = 0.01$) more than the placebo group at Week 12.

ii. Patient (diary) symptom assessments:

The groups were comparable at baseline for all the assessments. The mean daytime heartburn intensities were between 42.4 and 44.9 (on the 0-100 scale) in the three groups. The mean nighttime heartburn intensities were between 39.8 and 43.9. The mean regurgitation intensities ranged between 22.4 and 28.4.

Heartburn: During double-blind treatment, all three groups had improvements from baseline at all of the time points. The improvements were significant in virtually all of the cases and increased with duration of treatment. The cisapride 10 mg group's nighttime and combined heartburn intensities were reduced significantly ($P < 0.05$) more than the placebo group's at Week 4 (Table 20). In addition, the daytime, nighttime, and combined heartburn were reduced significantly ($P < 0.05$) more in the cisapride 20 mg group than in the placebo group at all times.

Regurgitation: Daytime regurgitation was improved to a significantly ($P = 0.01$) greater extent in the cisapride 20 mg group than in the placebo group's at Week 12. For nighttime regurgitation, the cisapride 10 mg group had significantly ($P = 0.03$) better results at Week 4 than the placebo group. The cisapride 20 mg group had significantly ($P = 0.02$) better results than the placebo group at Week 12. For the combined daytime and nighttime regurgitation assessments, the cisapride 20 mg group had significantly ($P = 0.01$) better results than placebo at Week 12.

Total symptoms: In totalling all of the daytime and nighttime heartburn and regurgitation assessments, the cisapride 10 mg group had a significantly ($P = 0.04$) greater reduction than the placebo group at Week 4 and the cisapride 20 mg group had significantly ($P < 0.05$) greater reductions than the placebo group 4 and 12 Week.

Table 20: Patients' (diary) assessments.

Assessment	Reductions from Baseline (LSM's)								
	Week 4			Week 12			Endpoint		
	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg
Heartburn:									
Daytime	9.1	14.4*	15.8**	17.6	23.5	27.8**	16.8	20.6	24.7**
Nighttime	7.3	16.2**	14.1**	15.5	22.3*	26.4**	15.2	20.6	23.0**
Combined	16.3	30.4**	30.1**	33.0	45.5	54.3**	32.0	41.0	47.8**
Regurgit.:									
Daytime	3.1	6.6	6.2	7.5	12.6	15.6**	7.7	9.4	12.5
Nighttime	1.2	7.3**	4.1	6.8	13.1*	13.6**	7.1	10.6	9.9
Combined	4.5	13.7*	10.3	14.4	25.6*	29.1**	15.0	19.9	22.3
Total	21.0	43.6**	40.5*	48.0	70.4*	83.0**	47.4	60.3	70.2*

** : $P \leq 0.05$ compared to the placebo group.

Maalox® tablet intake During the single-blind baseline period, the mean number of Maalox® tablets taken daily during the daytime were comparable among the groups and ranged from 1.9 in the cisapride 20 mg group to 2.3 in the placebo group. In addition, the cisapride 20 mg group took marginally ($P = 0.09$) more tablets at nighttime than the placebo group, 1.7 versus 1.4. The groups were comparable for the combined daytime and nighttime number of Maalox® tablets taken during baseline.

During double-blind treatment, the patients in all three groups reduced their intake of Maalox® tablets, both daytime and nighttime. As shown in Figure 13, the reduction in the number of daytime tablets taken was significantly larger in the cisapride 20 mg group than in the placebo group's at week 4 ($P = 0.02$), week 12 ($P = 0.04$) and overall ($P = 0.02$) but the difference was not significant at endpoint ($P = 0.06$). Although the trend was similar in the cisapride 10 mg group, no statistically significant difference was observed. As shown in Figure 14, the reduction in the number of nighttime tablets taken was smallest in the placebo group but largest in the cisapride 10 mg group, rather than in the cisapride 20 mg group. Reductions were significantly greater in the cisapride 10 mg group than the in the placebo group at week 4 ($P = 0.005$), week 12 ($P = 0.04$), endpoint ($P = 0.01$) and overall ($P = 0.02$). Reductions were significantly ($P = 0.03$) greater in the cisapride 20 mg group than in the placebo group at week 4.

The cisapride 10 mg group had a significantly ($P = 0.03$) larger reduction than the placebo group at Week 4 and the cisapride 20 mg group had significantly larger reductions in total Maalox tablet intake than the placebo group at week 4 ($P = 0.01$), week 12 ($P = 0.04$) and overall ($P = 0.03$).

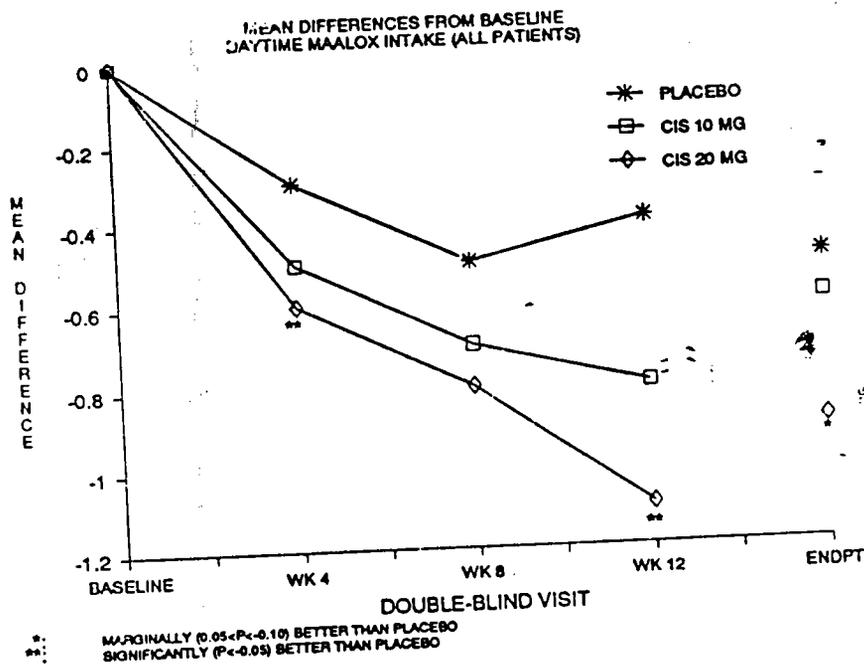


Figure 13. Daytime Maalox[®] intake.

Figure 14

Nighttime
Maalox[®]
intake.

b. Global assessments.

The results of the investigator and patient global assessments are shown in Figure 15.

The percentages of patients rated as having marked or moderate improvement by the investigator were 49%, 65% and 74% for the placebo, cisapride 10 mg and cisapride 20 mg groups, respectively. The percentages of patients rated as having marked or moderate improvement by the patients were 53%, 71% and 74% in the placebo, cisapride 10 mg and cisapride 20 mg groups, respectively. In addition, among those rated as having marked or moderate improvement, the percentage rated as having marked improvement was highest in the cisapride 20 mg group. The cisapride 20 mg group's results were significantly ($P \leq 0.01$) better than the placebo group's according to both assessments, although the improvement with cisapride 10 mg was numerically close, the difference was not statistically significant.

For all but one of the investigators, the percentage of patients rated as having marked or moderate improvement by the investigator was higher in the cisapride 20 mg group than in the placebo group. For the patient assessments, cisapride 20 mg was favored over placebo among six of the investigators (none favored cisapride by substantially larger margins than all of the others); placebo was favored over cisapride 20 mg for two investigators and were tied for the remaining two.

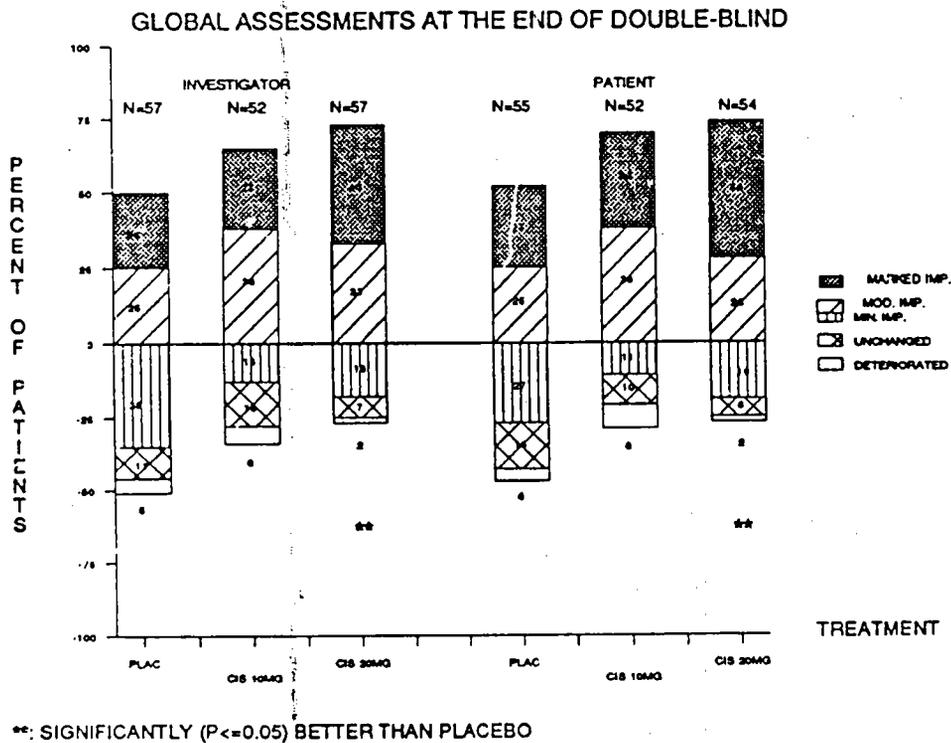


Figure 15. Investigators' and patients' global assessments.

c. Objective assessment

i. Endoscopy results: Approximately 70% of the patients in each of the three treatment groups who had both pre- and post-treatment endoscopies entered the study with grades of 1 or 2. About half of the patients within the placebo group entered with Grade 1 and about half within the cisapride 20 mg group entered with Grade 2, resulting in marginally ($P = 0.07$) different grade distributions at pre-treatment for these two groups.

Upon adjusting for differences in the baseline grade, the mean endoscopic grade was reduced by 0.6 in the placebo group, 0.8 in the cisapride 10 mg group and 0.9 in the cisapride 20 mg group. These reductions were all significant ($P < 0.001$), but none were significantly different from one another, although the difference between the cisapride 20 mg group and the placebo group approached significance.

The biggest difference between the cisapride 20 mg and placebo groups was in the number of patients who improved by two grades (15 versus 7). Altogether, 53%, 57% and 69% of the patients were improved in the placebo, cisapride 10 mg and cisapride 20 mg groups, respectively, with a significant ($P = 0.05$) difference between the placebo and cisapride 20 mg groups. The percentages of patients healed in the placebo, cisapride 10 mg and cisapride 20 mg groups were 36%, 41% and 51%, respectively, with again a significant ($P = 0.04$) difference between the placebo and cisapride 20 mg groups.

d. Subgroups of patients according to pre-treatment endoscopic grade (Table 21).

Table 21: Distribution of patients who had double-blind investigator symptom assessments among the subgroups, defined by pre-treatment endoscopy grades.

Subgroup	Placebo	Cis. 10 mg	Cis. 20 mg	Total
Grade 1	28	18	15	61
Grades 2, 3 or 4	29	35	44	108
Grade 4	5	6	8	19

There was no significant differences between the cisapride groups and the placebo group at any time in any of the subgroups considered for either the investigators or the patients' assessments.

e. Conclusions

After twelve weeks of treatment, cisapride 20 mg was significantly better than placebo for every assessment except nighttime Maalox[®] intake, where it was marginally superior. In addition, the cisapride 20 mg group had significantly better results on the global assessments than did the placebo group. When accounting for treatment-by-investigator interactions, these results were little affected after week 4 of treatment. The cisapride 10 mg group also had significantly better results than the placebo group in terms of symptom improvement and Maalox[®] intake at Week 4. All three groups tended to improve with increasing duration of treatment. The 20 mg QID dose was usually not significantly

different from the 10 mg QID dose. Compliance as assessed by tablet count was good and similar in all groups.

At endpoint, the cisapride 20 mg group again showed consistently better results compared to placebo. However, fewer of these results were significant compared to the study visit analyses. This may be due to the larger number of patients in the cisapride 20 mg group that prematurely discontinued compared to placebo (ten vs. two after Week 4). Of the 12 patients who prematurely discontinued from these two groups, five had failed to improve. However, only one from each group withdrew because of inadequate response and could be considered treatment failures. The remaining three patients who failed to improve actually withdrew for reasons unrelated to treatment as follows: one placebo patient was ineligible, and two cisapride patients had breast cancer and an ovarian mass, respectively. Thus, withdrawal of the larger number of patients from the cisapride 20 mg group does not support evidence against cisapride's effectiveness but does penalize the cisapride 20 mg group in the endpoint analyses.

Cisapride 10 mg showed consistent superiority over placebo for the number of nighttime Maalox[®] tablets taken, while cisapride 20 mg was consistently superior to placebo for the number of both daytime and nighttime Maalox[®] tablets taken. All three treatment groups reduced their intake of Maalox[®] tablets, usually significantly from baseline, although the baseline value was small (<4 for day and night combined).

In general, patients with more severe symptoms at baseline tended to have greater improvement during double-blind treatment, and cisapride tended to be more strongly superior to placebo in these cases. The subgroup analyses showed that cisapride 10 mg was substantially more effective than placebo among patients with Grades 2, 3, and 4 esophagitis compared to patients with Grade 1 esophagitis, although the difference did not reach statistical significance. The effectiveness of cisapride 20 mg was slightly enhanced among the patients with more severe esophagitis.

In addition, more than twice the number of patients in the cisapride 20 mg group compared to the placebo group improved by two grades (15 vs 7). Finally, the superior healing rate of cisapride 20 mg (51 vs 36%, $P=0.04$) compared to placebo was especially impressive since patients in the 20 mg group had more severe esophagitis at pre-treatment.

In conclusion, cisapride 10 mg was significantly better than placebo in improving symptoms of patients with chronic, documented GERD after four weeks of treatment and showed statistically significant superiority over placebo for the number of nighttime Maalox[®] tablets taken. After twelve weeks of treatment, cisapride 20 mg was significantly better than placebo in improving symptoms and healing esophagitis. Overall, cisapride 20 mg was not significantly different from cisapride 10 mg.

3. Reviewer's evaluation.

This double blind placebo-controlled study was identical to MC 1201 except that it did not have biopsies, LESP measurements or Bernstein tests. The study randomized

177 patients with GERD, with 60, 56, and 61 patients receiving placebo, cisapride 10 mg QID, and cisapride 20 mg QID, respectively.

Daytime heartburn as assessed by the investigators improved significantly in all three groups and cisapride 10 mg and 20 mg QID were significantly better than placebo at week 4, but only the 20 mg dose group was significantly better at week 12 and at endpoint. Nighttime heartburn improved significantly more only in the cisapride 20 mg group than in the placebo group and only at week 12. In the patients' assessed evaluation, improvement of both day- and nighttime heartburn was significantly better than in the placebo group at week 12 and endpoint only in the cisapride 20 mg QID group but both doses of cisapride improved significantly nighttime heartburn at week 4. The reduction of antacid consumption was significantly greater in the cisapride 10 mg group than in the placebo group at weeks 4, 12 and at endpoint by night, but not by day. The reduction of antacid consumption was significantly greater in the cisapride 20 mg group than in the placebo group at weeks 4 and 12 by day, but only at week 4 by night. Global assessment by investigator by the patients was significantly better only in the cisapride 20 mg QID group compared to placebo ($P < 0.01$). Endoscopy showed a significant improvement compared to baseline in all groups ($P < 0.01$), but there was no significant difference between the two groups. However, the number of patients who improved by two grades and the percentage of patients healed was significantly greater in the cisapride 20 mg QID group compared to placebo ($P < 0.05$).

IV. SAFETY OF CISAPRIDE

A. OVERVIEW

Description of the worldwide exposure of adults to oral cisapride up to March 31, 1990 (for clinical trials) and July 1, 1991 (for deaths and foreign spontaneous reports of adverse experiences) is based on the investigation of 979 adult patients in 42 clinical trials in the United States and in 3,081 patients in 46 controlled studies in 23 foreign countries. An additional 698 patients in 27 foreign studies have been reported in the literature or by other Janssen affiliates. Finally, 294 subjects (186 healthy volunteers and 108 patients) were exposed to cisapride on an acute basis during US clinical pharmacology studies and cisapride has also been given to over 1000 patients in the US on a compassionate use basis. Cisapride is approved for marketing in 41 countries.

No clinically relevant changes in blood pressure, heart rate, ECG, respiration rate or temperature were observed in healthy subjects at doses up to 40 mg QID for five days, or in constipated patients or patients with diabetes mellitus after single oral doses of up to 40 mg, repeated oral doses up to 10 mg TID for 12 weeks, or single IV doses up to 10 mg. Cisapride did not modify the blood pressure response of hypertensive patients to propranolol and did not stimulate prolactin release. It did not affect psychomotor function nor adversely alter the control of glycemia in diabetic patients, and had no antihemostatic effects.

B. ADVERSE EXPERIENCES IN CONTROLLED TRIALS

1. Extent of exposure

Of the 5581 total patients, 4060 were exposed to cisapride, either in double-blind or open phases. Of the 1257 patients in the US clinical trials, 979 were exposed to cisapride; 328 patients were exposed to cisapride in the US during the GERD clinical trials. The total duration of exposure during clinical trials worldwide represents 1263.7 patient years.

2. Demographics

Within each patient population, the demographics was similar among the double-blind cisapride (Table 22), placebo, and open-label cisapride groups. In addition, the US GERD patient population tended to have a higher proportion of males, and it was taller and heavier than the non-GERD populations. The demographics of the foreign patient populations were similar to the one of the US GERD population.

Table 22: Summary of patient demographics - Double-blind cisapride

Population	N	Sex % Male	Race % White	Age Mean yrs	Height Mean cm	Weight Mean kg
US All	754	41.0	89.5	42.9	168.3	73.1
US GERD	315	63.2	91.1	46.8	171.8	83.9
US Diabetic	175	30.9	82.9	38.0	166.9	66.8
US Non-diabetic	264	21.2	92.0	41.5	165.0	63.6
Foreign All	1650	56.5		48.1	168.5	71.3
Foreign GERD	1072	60.5		49.5	168.8	72.3
Foreign Non-GERD	578	45.4		44.2	167.2	67.5

3. Duration of exposure

Most trials in the United States were a double-blind placebo-controlled parallel design, ranging from 6 to 12 weeks in duration, followed by a two-year open long-term extension. The mean duration of exposure of cisapride worldwide was 87 days during double-blind periods and 132 days during open label periods. The mean duration of exposure to cisapride in the United States was 52 days during double-blind studies and 363 days in open studies. Foreign studies did not usually have open-label extensions; therefore, the mean duration of exposure to open label cisapride was shorter (47 days). On the other hand, several multi-country 12-week trials and four 6- to 12-month trials were conducted, resulting in a mean duration of 104 days for the foreign double-blind studies.

4. Dose

Differing dosage regimens have been investigated worldwide, primarily ranging from 2.5 mg TID to 20 mg QID, and these doses have been used for several indications. Patients in the US GERD studies received 10 mg or 20 mg QID (40- \leq 60 mg daily dose and \geq 80 mg daily dose). Patients in the foreign studies tended to receive lower daily doses, primarily due to the lower doses used for the non-ulcer dyspepsia indication. The difference in mean daily dose between the double-blind studies of 48 mg in the US versus 29 mg in other countries is primarily due to dosing regimens -- 20 mg QID was used in US GERD studies only and 5 mg TID was used in foreign dyspepsia studies.

5. Adverse experiences

Diarrhea was the most frequently reported gastrointestinal adverse experience (GIAE) for all patient groups, except for the US diabetic patients where vomiting, nausea, diarrhea, abdominal pain and constipation were the most frequent (Table 23). The patients who received placebo reported a frequency of gastrointestinal adverse experiences similar to, but slightly lower than, those who received cisapride, reflecting the nature of the disease in these populations.

Table 23: Summary of adverse experiences; GI Body Class

Population	Cisapride Double-blind			Placebo Double-Blind		
	N	% with AE	% with GI Class AE	N	% with AE	% with GI Class AE
US All	754	64.1	34.7	522	55.9	27.6
US GERD	315	69.5	35.9	191	54.5	22.5
US Diabetic	175	70.9	42.3	121	65.3	33.9
US Non-diabetic	264	53.0	28.4	210	51.9	28.6
Foreign All	1650	16.4	10.0	917	11.6	6.1
Foreign GERD	1072	19.6	11.6	541	11.8	6.1
Foreign Non-GERD	578	10.4	7.1	376	11.2	6.1

The most frequently reported non-GI adverse experiences in the US double-blind trials were headache (17% overall) and diarrhea (14.6% overall) for all groups except for the non-GERD diabetic group where vomiting (19.4%), nausea (16.6%), diarrhea (15.4%) and headache (13.7%) were the most frequent. Diarrhea and abdominal pain were most commonly reported in the foreign groups.

Based on the US clinical trials, there is a slight but fairly consistent increase in the percentage of adverse experiences as the dose increases. The foreign clinical trials do not show a similar trend, most likely due to the smaller number of patients who received a higher daily dosage.

The overall incidence of adverse experiences in the elderly was similar to that observed in the overall population but was statistically significantly ($P < 0.01$) higher in the cisapride group compared to placebo (Table 24). A similar difference was also observed in the GERD population subset, but not among US diabetics, where the incidence of adverse experiences tended to be higher in the placebo group than the cisapride group. These differences were caused primarily by differences in GI side effects (Table 24). As with the overall population, the incidence of adverse experiences in the elderly was not dose related.

Table 24: Summary of adverse experiences; Patients ≥ 65 years

Population	Cisapride Double-blind			Placebo Double-Blind		
	N	% with AE	% with GI Class AE	N	% with AE	% with GI Class AE
US All	67	61.2*	43.3*	45	37.8	15.6
US GERD	37	73.0*	54.1*	25	36.0	12.0
US Diabetic	11	54.5	36.4	3	66.7	33.3
US Non-diabetic	19	42.1	26.3	17	35.3	17.6
Foreign All	204	16.7	10.3	107	12.1	3.7
Foreign GERD	174	17.8	10.3	93	11.8	2.2
Foreign Non-GERD	30	10.0	10.0	14	14.3	14.3

*: $P < 0.01$ vs placebo

Table 25 presents a summary of the adverse experiences reported by more than 1% of those patients exposed to double-blind cisapride compared to placebo in the US GERD subpopulation that is the target population for the proposed indication.

6. Premature discontinuations

Table 26 summarizes the discontinuations by subpopulation, including those due to the Gastrointestinal Disorders classification. Overall, 5.7% of the US cisapride patients in double-blind studies discontinued due to adverse experiences compared to 2.9% of the placebo patients. Headache and gastrointestinal disorders (nausea, diarrhea, vomiting and abdominal pain) were the most common reasons for discontinuation, reflecting a pattern similar to the overall adverse experiences.

Unlike the overall adverse experience distribution, the pattern of premature discontinuations due to adverse experiences in double-blind studies do not appear to be related to the cisapride mode daily dose.

Table 25: Adverse experiences experienced by more than 1% of those patients exposed to double-blind cisapride compared to placebo in the US GERD subpopulation.

	Cisapride Incid. (%)	Placebo Incid. (%)
Total # of patients	315	191
Number of patients with AE	219 (69.5)	104 (54.5)
Headache	63 (20.0)	39 (20.4)
Diarrhea	47 (14.9)	23 (12.0)
Rhinitis	29 (9.2)	20 (10.5)
Abdominal pain	25 (7.9)	7 (3.7)
Constipation	23 (7.3)	7 (3.7)
Nausea	20 (6.3)	3 (1.6)
Sinusitis	16 (5.1)	11 (5.8)
Upper resp. tract infect.	16 (5.1)	7 (3.7)
Vomiting	15 (4.8)	2 (1.0)
Infection viral	15 (4.8)	6 (3.1)
Pain	12 (3.8)	5 (2.6)
Flatulence	9 (2.9)	3 (1.6)
Dizzy	8 (2.5)	3 (1.6)
Dyspepsia	8 (2.5)	1 (0.5)
Coughing	8 (2.5)	5 (2.6)
Pharyngitis	6 (1.9)	7 (3.7)
Urinary tract infection	6 (1.9)	0 (0.0)
Chest pain	6 (1.9)	3 (1.6)
Malaise	6 (1.9)	0 (0.0)
Arthralgia	4 (1.3)	3 (1.6)
Myalgia	4 (1.3)	3 (1.6)
Bronchitis	4 (1.3)	4 (2.1)
Dysuria	4 (1.3)	0 (0.0)
Injury	4 (1.3)	10 (5.2)
Back pain	4 (1.3)	10 (5.2)
Fever	4 (1.3)	2 (1.0)
Infection	4 (1.3)	1 (0.5)

In US GERD studies, 17/315 cisapride patients (5.4%) and 2/191 placebo patients (1.0%) discontinued; 1/27 cisapride patients discontinued in the open trials ($P < 0.025$). Eight patients discontinued due to GI disorders and five for CNS disorders. The open long-term cisapride patient experienced headaches and developed an extension of pre-existing hyperlipemia. The most common events were nausea, diarrhea and headache in six, four and four cisapride patients, respectively.

In foreign GERD studies, 51 (4.8%), 25 (4.6%), 11 (4.0%), and 8 (5.0%) discontinued due to adverse experiences for the cisapride controlled, placebo, active controlled and open cisapride groups, respectively. GI disorders (e.g. diarrhea and abdominal pain) were the most common events in all four of the groups. Intercurrent illness, CNS and general disorders also contributed to the discontinuations. Among the cisapride patients, headache was the next most common event after GI disorders.

Table 26: Summary of discontinuations due to adverse experiences

Population	Cisapride Double-blind			Placebo Double-Blind		
	N	% D/C	% GI Class D/C	N	% D/C	%GI Class D/C
US All	754	5.7	2.9	522	2.9	1.1
US GERD	315	5.4	2.5	191	1.0	0.0
US Diabetic	175	6.3	3.4	121	2.5	0.0
US Non-diabetic	264	5.7	3.0	210	4.8	2.9
Foreign All	1650	3.7	1.6	917	3.1	1.0
Foreign GERD	1072	4.8	2.1	541	4.6	1.5
Foreign Non-GERD	578	1.7	0.7	376	0.8	0.3

In other US studies, 11 (6.3%), 10 (4.8%), and 37 (10.3%) discontinued due to adverse experiences for the controlled cisapride, placebo and open cisapride groups, respectively. In both patient populations, the highest events associated with cisapride withdrawals were GI and CNS disorders.

In other foreign studies, the number and percentage of patients who discontinued were 10 (1.7%), 3 (0.8%), 4 (2.8%), and 7 (0.5%) for controlled cisapride, placebo, active control, and open cisapride groups, respectively.

In US Compassionate Clearance patients, 88 of 1014 patients discontinued due to adverse experiences (8.7%). Among the sub-populations who received cisapride, the rates were 4/60 (6.7%) for GERD, 21/238 (8.8%) for pseudo-obstruction, 38/301 (12.6%) for diabetic gastroparesis, 9/203 (4.4%) for idiopathic gastroparesis, 12/143 (8.4%) for post-surgical gastroparesis, and 4/69 (5.8%) for constipation. While GI disorders continued to be a major factor, CNS and cardiac disorders and laboratory abnormalities contributed to a greater extent than in the protocol study populations described above. It should be noted, however, that this very mixed population of patients generally had more than one illness, and that they received numerous concomitant medications.

In the US Clinical Pharmacology studies, 4/294 subjects exposed to cisapride discontinued due to adverse events. One of the discontinuations was for hepatitis, two were associated with laboratory abnormalities, the fourth was for vomiting.

7. Seizure and seizure-like activity

Based on a review of the worldwide reports of adverse experiences, seizures and hepatic abnormalities were considered potentially serious and have been addressed separately by the sponsor.

On March 25, 1988, a letter was sent to the FDA by the sponsor regarding the possibility of seizures in patients receiving cisapride. This letter was precipitated by a report from Canada which described a patient with pseudomonas sepsis who developed a grand mal seizure following 20 mg intravenous cisapride. This observation prompted the initiation of studies to determine if high dose cisapride would exaggerate seizure activity in rats given d,l-allylglycine, or would lower the threshold for induction of seizure activity in rats given bicuculline. Cisapride did not alter seizure activity in either of these tests.

Of the total seizure episodes reported, there were four adult seizure incidents reported from foreign countries; two from Canada, one from the U.K. and one from Japan. Two of these patients had a history of seizures, another patient had subsequent seizure activity after discontinuing cisapride and the other patient, who is referred to above had septicemia and meningitis, and a history of seizures.

In the US experience, there were four instances of grand mal seizures, one of petit mal and three cases of tonic-clonic convulsions. There were an additional 19 cases of abnormal movements, loss of consciousness or other CNS activity, which are included here as seizure-like activity. Thirteen of these cases occurred while patients were treated under a study protocol. One patient in a double-blind protocol had a seizure experience; however, this patient had her initial seizure while taking placebo. The other 12 patients had their experiences while participating in open long-term protocols, with the duration between starting cisapride until seizure-like activity ranging between two months and two years. There was no relationship between dose and this adverse event.

There were 14 instances of CNS complications in compassionate clearance patients which were included in the broad "seizure" definition. Of these, the diabetic gastroparesis patients contributed over half of the episodes. Several of these instances were related to hypoglycemic episodes. Of all 27 cases, three were judged to be "possibly," 13 "unlikely," and 11 as being "highly improbable" as far as relation to cisapride therapy was concerned. In both the "unlikely" and "highly improbable" cases, there were sufficient contributing factors to explain the reactions as reported. Twelve of these patients were re-challenged with cisapride, including two of the patients who had grand mal seizures, and none had a recurrence of seizure activity. Also, there were 14 patients with a history of seizure activity who were treated with cisapride (up to 80 mg/day for periods up to three years) without any reports of seizure activity.

In view of the clinical picture presented by these patients and their experience with cisapride, it is difficult to deduce that there is any relationship between cisapride therapy and seizure activity. In respect to the prior communications with the FDA and the inclusion of these experiences in the foreign package inserts, a statement that seizures have been reported in patients taking cisapride is to be included in the package insert.

8. Hepatic abnormalities

In the clinical experience with cisapride, there were a total of 18 reports of abnormal liver function. Ten of these occurred in the US experience and eight were reported from foreign studies and post-marketing surveillance.

In the US clinical studies and compassionate clearance experience with cisapride, there were ten reports of hepatic dysfunction. Three of these cases occurred during double-blind studies. There were also three placebo patients who had liver abnormalities reported during the double-blind trials (one hepatitis, and two elevated liver function tests). The three cases that occurred during double-blind cisapride were discontinued at the request of the sponsor due to abnormal liver function at entry into the study protocols. Another patient who had a history of elevated liver enzymes at entry into study, had an increase in LFT during six weeks of therapy at 60 mg/day and was discontinued. This patient's LFT remained elevated post-therapy at a level similar to pre-study values. There were no instances of jaundice or symptoms of hepatitis, and all patients recovered. One patient who was receiving TPN, was re-challenged with cisapride and LFT increased again following re-challenge.

Four of the eight foreign cases had jaundice and the other four had elevated LFT without symptoms. All eight patients discontinued cisapride therapy and seven of the eight patients recovered. The eighth patient, a 52-year-old male who participated in a double-blind trial in Belgium, was found to have colon cancer that had metastasized to the liver, thereby causing the elevated liver enzymes in plasma. This patient died some time after surgery for the cancer. Four of these foreign cases were considered possibly related to cisapride therapy because of time of onset, recovery after discontinuing cisapride therapy, and negative serology testing. However, causal relationship is not evident from the total experience with cisapride. The few cases of hepatic involvement in respect to the large number of patients exposed to cisapride suggest that the drug is devoid of hepatic toxicity.

9. Deaths

There were 73 deaths among the patients treated in the U.S., 45 of which were in the Compassionate Clearance Protocol (Table 27). Ten of the 28 "Protocol" patients died more than 30 days after discontinuation of cisapride. In addition, seven deaths were reported from other countries during studies or in the post-marketing surveillance. Finally, there were seven deaths in children under 12 years in the US and two in foreign countries. These nine deaths will be reviewed in the forthcoming NDA for the pediatric formulation.

In the US, one of the patients treated for GERD died 36 days after stopping cisapride therapy during the double-blind portion of the protocol due to respiratory failure. (The patient was receiving cisapride, 20 mg TID). Two other GERD patients died, one on therapy due to congestive heart failure, and one 57 days after stopping cisapride therapy due to cardiac arrest.

The largest number of deaths on cisapride (48/73 or 66%) occurred in patients with diabetic gastroparesis. This observation is probably related to the fact that many of these patients, especially those on compassionate clearance, had end-stage diseases with severe autonomic neuropathy, renal failure, and cardiovascular complications. Among these patients, the causes of death were consistent with insulin-dependent diabetic patients.

Table 27: CAUSE OF DEATH AMONG PATIENTS TREATED IN THE US.

Indication	Study	* Cardic-Vascular	** Cardiac	Respiratory	Renal	Infection Sepsis and other	Progress of Disease	Coma	Cancer	Suicide	Info. Not Available	TOTAL
1. GERD	Protocol	1 (1)	1 (1)	1								3 (2)
	Comp. Cl.											
2. DIABETIC	Protocol	4	3	3 (1)		3 (2)	1	3 (2)				17 (5)
	Comp. Cl.	12	3	3	2	4	3	2	1		1	31
3. NON-DIABETIC												
A. Idiopathic Gastroparesis	Protocol			1		1 (1)						2 (1)
	Comp. Cl.	1							1		1	3
B. Pseudo-Obst.	Protocol						1					1
	Comp. Cl.	3 (1)		1		1	2			1 (1)		8 (2)
C. Scleroderma	Protocol			3					1			4
	Comp. Cl.						3					3
D. Constipation	Protocol									1		1
	TOTAL	21 (2)	7 (1)	12 (1)	2	9 (3)	10	5 (2)	3	2 (1)	2	73 (10)

() Represents the number of those deaths that occurred >30 days after stopping cispapride therapy.

* Includes myocardial infarction, stroke, congestive heart failure, arteriosclerosis.

** Includes cardiac arrest, arrhythmias, and sudden death.

Among the seven patients from foreign countries, the causes of death were: two for sepsis, and one each for hypoglycemic coma, intra-abdominal cancer, suicide and pancreatitis. (The latter patient received cisapride as a suppository.) For one patient, a 90-year-old male from Portugal, there is no other information available.

In no single instance did an investigator implicate cisapride as a contributing factor to the death of a patient. There was no consistency in these deaths in respect to either dose or duration of therapy with cisapride. Evaluation of individual clinical conditions surrounding each of the deaths indicates that cisapride was not a factor in the death of any of these patients.

C. CLINICAL LABORATORY EVALUATIONS

Note: The patients who discontinued cisapride due to abnormalities in laboratory values are reviewed in the above Premature Discontinuations section.

There were no changes that would suggest that cisapride had any clinically significant effect on any of the laboratory parameters. There were occasional reversible elevations in liver function tests. Scatter plots of total bilirubin, SGOT, SGPT and GGT values at baseline ('pre') and during cisapride or placebo treatment indicated that cisapride did not cause any trend of change in any direction.

Because elevations in serum cholesterol and triglycerides were seen in the rat and dog toxicity studies, serum lipid profiles during clinical trials were evaluated. For the US GERD subpopulation, the mean change in cholesterol from baseline during double-blind cisapride ranged from 8.4 mg/dl (3.8% increase) at Week 4 to 4.6 mg/dl (2.0% increase) at Week 12. Values during placebo were fairly constant. The diabetic and non-diabetic subpopulations showed a similar increase during double-blind periods. The change in cholesterol values during open label cisapride was inconsistent and did not show any increasing or decreasing trends. The scatter plots of total cholesterol during double-blind cisapride and placebo and during open label cisapride showed a slight increase compared to baseline, but no increase over time and there appears to be no relationship to baseline values. The mean change of serum triglycerides from baseline was not different between double-blind cisapride and placebo. In the two studies where LDL and HDL were measured (US Multicenter GERD studies 1201 and 1203), LDL cholesterol increased in both cisapride and placebo groups, whereas HDL increased during cisapride (8.6% to 9.2%) and decreased with placebo (-1.6% to -2.2%). The LDL/HDL ratio decreased in the cisapride-treated patients, and the HDL as a % of total cholesterol increased.

In addition, there was no relation between dose of cisapride and change in cholesterol. Although there was a small increase in cholesterol during double-blind trials, this increase was within the normal range for total cholesterol and was due largely to a rise in HDL.

No clinically significant alterations in any of the laboratory parameters were seen in studies conducted in other countries.

D. SAFETY DATA FROM SOURCES OTHER THAN CLINICAL TRIALS

1. US compassionate clearance

As of March 31, 1990, 1014 adults have been exposed to cisapride on a compassionate clearance basis. The pattern of adverse experiences was very similar across indications within the compassionate clearance subset and also similar to the controlled trial experience. Again, the most common class of adverse experience was gastrointestinal disorders, accounting for 21.8% of the reported adverse experiences and the most frequently reported adverse experiences were headache, diarrhea, abdominal pain, nausea and vomiting.

Although the compassionate clearance patient population tended to have a more severe primary disease with multiple concurrent diseases, the pattern of reasons for discontinuation and adverse experiences associated with death paralleled that of the US controlled trial experience.

2. Adverse experiences in other foreign studies

The pattern of adverse experiences was similar to that of the controlled trials, with headache and gastrointestinal effects as the most commonly reported experiences (Table 28).

3. Foreign marketing experience

Serious events. Cisapride is approved for marketing in 41 countries. Since August 1988 when approval was obtained in Sweden, it is estimated that at least 12 million patients have received cisapride. In this interval, Janssen has received 30 reports of serious adverse experiences associated with the use of cisapride.

The most common serious events reported, seizures and abnormal liver function tests, (including hepatitis and cholestasis) were similar to those observed in the US clinical trials.

E. DRUG INTERACTIONS

Antacid coadministration did not affect the oral absorption of cisapride in healthy volunteers. However, cisapride accelerated the absorption of cimetidine, and cimetidine coadministration increased cisapride peak plasma concentrations and AUC, although it did not alter the time to peak concentration or the elimination half-life of cisapride. Therefore, it appeared that cimetidine inhibited cisapride metabolism, while cisapride accelerated the gastrointestinal absorption of cimetidine. Similarly, ranitidine tended to increase the bioavailability of cisapride and cisapride tended to accelerate the absorption of ranitidine.

Cisapride reduced the peak concentration of digoxin but it did not modify its AUC_{0-12h} . In

addition, cisapride prolonged the time to the peak concentration of digoxin.

No pharmacokinetic or clinical interactions were found between propranolol and cisapride.

In renal transplant recipients, the absorption of Cyclosporine A was found to be increased, requiring monitoring of Cyclosporine blood levels in those subjects (Gastroenterol 1991;100:A209).

In a placebo-controlled cross-over study, cisapride was indirectly shown to enhance the absorption of acenocoumarol and it significantly prolonged the coagulation time. Therefore, thrombotest values should be checked one week after the start or discontinuation of cisapride treatment in order to properly adjust acenocoumarol dosages. In contrast, cisapride had no significant effect on the PK of phenprocoumon, and there were no statistically significant interactions found between cisapride and warfarin.

Administration of cisapride did not significantly alter the time to the peak plasma concentration of ethanol, the peak concentration or the AUC_{0-4h} . However, cisapride slightly accelerated ethanol absorption and ethanol increased the bioavailability of cisapride (Table 29).

Cisapride increased the peak concentration of diazepam and shortened the time to the peak concentration, increased the AUC_{0-1h} , but did not alter its bioavailability. These changes in diazepam pharmacokinetics were associated with a lowered reaction-time response during the first 45 minutes after diazepam dosing, but did not alter self-rated sedation. There were no differences in reaction time after one hour.

Cisapride did not significantly changes the pharmacokinetics of antipyrine compared to the pretreatment values.

Plasma protein binding in the presence of other drugs

The plasma protein binding of cisapride was not influenced by high therapeutic concentrations of imipramine, propranolol, diazepam, tolbutamide, cimetidine, indomethacin or sulfamethazine. High concentrations of diphenylhydantoin (20 $\mu\text{g}/\text{ml}$) and warfarin (10 $\mu\text{g}/\text{ml}$) caused a relative increase of 8% and 33%, respectively, of the unbound cisapride fraction. Cisapride did not affect the binding of imipramine, propranolol, diphenylhydantoin, diazepam or warfarin.

Table 26: Adverse experiences reported in other foreign studies.

	Cisapride			Placebo Incid. (%)	Active Incid. (%)
	Total Incid. (%)	≤40 mg Incid. (%)	>40 mg Incid. (%)		
# AE pts/Total # pts	60/698 (8.6)	57/635 (9.0)	3/63 (4.8)	29/361 (8.0)	9/78 (11.5)
# pts D/C due to AE	10/698 (1.4)	10/635 (1.6)	0	3/361 (0.8)	6/78 (7.7)
Diarrhea	9 (1.3)	9 (1.4)	--	1 (0.3)	1 (1.3)
Nausea	7 (1.0)	6 (1.0)	1 (1.6)	1 (0.3)	--
Abdominal cramps	6 (0.9)	6 (1.0)	--	--	--
Stomach pain	1 (0.1)	1 (0.2)	--	1 (0.3)	--
Constipation	3 (0.4)	3 (0.5)	--	--	--
Flatulence	1 (0.1)	1 (0.2)	--	--	--
Borborygmi	1 (0.1)	1 (0.2)	--	--	--
Indigestion	1 (0.1)	1 (0.2)	--	--	--
cDysphagia	1 (0.1)	1 (0.2)	--	--	--
Rectal tenesmus	1 (0.1)	1 (0.2)	--	--	--
Strong smelling urine	--	--	--	1 (0.3)	--
Polyuria	3 (0.4)	3 (0.5)	--	1 (0.3)	--
Stimulated appetite	2 (0.3)	2 (0.3)	--	--	--
Headache	5 (0.7)	4 (0.6)	1 (1.6)	5 (1.4)	--
Migraine	1 (0.1)	1 (0.2)	--	--	--
Dizzy	5 (0.7)	5 (0.8)	--	6 (1.7)	--
Light-headed	3 (0.4)	3 (0.5)	--	1 (0.3)	--
Vertigo	1 (0.1)	1 (0.2)	--	1 (0.3)	--
Drowsy	1 (0.1)	1 (0.2)	--	--	--
Tiredness	1 (0.1)	--	1 (1.6)	--	--
Somnolence	--	--	--	--	1 (1.3)
Insomnia	--	--	--	--	1 (1.3)
Difficulty taking med	--	--	--	1 (0.3)	--
Twitching	--	--	--	1 (0.3)	--
Tremor	--	--	--	1 (0.3)	--
Anxiety	--	--	--	2 (0.6)	1 (1.3)
Discomfort	1 (0.1)	1 (0.2)	--	--	--
Numbness	--	--	--	1 (0.3)	1 (1.3)
Tachycardia	2 (0.3)	2 (0.3)	--	--	--
Tension in breasts	2 (0.3)	2 (0.3)	--	--	--
Pruritus, rash	2 (0.3)	2 (0.3)	--	2 (0.6)	--
Micturition	--	--	--	2 (0.6)	--

Table 29: Cisapride-ethanol interaction in sixteen healthy volunteers.

1. Ethanol kinetics following intake of 0.7 g/kg ethanol		
	Control	Cisapride coadministration
T _{max} (min)	73 ± 27	64 ± 22
C _{max} (g/l)	0.75 ± 0.13	0.75 ± 0.14
AUC _{0-4h} (g.h/l)	2.08 ± 0.41	2.03 ± 0.41
2. Cisapride kinetics following a 10 mg cisapride tablet		
	Control	Ethanol coadministration
T _{max} (min)	135 ± 33	146 ± 44
C _{max} (ng/ml)	49.9 ± 16.6	65.0 ± 16.4*
AUC _{0-4h} (ng.h/ml)	113.3 ± 40.6	138.3 ± 48.7*

*P < 0.01

V. LABELING AND PACKAGE INSERT

The package insert will be defined at a later time based on further review and additional information that is not available at this time.

VI. GENERAL CONCLUSIONS

- Three double-blind randomized multicenter trials (MC 121-125;851, MC 1201, and MC 1203) were designed to evaluate the efficacy of cisapride in the treatment of gastroesophageal reflux disease (GERD) characterized by symptoms of heartburn, regurgitations and epigastric pain or endoscopic evidence of esophagitis.
- Study MC 121-125;851 demonstrated that cisapride, 10 mg QID, was superior to placebo in improving subjective symptoms of nighttime heartburn, in decreasing antacid consumption, and in ameliorating global assessment by investigator as well as objective signs of esophagitis (greater reduction of the longest diameter of the largest ulcer, greater mean reduction in the number of erosions when patients starting out with an ulcer were excluded from analysis, greater proportion of normalization of abnormal baseline biopsies, greater improvement of Bernstein test). In patients without esophageal ulcers, subgroup analysis also demonstrated a significant improvement of nighttime heartburn and significantly better overall investigator global assessment and joint improvement of day- and nighttime

heartburn plus antacid use. Similar results were observed in the subgroup of patients with low LESF.

3. Study MC 1201 demonstrated that cisapride 10 mg QID was significantly better than placebo in improving the subjective symptoms of daytime and nighttime heartburn, in decreasing antacid consumption, and in the global assessment by both investigators and patients. However, objective signs of esophagitis improved more than with placebo only in the grade 1 patient subgroup (greater improvement of LESF and Bernstein test). Concordance analysis showed some significant superiority in favor of cisapride 10 mg QID. The 20 mg QID dose showed similar trends, but only a few differences compared to placebo reached statistical significance.
4. The design of MC 1203 was identical to that of MC 1201 except that there was no biopsies, LESF measurements or Bernstein tests. In this trial, cisapride again produced a significantly greater subjective improvement than placebo. However, only the 20 mg QID dose was consistently and significantly superior to placebo, although the 10 mg QID dose was significantly superior to placebo in reducing investigators' and patients' symptom assessment at week 4. In addition, endoscopy demonstrated that the number of patients who improved by two grades and the percentage of patients healed was significantly greater in the cisapride 20 mg QID group compared to placebo.
5. Thus, two protocols (MC 121-125;851 and MC 1201) demonstrate that cisapride 10 mg QID is significantly superior to placebo in improving nighttime heartburn and antacid intake in patients with GERD symptoms. A third protocol (MC 1203) demonstrates that this dose of cisapride is also more effective than placebo at week 4, although only the 20 mg QID dose was consistently and significantly superior to placebo later in the trial.
6. Safety data obtained from those trials and from multiple other sources show that cisapride is generally well tolerated in patients with GERD. The side effects are mostly abdominal pain, constipation, nausea and vomiting. Interestingly, drug-drug interactions demonstrate the efficacy of cisapride as a gastrokinetic agent because it increases the bioavailability of several agents, which will require some adjustment of any polypharmacology. Finally, cisapride should be administered with caution in patients with hepatic and liver insufficiency.

Therefore, I recommend approval of cisapride 10 mg QID for the symptomatic treatment of GERD patients. This treatment should be planned for 12 weeks



Andre Dubois, M.D., Ph.D.

This report contains 60 pages of text, including 15 figures and 29 tables.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

SUMMARY OF FOREIGN STUDIES

NDA 20-210

Propulsid™ (cisapride) Tablets

10 March 1993

Andre Dubois, M.D., Ph.D.

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I. Double-Blind Evaluation of Cisapride in the Treatment of Grades II and III Esophagitis.

Investigators: L. Lepoutre, M.D. et al. Belgium

Twenty-one patients were enrolled in a double-blind, placebo-controlled, multicenter study to determine the effects of oral cisapride on symptoms and lesions associated with gastro-esophageal reflux in patients with documented Grade II or Grade III esophagitis. Eleven patients were randomized to the cisapride group; ten patients were randomized to the placebo group. Nine patients discontinued prematurely, one due to an adverse experience. Only two were not evaluable. However, all patients with data were included in the analysis.

For the first seven days of treatment, each patient took one-half tablet of cisapride 10 mg or placebo 15-30 minutes before each meal and at bedtime. Thereafter, each patient took a whole tablet of cisapride 10 mg or placebo q.i.d. Patients were evaluated at Week 8 of double-blind treatment. If the patient was considered to be "cured" or showed "no distinct improvement", the patient's blinding code could be broken and, if on cisapride, the patient could be withdrawn from the study. Other patients were to remain in the study for 16 weeks. Drug effectiveness was evaluated by symptom assessment, macroscopic and microscopic endoscopy and global assessments.

Symptom severities: Both treatment groups improved from baseline in all the symptoms, except anorexia (which they generally did not have at baseline). In the cisapride group, the improvements were significant for daytime heartburn at Week 8 and Endpoint and for the reflux symptom total score and the total symptom score at Weeks 8 and 16 and Endpoint; in the placebo group the improvements were significant for the reflux symptom total score and for the total symptom score at Week 8 and Endpoint.

The cisapride group had larger mean reductions from baseline than the placebo group at all analysis time points for all the reflux symptoms except nighttime regurgitation. This resulted in the cisapride group having a marginally, significantly ($p=0.06$) larger reduction in the reflux symptom total severity than the placebo group at Week 8 and a significantly ($p=0.04$) larger reduction at Endpoint.

The differences from baseline at Endpoint for the reflux symptoms were:

<u>Symptom</u>	<u>Cisapride</u>	<u>Placebo</u>	<u>p-value</u>
Daytime heartburn	-1.4	-0.6	0.17
Nighttime heartburn	-0.7	-0.2	0.66
Daytime regurgitation	-1.2	-0.6	0.34
Nighttime regurgitation	-0.4	-0.4	0.92
Reflux symptom total	-3.6	-1.8	0.04

There were few differences of any type with the non-reflux symptoms. Since the patients did not really suffer from these at baseline, this is not surprising.

Global assessments: At all analysis time points, the cisapride group received better ratings from both the investigator and patient. At Endpoint with the investigator assessment, the cisapride group received significantly ($p=0.03$) better ratings than the placebo group as seven of the 11 (64%) cisapride patients versus only one of the 9 (11%) placebo patients were rated "Excellent". With the patient assessment at Endpoint, the cisapride group received marginally ($p=0.07$) better ratings than the placebo group as 64% of the cisapride patients versus 22% of the placebo patients were rated "Excellent". At Weeks 8 and 16 with the investigator assessment, the cisapride group received marginally better ratings ($p=0.10$ at Week 8, $p=0.08$ at Week 16), and with the patient assessment, the cisapride group also received better, though not significantly better, ratings.

Endoscopic assessments

At baseline, the cisapride group's mean grade was significantly ($p=0.03$) more severe than the placebo group's (2.4 vs. 1.9). At Weeks 8 and 16 and Endpoint, the cisapride group had mean grade reductions significantly larger than the placebo group. The changes from baseline were:

<u>Time point</u>	<u>Cisapride</u>	<u>Placebo</u>	<u>p-value</u>
Week 8	-1.6	-0.4	<0.01
Week 16	-2.3	-1.0	0.03
Endpoint	-2.1	-0.4	<0.01

Although the cisapride group started out with the more severe mean grade, by Week 8 its mean grade was clearly less severe than the placebo group's. At Endpoint, the mean grades were 0.3 for the cisapride group versus 1.4 for the placebo group. (In order to further show that the superior results in the cisapride group were not simply due to the fact that its mean grade at baseline was more severe, an analysis of covariance on the ranks of the differences from baseline with baseline ranks as the covariate was performed. The cisapride group again had significantly, $p<0.01$, better results at Week 8 and Endpoint and marginally, $p=0.06$, better results at Week 16.)

All of the placebo patients began the study with Grade II, except for one who began with Grade I, while only 7 of the 11 cisapride patients had Grade II, the other four having the more severe Grade III. At Week 8 and Endpoint, the cisapride group had significantly ($p<.01$) more patients with an improved grade than placebo: all the cisapride patients improved versus only 3 of the 9 placebo patients. At Endpoint, 8 of the 11 patients in the cisapride group were healed versus only 1 of 9 in the placebo group ($p=.01$). Of the eight healed cisapride patients, six had initial grades of II, the other two had initial grades of III.

At all time points, the cisapride group received significantly ($p\leq.01$) better ratings for endoscopic global evaluation results than the placebo group. At Endpoint, all but one of the 11 cisapride patients were rated as having a "distinct improvement," while 5 of the 8 rated placebo patients were deemed having "no clear change."

Safety Results

There were no significant between-group differences regarding vital signs, though at Week 8 there was a marginal ($p=0.09$) difference in the change from baseline of diastolic blood pressure (the cisapride group's mean decreased by 2.7 mmHg; the placebo group's mean increased by 4.4 mmHg).

In addition, patient #15 (cisapride) from Dr. Lepoutre's center experienced severe pruritus and was prematurely discontinued. This was the only adverse experience reported.

CONCLUSIONS

Cisapride 10 mg q.i.d. was significantly better than placebo in improving endoscopic grade in patients with esophagitis. Reflux symptom intensities improved substantially from baseline after cisapride, and significantly ($p=0.04$) more than with placebo at Endpoint. Also, the investigator rated the cisapride group significantly better on the global assessments than the placebo group at Weeks 8 ($p\leq 0.10$) and 16 ($p=0.08$) and at Endpoint ($p=0.03$). Cisapride was well-tolerated.

II. Double-Blind Evaluation of Cisapride in the Treatment Chronic Symptomatic Reflux Esophagitis.

Investigators: L. Martin-Abreu, M.D. et al, Mexico, Portugal, Italy, and Brazil.

A total of 213 patients enrolled in this international, multicenter, double-blind, placebo-controlled, six-week study to determine the effects of oral cisapride on symptoms associated with gastro-esophageal reflux in patients with documented Savary-Miller Grades 0, I or II esophagitis. Seven of the 17 investigators agreed to extend the treatment duration to twelve weeks. A total of 199 patients had post-baseline data and, of these, 52 had data beyond the Week 6 visit.

Patients with documented Savary-Miller Grades 0, I or II esophagitis and a minimum of a three-month history of gastroesophageal reflux symptoms were eligible for enrollment. At the end of a two-week single-blind placebo baseline period, the investigators evaluated the patients' symptom severity and frequency scores as criteria for inclusion in the double-blind phase of the study. Enrolled patients were then randomized to receive double-blind cisapride 10 mg or placebo 30 minutes before each meal and at bedtime for six weeks (QID). Patients were permitted to continue treatment for an additional six weeks (at the discretion of the investigator). Effectiveness was measured by symptom assessments and, optionally, endoscopy (compulsory for patients receiving 12 weeks of treatment), biopsy, manometry, pH probe studies and gastric scintigraphy studies.

Intent-to-treat AnalysisSubjective assessments

Baseline comparisons: Considering all of the patients, the groups were generally comparable to each other, with the exception of early satiety severity and the sum of the non-reflux symptom severities, which were significantly more severe in the cisapride group. The severity scores and episode frequencies at baseline were generally highest for daytime heartburn. The symptoms were generally more severe for the reflux symptoms (heartburn and regurgitation) than for the others; the mean severity scores were lower than 0.5 (on a 0-3 scale) for nausea, vomiting, and anorexia.

Considering only the patients continuing beyond Week 6, the groups were comparable for all of the parameters except that the cisapride group had at least marginally significantly ($p \leq 0.09$) more severe and frequent nighttime heartburn than the placebo group.

Symptom severities: Both groups had significantly reduced severities from baseline for most symptoms at most time points. The cisapride group had significantly ($p \leq 0.02$) reduced heartburn severity, both day and night, relative to placebo at Weeks 9, 12 and Week 12-Endpoint. The mean reductions were about 1.4 for the cisapride group and 0.7 for the placebo group. The cisapride group also had marginally ($p = 0.06$) reduced nighttime heartburn relative to placebo at Week 3. The cisapride group also had at least marginally significantly reduced regurgitation severity relative to placebo: at Week 9 ($p = 0.03$) for daytime severity, and at Weeks 3 and 9 ($p \leq 0.08$), and at Week 12 and Week 12-Endpoint ($p \leq 0.01$) for nighttime severity. When these four symptoms (daytime/nighttime heartburn and regurgitation) were combined, the cisapride group was marginally significantly better than placebo at Week 3 ($p = 0.06$) and significantly ($p < 0.01$) better at Weeks 9 and 12 and at Week 12-Endpoint.

For the non-reflux symptoms, the cisapride group had significantly greater reductions than the placebo group at several time points, mostly after Week 6:

<u>Symptom</u>	<u>Weeks</u>
Bloating/distension	9
Eructation	9, 12, 12-Endpoint
Post-prandial bloating	12, 12-Endpoint
Non-reflux symptoms total	6-Endpoint, 9, 12, 12-Endpoint

The cisapride group had a significantly ($p = 0.04$) higher score (more severe) than the placebo group at baseline on the non-reflux symptom total score, indicating that they had more room to improve; at Weeks 9, 12 and 12-Endpoint, their mean symptom score was lower than the placebo group's. Finally, the cisapride group had a significantly greater reduction than the placebo group for the total symptom severity score at Weeks 3 ($p = 0.05$), 6-Endpoint ($p = 0.03$), 9 ($p < 0.01$), 12 ($p < 0.01$) and 12-Endpoint ($p < 0.01$).

Analyses at or before Week 6 (when country was in the statistical model) resulting in at least marginally significant differences between the treatments were accompanied by non-significant treatment-by-country interactions ($p \geq 0.48$). The cisapride group had better results than the placebo group in all of the countries for nighttime heartburn and bloating/distention; in four of the five countries for the Week 3 nighttime regurgitation (Brazil being the exception), Week 3 reflux total symptom assessment (Argentina being the exception), and the Week 3 and 6-Endpoint total symptom assessments (Argentina again being the exception); and in three of the five countries for the Week 6-Endpoint non-reflux total symptom assessment (Argentina and Brazil being the exceptions).

Most of the significant results occurred after six weeks of treatment when only the reduced subset of the patients (mostly from Italy) continued receiving treatment. In this subset, the cisapride group was generally superior to the placebo group at Week 6 and Week 6-Endpoint, as well as after Week 6. The scores at Week 6 and Week 6-Endpoint were generally better for the cisapride group and worse for the placebo group in this subset than among all patients. (However, the significant results at Week 3 among all patients were not due mostly to the patients from Italy. The superiority of cisapride to placebo was at most second largest among the Italian investigators.)

Symptom frequencies: Both groups had significantly reduced frequencies for all of the symptoms at most time points. The cisapride group had a significantly ($p \leq 0.03$) greater reduction than the placebo group in the number of nights with heartburn at Weeks 9, 12 and 12-Endpoint. However, among the patients included in the analyses at these weeks, the cisapride group had significantly ($p = 0.03$) more evenings with heartburn than did the placebo group at baseline; from Week 9 on the groups had about the same number of evenings with heartburn. There were no other significant differences, although the cisapride group displayed marginally significant superiority to the placebo group at Week 12 for daytime heartburn and both daytime and nighttime regurgitation.

The results at all weeks for the subset of patients who continued beyond Week 6 are in Table SBJ.4B. As with the severities, cisapride was more strongly favored up to Week 6 in this subgroup than among all the patients.

Global and other subjective assessments: The cisapride group reported themselves as feeling significantly more improved, according to the Visual Analog Scale (VAS) and the number of Maalox® tablets consumed, during treatment than did the placebo group at all weeks except Week 9, when the cisapride group was only marginally significantly ($p = 0.06$) better than placebo. The mean improvement scores for the cisapride group ranged between 40 and 49 (on the 100-point scale) after Week 3, while they ranged only between 25 and 33 for the placebo group. The treatment-by-country interactions were non-significant ($p \geq 0.78$) and the cisapride group had better results than the placebo group in all five countries.

The cisapride group reduced their mean intake of Maalox® more than the placebo group at all treatment weeks, but this did not reach significance until Week 12 ($p = 0.03$) at which time the cisapride group averaged less than one tablet a day while the placebo group was

still taking an average of 1 1/2 tablets a day. At Week 12-Endpoint, the cisapride group had marginal superiority ($p=0.08$) to placebo.

The results from the VAS and Maalox® tablets analyses in the subset of patients who continued beyond Week 6 were similar to those with all of the patients.

The global assessment results, especially those of the investigators, strongly favored cisapride. The cisapride group was given significantly higher improvement ratings than the placebo group by the investigators at all of the time points. At Week 6-Endpoint ($p=0.01$), 66% of the cisapride patients were rated "excellent" or "good" vs. 53% of the placebo patients. Among the patients continuing beyond Week 6, the percentages rated "excellent" or "good" at Week 12-Endpoint ($p=0.01$) were 68% in the cisapride group and 37% in the placebo group. For the patients' ratings, the cisapride group received marginally, significantly more favorable ratings than the placebo group at Week 6 and significantly ($p=0.04$) more favorable ratings at Week 6-Endpoint. At this time point, 72% of the cisapride patients rated themselves "excellent" or "good" versus only 51% of the placebo patients.

An alternate analysis of the global assessments in Appendix 3 shows that, up to Week 6, there were no significant treatment-by-country interactions. (After Week 6, country was not in the analysis.) The cisapride group had more patients rated "excellent" or "good" than the placebo group in at least three of the five countries, with the best results generally being in Brazil. The numbers and percentages (in parentheses) of patients rated "excellent" or "good" at Week 6-Endpoint in each country were as follows:

Country	Investigator Assessment		Patient Assessment	
	Cisapride	Placebo	Cisapride	Placebo
Italy	15(45)	9(27)	13(50)	8(30)
Portugal	8(80)	7(70)	7(70)	6(60)
Mexico	20(80)	18(69)	20(80)	19(68)
Argentina	8(57)	9(64)	10(71)	9(64)
Brazil	15(88)	9(60)	16(94)	6(40)

Even with Brazil removed from the analysis of the investigator assessment, the cisapride group was still significantly better ($p=0.03$) than the placebo group at Week 6 and marginally ($p=0.07$) better at Week 6-Endpoint. When Brazil was removed from the analysis of the patient assessment, cisapride still had better results than placebo, but by non-significant amounts at both Week 6 ($p=0.24$) and Week 6-Endpoint ($p=0.27$).

Endoscopic Assessments

As already indicated, of the patients who had an endoscopic evaluation beyond baseline, most had either a Week 6 or a Week 12 endoscopy, but not both. Therefore only one Endpoint analysis, using each patient's final endoscopy, was performed.

There were no significant differences in change in grade between cisapride and placebo, although at Week 12 the cisapride group's mean grade reduction of 0.5 approached marginal significance ($p=0.14$) in comparison to the placebo group's mean reduction of 0.1.

There were no significant differences between the groups in terms of the grade frequencies cross-classified by baseline and treatment visit and also presents the numbers of patients whose lesions improved or were healed.

The results of the global endoscopy evaluations show that, at Week 6, there were no differences between the groups, but the cisapride group received significantly better ratings than the placebo group at Week 12 ($p < 0.01$) and Endpoint ($p = 0.05$). At Week 12, 73% of the cisapride patients versus 30% of the placebo patients were considered improved; at Endpoint, the respective percentages were 78% and 62%.

Evaluability Analysis

The primary parameters were re-analyzed in the evaluable patients. Overall, the results were very similar to those of the intent-to-treat analysis. There were, however, some additional time points at which cisapride was marginally significantly superior to placebo for the severity assessments: Weeks 3 and 6-Endpoint for daytime heartburn, and Week 3 for daytime regurgitation. In the patients' global assessments, cisapride was at least marginally superior to placebo at all of the time points except Week 9, while in the intent-to-treat analysis this was the case only at Weeks 6 and 6-Endpoint. Finally, the cisapride group had a marginally, significantly greater mean reduction than the placebo group for the endoscopic grade at Week 12; at no week was cisapride at least marginally better than placebo in the intent-to-treat analysis.

Safety Results

Adverse experiences: Fourteen (14%) of the cisapride patients and 10 (9.7%) of the placebo patients experienced adverse effects. Diarrhea was the most prevalent adverse effect, experienced by five patients in each group. Other adverse experiences reported by more than one patient were dizziness (three cisapride patients and two placebo patients) and constipation (two cisapride patients and one placebo patient). Two cisapride patients prematurely discontinued due to adverse experiences: Patient #49 had moderate somnolence, Patient #148 had severe diarrhea. Two placebo patients (#03 and #17) prematurely discontinued due to severe diarrhea.

Vital signs: There was just one significant difference between the groups: at Week 3, the cisapride group's mean heart rate decreased by 0.3 beats, while the placebo group's increased by 0.8 beats.

CONCLUSIONS

In the intent-to-treat analysis, the cisapride group improved significantly over the placebo group for all of the primary symptom severities after six weeks of treatment. By Week 3, the cisapride group was marginally superior to the placebo group for nighttime heartburn and regurgitation. Cisapride also significantly reduced some non-reflux symptoms (i.e., eructation and postprandial bloating) in comparison to placebo after Week 6. The results of the frequency assessments also showed that the cisapride group was generally improved over the placebo group after six weeks of treatment.

The other subjective assessments also support the effectiveness of cisapride. On the Visual Analog Scale, cisapride patients rated themselves significantly more improved at all time points except Week 9 in comparison to placebo. Maalox® intake was at least marginally reduced in cisapride patients at Week 12 ($p=0.03$) and Week 12-Endpoint ($p=0.08$). On the investigator's global assessments, the cisapride group received significantly better ratings than the placebo group at all analyzed time points. The patient global assessments also significantly favored cisapride.

A majority of the patients did not continue on for the optional additional six weeks of treatment. For the subgroup that continued treatment beyond six weeks, cisapride was generally superior to placebo by Week 6 and Week 6-Endpoint as well as Week 12 and Week 12-Endpoint. Compared to placebo, cisapride 10 mg QID significantly improved the patients' global assessment scores and the primary symptoms of reflux (day and nighttime heartburn and regurgitation) and also the non-reflux symptoms after six weeks of treatment. Significant improvement in global endoscopic assessments was seen in patients after 12 weeks of treatment.

Adverse experiences between the two groups were similar and consisted mainly of diarrhea, dizziness and constipation. Two cisapride patients discontinued prematurely, one due to somnolence and one because of diarrhea; two placebo patients discontinued prematurely due to diarrhea.

III. Double-blind, placebo-controlled comparison between three cisapride dose schedules in the symptomatic treatment of gastroesophageal reflux (GERD)

Investigator: L. Pita-Fernandez, M.D., Spain

Sixty patients were enrolled in a double-blind, placebo-controlled study to compare the effects of three dosages of oral cisapride on symptoms associated with gastro-esophageal reflux (GERD). Forty patients were evaluable.

Patients were randomized to receive either 5, 10 or 20 mg cisapride or placebo 15 to 30 minutes before each meal (t.i.d.) for four weeks. At Weeks 2 and 4, symptoms were re-evaluated and the investigator and patient each completed global assessments.

Intent-to-treat analyses showed that both cisapride 10 mg and 20 mg significantly reduced the severity of individual reflux symptoms, total reflux symptoms score and total symptoms score in comparison to cisapride 5 mg and placebo at Week 2 and Overall. In addition, cisapride 10 mg also reduced the severity of these parameters at Week 4. Except for regurgitation severity (day) among the evaluable patients, there were no significant differences between cisapride 10 mg and cisapride 20 mg. Cisapride 20 mg was associated with more adverse experiences than either the 10 mg or 5 mg dose.

Effectiveness Results

1. Intent-to-treat Analysis

a. Symptom assessments: The groups were comparable at baseline for all assessments. Heartburn was the most severe symptom, followed by early satiety. Vomiting had the lowest severity scores.

All four groups experienced a reduction from baseline in the severity of virtually all the symptoms at most of the time points, quite often by significant amounts.

All three cisapride groups had greater reductions in severity than the placebo group in daytime heartburn. These were significant for the 20 mg group at Week 2 ($p=0.02$) and Overall ($p=0.03$) and at all time points ($p=0.01$) for the 10 mg group. The mean reductions ranged between 1.1 and 1.4 (on a 0-3 scale) for the 20 mg group, 1.1 and 1.7 for the 10 mg group, and 0.1 and 0.6 for the placebo group. The 10 mg group's mean reduction was marginally, significantly better than the 5 mg group's at Week 4. See Figure 1 for a graphical representation of the mean changes.

All three cisapride groups had greater reductions in severity than the placebo group in nighttime heartburn, as well. The reductions in the cisapride groups were all significant, while the placebo group's was not; however, there were no significant differences between the cisapride and placebo groups. See Figure 2.

For both daytime and nighttime regurgitation, all three cisapride groups again had greater reductions in severity than the placebo group. Most of these reductions were significant in the 20 and 10 mg groups while none were in the placebo group. For daytime regurgitation, the cisapride 20 mg group's mean reduction was about 0.5 units while the placebo group's ranged between -0.1 and 0.2. This difference between the groups was significant at Week 2 ($p=0.03$) and marginally so in the Overall analysis. The cisapride 10 mg group's mean reduction ranged between 0.8 and 1.2 and was significantly greater than the placebo group's at all time points ($p<0.01$). Also, the cisapride 10 mg group's reductions were marginally, significantly greater than the cisapride 5 mg group's at both Weeks 2 and 4. There were no significant differences between the groups in nighttime regurgitation. Figure 3 shows the group means for daytime regurgitation and Figure 4 shows them for nighttime regurgitation.

When the four reflux symptoms were totalled, all four groups had significant reductions from baseline at all time points, with the exception of the cisapride 5 mg and placebo groups at Week 2. The mean reductions in the cisapride 20 mg group were significantly greater than the placebo group's at Week 2 ($p<0.01$) and Overall ($p=0.03$) and marginally so at Week 4. The cisapride 10 mg group had significantly greater reductions than the placebo group at all time points ($p\leq 0.01$).

There were two non-reflux symptoms for which the cisapride groups displayed at least marginally significantly greater reductions than the placebo group. The 5 mg group had a significantly greater nausea reduction than placebo (and also the cisapride 10 mg group) at

Week 4, but this is probably because they had a greater amount of nausea at baseline: by Week 4 the actual amounts of nausea were approximately the same. All three cisapride groups had marginally greater reductions than the placebo group for anorexia at Week 2. When the non-reflux symptoms were totalled, the cisapride 20 mg group had significantly ($p=0.04$) greater reductions than both the placebo and cisapride 5 mg groups at Week 2.

Both the cisapride 20 mg and 10 mg groups had significantly greater reductions than the placebo group in the total symptom severity score: at Weeks 2 ($p<0.01$) and Overall ($p=0.03$) for the 20 mg group, and at Weeks 2 ($p<0.01$), 4 ($p=0.04$) and Overall ($p=0.02$) for the 10 mg group. The percentage reductions in the means were:

	<u>Cis 20 mg</u>	<u>Cis 10 mg</u>	<u>Cis 5 mg</u>	<u>Placebo</u>
Week 2	58	46	25	15
Week 4	74	75	58	44
Overall	66	56	42	30

b. Visual Analogue Scale: The groups were comparable at baseline. All the groups improved on treatment by significant amounts. The cisapride 10 mg group improved the most, significantly more so than both the placebo group ($p=0.03$) and the cisapride 5 mg group ($p=0.04$) at Week 2 and marginally more so than the 5 mg group in the Overall analysis.

c. Global assessments: These results are in Table SBJ.3 and Figures 5 and 6. The numbers (percentages) rated "Excellent" or "Good" were as follows:

	<u>Cis 20 mg</u>	<u>Cis 10 mg</u>	<u>Cis 5 mg</u>	<u>Placebo</u>
Inv. Assessment				
Week 2	10 (77)	10 (67)	6 (40)	6 (43)
Week 4	10 (77)	12 (92)	8 (53)	7 (50)
Pat. Assessment				
Week 2	10 (77)	9 (60)	6 (40)	6 (43)
Week 4	10 (77)	12 (92)	8 (53)	6 (43)

The cisapride 20 mg group had significantly ($p=0.02$) better ratings than placebo on both the investigator's and patient's assessment at Week 2. The cisapride 10 mg group had marginally, significantly better ratings than placebo on the patient's assessment at Week 2 and significantly better ratings on both the investigator's ($p=0.05$) and patient's assessments ($p=0.02$) at Week 4.

In addition, the cisapride 5 mg group's ratings were significantly worse as compared to the cisapride 20 mg group's at Week 2 on both the investigator and patient assessments and also as compared to the cisapride 10 mg group's at Week 4 on the investigator assessment.

The chart below lists the parameters for which there were significant differences between any of the cisapride groups and the placebo group in the intent-to-treat analysis.

The chart entries indicate at which weeks (O=Overall), if any, the significant differences

occurred:

<u>Parameter</u>	<u>Cis. 20 mg</u>	<u>Cis. 10 mg.</u>	<u>Cis. 5 mg.</u>
Heartburn-day	2, 0	2, 4, 0	
Regurgitation-day	2, 0 ^M	2, 4, 0	
Reflux symptom total	2, 4 ^M , 0	2, 4, 0	
Nausea			4
Non-reflux symptom total	2		
Total symptoms	2, 0	2, 4, 0	
Visual Analogue Scale			2
Investigator's global*	2	4	
Patient's global*	2	2 ^M , 4	

*: Not assessed in an Overall analysis

M: Marginally, significantly better than placebo

The cisapride 10 mg tid group was effective relative to placebo. The cisapride 20 mg tid group was effective relative to placebo at Week 2 but, due to the increased placebo response, not at Week 4. However, the cisapride 20 mg group was marginally better than the placebo group in the total of the four reflux symptoms at Week 4, and on each individual reflux symptom at Week 4 the 20 mg group had a larger (but non-significant) reduction in severity than the placebo group. Cisapride 5 mg tid was not shown to be an effective dose in this study.

A few comparisons between the cisapride groups were at least marginally significant. In these comparisons, the 5 mg group was found inferior, with the exception of nausea at Week 4, where the 5 mg group was significantly better than the 10 mg group (but this was probably due to the 5 mg group having a greater mean severity at baseline).

2. Evaluable Patients Analysis

a. Symptom assessments: In the daytime heartburn severity assessment, cisapride 20 mg was significantly better than placebo in the Overall analysis, while cisapride 10 mg was significantly better at Week 2 and Overall and marginally better at Week 4. In the nighttime heartburn assessment, cisapride 20 mg was marginally, significantly better than placebo at Week 2 and Overall; cisapride 10 mg was significantly better at Week 2; cisapride 5 mg was significantly better at Week 2 and marginally better in the Overall analysis.

In the daytime regurgitation severity assessment, cisapride 10 mg was significantly better than placebo at Weeks 2, 4 and Overall. Also, cisapride 10 mg had marginally larger reductions than cisapride 20 mg at all time points, but this is probably due to the 10 mg group having a significantly greater severity at baseline. There were no significant between-group comparisons in nighttime regurgitation.

Both cisapride 20 and 10 mg were significantly better than placebo for the total of the reflux symptoms at Week 2 and Overall. In addition, cisapride 10 mg was marginally better at Week 4.

The cisapride 20 and 10 mg groups did not do quite as well here as in comparison to the results from the intent-to-treat analysis. This is partly due to the reduced sample size and to the increased placebo response in the evaluable patients analysis. On the other hand, for nighttime heartburn severity, the cisapride groups were either significantly or marginally better than placebo in the evaluable patients analysis while they were not in the intent-to-treat. This was due to the increased cisapride response in the evaluable patients analysis.

b. Visual Analogue Scale: The placebo group had marginally, significantly worse scores than the cisapride 20 and 10 mg groups at baseline. Despite this, the cisapride 10 mg group improved marginally, significantly more than the placebo group at Week 2.

c. Global assessments: At Week 2, both the cisapride 20 and 10 mg groups had significantly better ratings than placebo on both the investigator's and patient's assessments. At Week 4, the cisapride 10 mg group had significantly better ratings than placebo on both assessments, but the cisapride 20 mg group had significantly better ratings on only the patient's assessment. There were some significant differences between the cisapride groups, too. The 20 mg group was better than the 5 mg group on both assessments at Week 2 and marginally better on the investigator's assessment at Week 4. The 10 mg group was at least marginally, significantly better than the 5 mg group on both assessments at both weeks.

Safety Results

1. Adverse experiences: Three patients in the cisapride 20 mg group, one each in the cisapride 10 and 5 mg groups, and two in the placebo group had adverse experiences. No adverse experience occurred in more than one patient in any group. One patient in the 20 mg group had severe diarrhea, headaches, and palpitations, which led to premature discontinuation. One patient in the 10 mg group also prematurely discontinued due to adverse experiences: he had severe epigastric pain and heartburn (WHO term classification of dyspepsia).

2. Vital signs: The changes from baseline were slight and non-significant, except for the placebo group having a significant mean increase in their systolic blood pressure at Week 4 and Overall. Their Week 4 increase of 5.7 mmHg was marginally, significantly different from the cisapride 20 mg group's mean decrease of 2.7 mmHg. The cisapride 20 mg and placebo groups also had a significant difference on diastolic blood pressure, but in the opposite direction: at Week 2, the 20 mg group's mean pressure increased by 5 mmHg, while the placebo group's decreased by 3.6 mmHg. In the Overall analysis, the two groups were marginally, significantly different in diastolic blood pressure.

CONCLUSIONS

In this group of 60 patients, both the 10 and 20 mg doses of cisapride were significantly better than 5 mg and placebo in reducing the severity of individual reflux symptoms, total reflux symptoms score and total symptoms score overall. There were no significant differences between the 10 and 20 mg doses. However, the 20 mg dose of cisapride was associated with more adverse experiences than either the 5 or 10 mg dose. Cisapride 5 mg was ineffective, and the optimal cisapride dosage for improving symptoms associated with GERD was 10 mg t.i.d.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

SAFETY UPDATE FOR PROPULSID™ (CISAPRIDE) TABLETS

NDA 20-210

19 July 1993

MEDICAL REVIEWER

Andre Dubois, M.D., Ph.D.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
SAFETY UPDATE FOR PROPULSID™ (CISAPRIDE) TABLETS

NDA 20-210

Name of Drug: Propulsid™ (cisapride) Tablets

Sponsor: Janssen Research Foundation

Formulation: Tablets 10 mg for oral administration.

Route of Administration: Oral

Proposed Indications: Treatment of gastroesophageal reflux disease (GERD) characterized by symptoms of heartburn, regurgitations and epigastric pain or endoscopic evidence of esophagitis.

Date of Submission: 5 February 1993. Received on 9 February 1993

Material Submitted: One volume, plus two postmarketing reports received on 25 February 1993.

Date Reviewed: 19 July 1993

Reviewer: Andre Dubois M.D., Ph.D.

Introduction.

The NDA that was previously reviewed presented worldwide exposure of adults to oral cisapride up to March 31, 1990 (for clinical trials) and July 1, 1991 (for deaths and foreign spontaneous reports of adverse experiences). It is based on the investigation of 979 adult patients in 42 clinical trials in the United States and in 3,081 patients in 46 controlled studies in 23 foreign countries. An additional 698 patients in 27 foreign studies have been reported in the literature or by other Janssen affiliates. Finally, 294 subjects (186 healthy volunteers and 108 patients) were exposed to cisapride on an acute basis during US clinical pharmacology studies, and cisapride has also been given to more than 1,000 patients in the US on a compassionate use basis. Cisapride is approved for marketing in 41 countries.

The present safety update report provide data on patients treated with cisapride from 3/31/90 to 7/1/92, while patient deaths are included up to 10/30/92. There were no patients treated for GERD in any double-blind studies, but 74 patients were treated for GERD in open label studies.

I. U.S. CONTROLLED STUDIES

1. Demographics and exposure.

Table I lists the number of patients by indication and treatment in U.S. post NDA studies, some of these patients having received both placebo and cisapride. The non-GERD non-diabetic indications included patients with idiopathic gastroparesis, intestinal pseudo-obstruction, and constipation-predominantly irritable bowel.

Table I. Number of patients by indication and treatment in U.S. post NDA studies. (Data from sponsor's Table PAT. 1, modified in the 29 June 1993 response to inquiry)

	Double-blind		Open cisapride	Total cisapride	All -patients
	Cisapride	Placebo			
Total number of patients	288(182)	164(108)	522	628	684
GERD patients	49	25	74	74	74
Non-GERD					
Diabetics	14(8)	7(4)	122	128	131
Non-diabetics	274(174)	157(104)	326	426	479

Note: The numbers in parentheses in the double blind columns represent the number of patients in each group that went on to open label cisapride. In addition, the double blind GERD patients were already included in the original NDA, and they all went on to open label ($49 + 25 = 74$)

Seventy-six percent of the patients were female, and the mean age was 39 years with a range of 17 to 78 years. The mean duration of exposure was 45.5 days for the double blind studies, and 384 days for the open label study. The total exposure to cisapride was 35.8 years in the double blind studies, and 548.8 years for open label, to a total of 584.7 years. Mean doses were 59.3 and 52.5 mg/day for double blind and open label studies, respectively. Some patients were in both the double-blind and the open cisapride.

2. Discontinuations.

Table II (data excerpted from sponsor's Table USA. 1) lists the reasons for discontinuation of cisapride in U.S. post NDA studies. In the double-blind studies, there was no difference between the % of discontinuation for cisapride-treated (17%) and placebo-treated patients (18.9%). In open treatment studies, the mean duration of treatment was 384 days, i.e. much longer than the double-blind phase where it was 45.5 days. In addition, the % discontinuation for adverse experience and inadequate response was three-fold higher than during the double-blind phase (67.2% vs 17%).

Discontinuation of cisapride due to adverse experiences was less frequent in the post-NDA

period (4.2%) than during the NDA period (5.7%, not shown on table II). In contrast, discontinuation in placebo-treated patients was more frequent during the post-NDA period (4.3%) than in the original NDA (2.9%, not shown on table II). In the post-NDA open-label studies, discontinuation occurred in 13.8% of cisapride patients i.e. slightly higher than during the already reviewed NDA period where it was 10.7% (not shown on table II).

Gastrointestinal disorders were the cause of most discontinuations. In the post-NDA double-blind studies, 2.4% of cisapride-treated patients discontinued due to G.I. adverse experiences vs. 1.8% of placebo-treated patients (Table II). This frequency was similar to that observed during the NDA (2.9% for cisapride vs 1.1% for placebo (not shown on table II). Discontinuations due to central and peripheral nervous system disorders was lower (1% for cisapride vs. 6% for placebo in double-blind trial and 2.7% in the open-label for the post-NDA observation period). One discontinuation was due to tremors, but convulsions were not reported to cause discontinuation in the post-NDA experience. In the double blind cisapride-treated patients, no discontinuation related to heart rate and cardiac rhythm disorders was reported vs. a 0.6% incidence in placebo-treated patients. Open-label administration of cisapride resulted in three discontinuations (0.6%) related to heart rate and cardiac rhythm disorders, (palpitation: 1; arrhythmia: 1; and death due to cardiac arrest: 1 in a diabetic patient with gastroparesis who died of pneumocystosis pneumonia).

Table II. Reason for discontinuation in U.S. post NDA studies. (Data excerpted from sponsor's Table USA. 1)

	Double-blind		Open cisapride N (%)
	Cisapride N (%)	Placebo N (%)	
Entered	288	164	522
Discontinued	49 (17%)	31 (18.9%)	351 (67.2%)
Adverse experience (total)	12 (4.2%)	7 (4.3%)	72 (13.8%)
Adverse experience (GI disorders)	7 (2.4)	3 (1.8)	36 (6.9)
Inadequate response	19 (6.6%)	14 (8.5%)	140 (26.8%)
Chose to discontinue	2 (0.7%)	2 (1.2%)	34 (6.5%)
Lost to follow up	3 (1%)	2 (1.2%)	38 (7.3%)
Uncooperative	3 (1%)	1 (0.6%)	14 (2.7%)
Ineligible	6 (2.1%)	3 (1.8%)	2 (0.4%)
Asymptomatic/Insufficient response	0 (0%)	0 (0%)	2 (0.4%)
Withdrew consent	0 (0%)	1 (0.6%)	9 (1.7%)
Other reason	4 (1.4%)	1 (0.6%)	40 (7.7%)

Discontinuation due to metabolic and nutritional disorders occurred in 1.7% of the post-NDA open-label cisapride patients, and in 1.0% in the NDA. This slight increase may be due to the increased number of diabetics receiving cisapride over a longer period of time.

3. Adverse experiences

The overall frequencies of adverse experiences reported in the U.S. population are listed in Table III for the NDA experience, in Table IV for the post NDA experience, and in Table V for the combined NDA and post NDA experience. Data have been excerpted from the sponsor's Tables USA. 3 and 4. In the double-blind phase, adverse experiences reported by the cisapride-treated patients was higher in the post-NDA studies (79.9%) than in the NDA studies (64.1%). The open-label studies and the total cisapride experience displayed the same increase in incidence of adverse experience. Finally, a similar increase in incidence was also seen in the placebo-treated patients, where there was an increase from 55.9% in the NDA to 78.0% in the post-NDA period. As suggested by the sponsor, these increases probably reflect the fact that the indications for cisapride therapy were more severe in the post-NDA experience than in the NDA (GERD). Tables III, IV, and V also list the frequencies of gastrointestinal and heart rates and rhythm disorders.

a. Gastrointestinal side effects represent the highest incidence of adverse events. In the NDA double-blind studies, diarrhea, abdominal pain, nausea, vomiting and constipation were more frequently reported by patients receiving cisapride than by those receiving placebo (Table III). In the post-NDA double-blind studies, only diarrhea, abdominal pain and constipation were more frequently reported by cisapride-treated patients than by placebo-treated patients, whereas nausea and vomiting were reported 2.5 to 3 times more frequently by placebo-treated patients than by cisapride-treated patients (Table IV). Overall, gastrointestinal adverse reactions were reported with similar frequencies in double blind cisapride and placebo groups when stratified by gender, race, dose, and duration of treatment. However, diarrhea was reported by 108/691 females (15.6%) vs. 40/351 males (11.4%), and abdominal pain was reported by 82/691 females (11.9%) and by 24/351 males (6.8%). In addition, the total frequency of gastrointestinal side effects increased when open cisapride was taken for 3-12 months (195/354, 55.1%) compared to 1-3 months (54/146, 37%), and it increased further when open cisapride was taken for >12 months (229/327, 70%). This frequency increase was evenly distributed among the various side effects reported, and similar increases were observed when considering the total cisapride group (double blind plus open label).

b. Heart rate and cardiac rhythm disorders was reported with a similar frequency in cisapride-treated patients and in placebo-treated patients overall (Table V), although the incidence was higher for cisapride in the NDA double-blind studies (Table III) and lower in the post NDA double-blind studies (Table IV). In contrast, the frequency increased from 3.6% to 5.7% in the open label cisapride NDA vs. post-NDA, possibly because of the different population treated, or perhaps because of the longer duration of exposure to cisapride. This type of adverse experience is also discussed below under III. Data on non-U.S. experience, below. Heart rate and cardiac rhythm disorders were reported with similar frequencies in double blind cisapride and placebo groups when stratified by gender, race, dose, and duration of treatment. In addition, the total frequency of these adverse reactions increased when open cisapride was taken for 1-3 months (5/146, 3.4%) and 3-12 months (17/354, 4.8%) compared to <1 month (2/165, 1.2%), and it increased further when open cisapride was taken for >12 months (21/327, 6.4%). This increase was evenly distributed among the various side effects reported, although heart block was reported in only one case who received ≥ 80 mg cisapride double blind for 1-3 months. Finally, similar

increases were observed when considering the total cisapride group (double blind plus open label) although, as expected, heart block was observed only in the case who received ≥ 80 mg cisapride double blind for 1-3 months.

Table III. Summary of adverse experience by WHO body class and treatment group (NDA)(Data excerpted from sponsor's Table USA. 3).

WHO body class/ WHO preferred term	Double-blind			Open Cisapride	Total Cisapride
	Cisapride	Placebo	Metoclopramide		
Total number of patients	754	522	11	523	979
Number with adverse experience (%)	485 (64.1)	292 (55.9)	6 (54.5)	390 (74.6)	732 (74.8)
GI disorders (%)	262 (34.7)	144 (27.6)	4 (36.4)	247 (47.2)	454 (46.4)
diarrhea	110 (14.5)	61 (11.7)	0	90 (17.2)	187 (19.1)
abdominal pain	65 (8.6)	35 (6.7)	0	89 (17)	141 (14.4)
nausea	59 (7.8)	24 (4.6)	0	91 (17.4)	145 (14.8)
vomiting	55 (7.3)	23 (4.4)	4 (36.4)	72 (13.8)	121 (12.4)
constipation	42 (5.6)	16 (3.1)	0	31 (5.9)	69 (7)
flatulence	19 (2.5)	13 (2.5)	0	41 (7.8)	58 (5.9)
dyspepsia	14 (1.9)	2 (0.4)	0	22 (4.2)	34 (3.5)
hematemesis	8 (1.1)	3 (0.6)	0	4 (0.8)	12 (1.2)
eructations	6 (0.8)	1 (0.2)	0	7 (1.3)	13 (1.3)
Heart rate & rhythm disorders (%)	11 (1.5)	2 (0.4)	0	19 (3.6)	28 (2.9)
Palpitations	7 (0.9)	1 (0.2)	0	10 (1.9)	15 (1.5)
Tachycardia	1 (0.1)	0	0	5 (1.0)	6 (0.6)
Arrhythmia	1 (0.1)	1 (0.2)	0	2 (0.4)	3 (0.3)
Atrial fibrillation	1 (0.1)	0	0	1 (0.2)	2 (0.2)
Heart block	1 (0.1)	0	0	0	1 (0.1)
Supraventr. Tachyc.	0	0	0	1 (0.2)	0
Cardiac arrest	0	0	0	1 (0.2)	1 (0.1)

Table IV. Summary of adverse experience by WHO body class and treatment group (post NDA)(Data excerpted from sponsor's Table USA. 3).

WHO body class/ WHO preferred term	Double-blind		Open Cisapride	Total Cisapride
	Cisapride	Placebo		
Total number of patients	288	164	522	628
Number with adverse experience (%)	230 (79.9)	128 (78.0)	457 (87.5)	553 (88.1)
GI disorders (%)	127 (44.1)	66 (40.2)	327 (62.6)	389 (61.9)
diarrhea	38 (13.2)	10 (6.1)	104 (19.9)	127 (20.2)
abdominal pain	41 (14.2)	18 (11)	116 (22.2)	141 (22.5)
nausea	20 (6.9)	28 (17.1)	136 (26.1)	149 (23.7)
vomiting	15 (5.2)	25 (15.2)	131 (25.1)	139 (22.1)
constipation	28 (9.7)	7 (4.3)	76 (14.6)	93 (14.8)
flatulence	17 (5.9)	8 (4.9)	42 (8.0)	51 (8.1)
dyspepsia	14 (4.9)	5 (3)	45 (8.6)	54 (8.6)
hematemesis	1 (0.3)	1 (0.6)	7 (1.3)	7 (1.1)
eructations	3 (1)	1 (0.6)	18 (3.4)	21 (3.3)
Heart rate & rhythm disorders (%)	5 (1.7)	6 (3.7)	30 (5.7)	34 (5.4)
Palpitations	2 (0.7)	4 (2.4)	15 (2.9)	17 (2.7)
Tachycardia	1 (0.3)	2 (1.2)	9 (1.7)	10 (1.6)
Arrhythmia	3 (1.0)	0	6 (1.1)	3 (0.5)
Atrial fibrillation	0	0	0	9 (1.4)
Heart block	0	0	0	0
Supraventr. Tachyc.	0	0	1 (0.2)	1 (0.2)
Cardiac arrest	0	0	1 (0.2)	1 (0.1)

Table V. Summary of adverse experience by WHO body class and treatment group (NDA and post NDA combined)(Data excerpted from sponsor's Table USA. 4).

WHO body class/ WHO preferred term	Double-blind			Open Cisapride	Total Cisapride
	Cisapride	Placebo	Metoclopramide		
Total number of patients	1042	686	11	996	1447
Number with adverse experience (%)	713 (68.4)	420 (61.2)	6 (54.5)	798 (80.1)	1160 (80.2)
GI disorders (%)	389 (37.3)	210 (30.6)	4 (36.4)	534 (53.6)	767 (53.0)
diarrhea	148 (14.2)	71(10.3)	0 (0)	178 (17.9)	291 (20.1)
abdominal pain	106 (10.2)	53 (7.7)	0 (0)	193 (19.4)	266 (18.4)
nausea	79 (7.6)	52 (7.6)	0 (0)	205 (20.6)	259 (17.9)
vomiting	70 (6.7)	23 (3.4)	0 (0)	101 (10.1)	152 (10.5)
constipation	70 (6.7)	48 (7)	4 (36.4)	181 (18.2)	225 (15.5)
flatulence	36 (3.5)	21 (3.1)	0 (0)	74 (7.4)	99 (6.8)
dyspepsia	28 (2.7)	7 (1)	0 (0)	60 (6)	80 (5.5)
hematemesis	9 (0.9)	2 (0.3)	0 (0)	21 (2.1)	30 (2.1)
eructations	9 (0.9)	4 (0.6)	0 (0)	11 (1.1)	19 (1.3)
Heart rate & rhythm disorders (%)	16 (1.5)	8 (1.2)	0	45 (4.5)	57 (3.9)
Palpitations	9 (0.9)	5 (0.7)	0	25 (2.5)	32 (2.2)
Tachycardia	2 (0.2)	2 (0.3)	0	11 (1.1)	13 (0.9)
Arrhythmia	4 (0.4)	1 (0.1)	0	8 (0.8)*	10 (0.7)
Atrial fibrillation	1 (0.1)	0	0	1 (0.1)	2 (0.1)
Heart block	1 (0.1)	0	0	0	1 (0.1)
Supraventr. Tachyc.	0	0	0	1 (0.1)	1 (0.1)
Cardiac arrest	0	0	0	2 (0.2)	2 (0.2)

*: A total of 7 cases of arrhythmia (2 ventricular arrhythmia, 5 arrhythmia and no atrial arrhythmia), are listed in the table provided by the sponsor (Table USA. 4), whereas the sponsor's Table USA. 3 and this review's Tables III and IV list 2 and 6 cases of arrhythmia, respectively. Although the sponsor provides no explanation for the discrepancy, this may be due to the fact that one subject was included both in the NDA and in the post NDA incidence.

Other frequently reported side effects reported by the sponsor but not listed on the above tables were:

a. Central and peripheral nervous system disorders were reported by 32% of cisapride patients in the post NDA double blind studies, an increase from 22% in the NDA for the double blind studies. A similar, albeit numerically smaller, increase was observed in the placebo treated patients (22.0% to 29.9). Headache had the highest frequency, increasing from 17.1% (NDA) to 25% (post-NDA) in cisapride-treated patients and from 15.3% (NDA) to 22.6% (post-NDA) in placebo-treated patients. In double-blind studies, six cisapride patients reported tremors, which were not observed in any of placebo patients while open-label cisapride was

associated with eight reports of tremors. Convulsions were not reported in the post-NDA studies, compared to five such reports in the NDA. One case of grand mal seizure that was reported in the NDA is also reported here by the sponsor as the study of this case was completed after the submission of NDA.

b. Metabolic and nutritional disorders were observed with similar frequency for cisapride and placebo in the double-blind studies (5.2% vs 5.5%, respectively). However, these disorders were observed in 15.9% of the total cisapride population in the post NDA studies. This increase is probably due to inclusion of diabetic patients treated over long periods during open-label studies. Thus, adverse experiences commonly reported by insulin-dependent diabetics were observed: dehydration, hypoglycemia, ketosis and hyperglycemia.

3. Deaths

Seven patients who were treated under protocol-controlled studies died since 30 March 1991, the cut-off date for the material submitted in the NDA, but six of these deaths were reported in the NDA because they occurred between March 30, 1991 and the actual date at which the NDA was submitted. These deaths were discussed in the original Medical Officer's review. One additional death not described in the NDA was in a 43-year-old male with diabetes mellitus and gastroparesis who also had hypertension, coronary artery disease, anemia and end-stage renal disease which led to a renal transplant on January 6, 1991. He had taken cisapride for almost two years, usually at 60 mg/day. He stopped cisapride therapy on 18 December 1991, 41 days prior to his death. He developed complications leading to pneumocystosis pneumonia, which was the reported cause of death on January 29, 1991.

II. UPDATE OF U.S. PATIENTS TREATED ON A COMPASSIONATE BASIS.

The indications for which cisapride was administered were:

- gastroesophageal reflux disease (48 patients) and

Discontinuation due to adverse experiences occurred in 48 of these patients. These adverse experiences were similar to those reviewed above in Section I for controlled studies, were usually multiple and included the following:

- headache (9 patients)
- nausea (6 patients)
- vomiting (6 patients)
- abdominal pain and cramping (12 patients)
- diarrhea (9 patients)

- bloating (2 patients)
- blurred vision (4 patients)
- rash (1 patient)
- palpitations and increased heart rate (1 patient)*.
- loss of consciousness for 3 minutes (1 patient)**

* 39-year-old female treated for _____ received cisapride at 60 mg/day for 4 days. Discontinuation of cisapride resulted in recovery and there was no rechallenge. ** 36-year-old female, treated for _____ symptoms on the second day of treatment at a dose of 20 mg TID. Discontinuation of cisapride resulted in recovery and there was no rechallenge.

Deaths occurred in 23 patients between March 1991 and November 1, 1992, 8 of which were insulin-dependent diabetics treated for _____, 3 patients, 1 patient and one _____ patient. The daily dose of cisapride was usually 60 mg/day, except for 3 patients given 80 mg/day. Therapy was given from 56 to 1090 days. No death were associated with the initiation of cisapride, and most patients had been taking cisapride for extended periods of time before their death. The causes of death were listed as follows:

- sepsis due to fungal infection
- uremia
- massive transmural bowel infarction
- two cases of thrombotic coronary heart disease
- two cases of chronic renal failure in diabetic patients
- probable terminal cardiac arrhythmia 4 months after anterior myocardial infarct
- suicide (patient shot herself)
- complication of chordoma (no other information available)
- respiratory arrest in a type I diabetic patient taking multiple medications
- cardiorespiratory arrest due to hypertensive cardiovascular disease/diabetes mellitus
- two cases of myocardial infarction due to atherosclerosis and diabetes mellitus
- brain hemorrhage due to acute episode of hypertension
- cerebrovascular accident due to diabetes
- adenocarcinoma of the lung
- septicemia
- cardiopulmonary arrest due to polymyopathy
- cardiac arrest during transportation
- cardiopulmonary arrest in an insulin-dependent diabetic
- cardiac arrhythmia secondary to severe hypoxia due to pulmonary failure

These causes are similar to those discussed in the original NDA review.

Patients given cisapride for compassionate use in general belong to a more medically fragile group and the incidence of deaths and drop-outs is expected to be higher in this group than in patients treated for GERD. However, the type of reactions that were observed were similar to those observed with a lesser frequency in controlled studies patients.

III. DATA ON NON-U.S. EXPERIENCE.

Thirty serious adverse drug experiences were reported for the period 6/1/90 to 7/1/92, and these should be listed in the labeling. They included:

- central nervous system (12 cases), including convulsions (6 cases) and extrapyramidal events (5 cases)
- hepatic dysfunction (4 cases), including hepatitis (1 case), jaundice (2 cases), and elevated liver enzymes (1 case).
- blood abnormalities (3 cases) including leukopenia (1 case), aplastic anemia and pancytopenia (1 case) and granulocytopenia (1 case)
- cardiovascular events: bradycardia with syncope (1 case) and one myocardial infarction (1 case)
- pancreatitis (2 cases): one recovered and no other information is available on the other patient
- extrapyramidal symptoms (3 cases) [one 16 year old girl receiving concurrently cimetidine, one in a 72 year old female receiving concurrently diazepam and dolviran, and one 75 year old female receiving concurrently metoclopramide and sulphiride]
- dyskinesia in a 46 year old female [other medications not stated]
- tardive dyskinesia, muscle rigidity and convulsions in an 80 year old female receiving diazepam, kodimagnyl and lactulose
- malignant lymphoma (1 case)

In general, this reviewer agrees with the sponsor statement that there is no clear relationship between these adverse experiences and cisapride. However, the one report of extrapyramidal symptoms in a 16 year old girl receiving concurrently only cimetidine is intriguing, and will warrant further analysis if a pediatric indication is submitted. Specifically, the sponsor should, at that time, determine the frequency of extrapyramidal reactions in pediatric patients receiving histamine H₂ receptor antagonists at high doses, as well as in association with cispride.

In addition, an article in the British Medical Journal reported that seven patients experienced tachycardia during treatment with cisapride (Sten Olsson and I Ralph Edward. Tachycardia During Cisapride Treatment Brit Med J 1992;305:748-9). Importantly, all symptoms disappeared 1 to 5 days after cisapride was withdrawn, and the symptoms returned in the 3 patients who were rechallenged. At the request of the FDA, the sponsor, to whom these cases had not been reported, requested additional information from each of the four countries concerned. In a 21 December 1992 letter to the FDA that is included in volume 11.1, the sponsor provides the following limited information obtained on 3 of the 7 cases.

The first patient was a 57-year-old female receiving 30 mg/day of cisapride for gastroesophageal reflux. Palpitations began one day after starting treatment with cisapride, and stopped three days after discontinuation of the drug. No information regarding rechallenge is available.

The second patient, a 62-year-old diabetic male treated with cisapride at 15 mg/day for gastroesophageal reflux, experienced supraventricular extrasystoles

after one day of cisapride therapy. Cisapride was discontinued and extrasystoles disappeared within one day. Severe extrasystoles were observed upon rechallenge.

The third patient, a 47-year-old male receiving cisapride at 30 mg/day for experienced paresthesia, palpitations and pain 15 days after onset of therapy, and the symptoms continued for 2 months. Symptoms disappeared 5 days after discontinuation of treatment.

This British Medical Journal article prompted two additional letters to the Editor. In the first of these letters (Brit Med J 1992;305:1015), Inman and Kubota reviewed their own cardiac monitoring data in 13,233 patients receiving cisapride, and observed that the frequency of tachycardia, extrasystoles, and palpitations in this group was 0.8/1000, similar to the frequency observed after other medications. In addition, they reviewed 104 cardiac monitoring data in patients with palpitations (N=67), tachycardia (N=23), extrasystoles (N=5), and heart block (N=9). They concluded that all these events were coincidental. In the second letter, Humphrey and Bunce (Brit Med J 1992;305:1015) note that 5-HT₄ receptors are present in both the pig heart and the human right atrium, and that 5-HT₄ receptor agonists produce tachycardia in a pig model (Villalon CM, den Boer MO, Heiligers JP, Saxena PR. Further characterization, by use of tryptamine and benzamide derivatives, of the putative 5-HT₄ receptor mediating tachycardia in the pig. Br J Pharmacol 1991;102:107-112). They conclude that the tachycardiac response to cisapride in humans may be due to activation of atrial 5HT₄ receptors. In addition they hypothesize that the low frequency of this occurrence in clinical practice may be due to the weakness of the agonistic properties of cisapride at the level of these receptor in the human heart.

The sponsor also received information on 4 additional cases from the UK that were not reported in the Olsson and Edwards article. These cases were 46- to 67-year-old females treated with cisapride 30 mg/day (one patient dose unknown) for constipation (one case), gastroesophageal reflux or esophagitis (3 cases). Symptoms included palpitations (2 cases), tachycardia, dyspnea, hypertension and chest pain (1 case), and sinus tachycardia and angina pectoris (1 case). Three of those patients recovered after cisapride discontinuation, while the response of the fourth subject was unknown. The sponsor states that review of these cases indicates that none of these 11 cases had an unexpected event, or serious outcome that would warrant a 10-day report.

The sponsor's review of the total safety database on cisapride (979 patients in U.S. controlled studies, 3081 patients in non-U.S. studies and 1014 from U.S. Compassionate Clearance) indicates that there were 55 reports classified as "Heart Rate and Rhythm Disorders". The sponsor provided 6 tables that are attached as an Appendix to this Report. These tables were labeled using arabic numerals from 1 to 6, as apposed to the tables included in this report, which are labeled using roman numerals. Based these tables, the sponsor stated:

"Fourty of these 55 were palpitation (n =28) or tachycardia (n =12). Thirteen patients prematurely discontinued: four from the U.S. trials (1 due to palpitation, 1 arrhythmia, 1 cardiac arrest and 1 atrial fibrillation), one in foreign trials (due to palpitation) and eight in the U.S. Compassionate Clearance (2 due to palpitation, 2 tachycardia, 1 ventricular tachycardia, 2 cardiac arrest and 1 arrhythmia). Of the 55 reports, 48 were from patients in the US (28 in controlled

studies and 20 in Compassionate Clearance). Of the 28 reports in the controlled studies, 11 occurred during double blind treatment, none of whom discontinued. Of the 28 U.S. study patients who had the designation Heart Rate and Rhythm Disorders, 15 had palpitation and 6 tachycardia. Of the 20 Compassionate Clearance patients, 7 had palpitation and 6 tachycardia. Of the 328 patients enrolled in the US GERD studies, there were 5 reports classified as Heart Rate and Rhythm Disorders (Table 4). There were no premature discontinuation. The incidence rate was 0.6% for palpitation and 0.3% for tachycardia; the incidences in GERD patients who received placebo were 0.5% and 0% respectively."

In addition, the sponsor states:

"Since the introduction of cisapride in 1988, more than 70 million patients have been treated worldwide and the product is available in 56 countries. In view of this extensive use, it is not unusual to observe commonly reported complaints such as palpitations or extrasystoles. The incidence of such adverse events associated with cisapride treatment that have been reported to the sponsor to date is 2 per 10 million patients treated worldwide. "

Finally, the sponsor received four 10-day safety reports on six patients since the filing of the NDA, and these have been submitted previously by the sponsor to the FDA. Three of these were included in the cases reviewed above. The remaining three cases were as follows:

The first one, filed 14 May 1992, reports a case of convulsions in a newborn delivered by cesarean section under epidural anesthesia and administration of 50 mg clorazepate. There was no sign of fetal distress until 5 min after birth when the newborn displayed bradycardia, pallor, hypertonic movements and cyanosis. The mother had scleroderma and she had taken 40 mg cisapride daily throughout her pregnancy, in addition to colchicine during the first month and 300 mg vitamin E daily, probably throughout pregnancy. A follow up, filed July 27, 1992 reports that the child experienced similar convulsive episodes on day 2 and four weeks later, despite the treatment with phenobarbital that was instituted on day 2. Phenobarbital dosage was increased, and diazepam was added to the treatment. However, the child was still experiencing clonic convulsions by the age of 5 months. This reviewer agrees with the suggestion made by the sponsor that clorazepate may have been responsible for the incident. However, prematurity and fetal distress during pregnancy may have predisposed the child to idiopathic epilepsy, as suggested by the physician.

Two other cases, reported on 12 December 1992 were patients who developed toxic epidermal necrolysis (TEN) and subsequently died. One patient was a 69-year-old female with liver cirrhosis who received suspension cisapride for 1 month before developing TEN. She was receiving multiple medications including furosemide, which has been reported to be associated with severe dermatologic reactions. She apparently recovered from this complication, but she died 6 days later of cardiocirculatory arrest. The other patient was a 36-year-old female suffering from various diseases including leukemia, liver cirrhosis, dyspepsia, ... and receiving 40 different medications including cisapride suspension for the indication of cirrhosis. She developed TEN 11 days after starting cisapride, and 1 day after completion of a 7-day treatment with ciproflaxin.

This latter agent has been associated with severe skin reaction including TEN. The patient died of intracranial bleeding 18 days later. In the same letter dated 3 December 1992, a third case was reported for which the diagnosis of TEN is possible. This is a 59-year-old male who developed a purpuric rash after 5 days of 30 mg p.o. cisapride. Follow-up was in progress at that time.

IV. POSTMARKETING REPORT OF THROMBOCYTOPENIA

A postmarketing report of two cases of thrombocytopenia was filed by the sponsor on 22 February 1993.

The first case is a 62-year-old female who was taking 60 mg cisapride per day for an unspecified indication. She developed purpura of the lower extremities 48 h after initiation of therapy. Platelets decreased to 13,000 and then 4,000, and multiple bleeding sites and hemorrhages were observed. Lansoprasole, which was concurrently administered was immediately discontinued, while cisapride was continued for 4 days. The diagnosis of cytomegalovirus infection was made, and the patient recovered. Cisapride and lansoprazole were not restarted. However, based on the case for which follow-up information is provided below, it appears that the purpura was not related to cisapride administration.

The second case is that of a 37-year-old female who was given a 4-day course of 7.5 mg cisapride per day for [redacted] and developed gingival bleeding and purpura 8 days after the end of this treatment. She was hospitalized and hematuria and thrombocytopenia as low as 21,000 was recorded. Bone marrow biopsy showed a decrease in megakaryocytes and a test for antiplatelet antibody was negative. At the time of hospitalization, the patient had a respiratory infection and was taking multiple medications, which suggests that either viral infection or other medication may have caused the adverse event.

The same letter provides follow-up information on another case of thrombocytopenia reported to the Agency on 28 January 1993. In that patient, asymptomatic thrombocytopenia at 53,000 was noted during cisapride therapy for [redacted]. Platelet count normalized after cessation of cisapride, but rechallenge with cisapride did not cause a relapse of thrombocytopenia, and the patient has been maintained on cisapride without further complications. This event was attributed to an intercurrent viral illness.

V. GENERAL CONCLUSIONS

Safety data reported in the present safety update confirm the conclusion drawn in this reviewer's evaluation of the NDA, i.e. that cisapride is generally well tolerated in patients with various diseases including GERD. Gastrointestinal side effects are the most frequently reported adverse effects, and these include abdominal pain, constipation, nausea and vomiting. In the sponsor's NDA plus post-NDA database, a total of eight patients were treated with open cisapride after discontinuing double-blind treatment due to adverse experiences, indicating that a majority of the

adverse reactions reported by the sponsor do not reappear when challenged on an open label basis. However, heart rate and rhythm disorders should be discussed in the labeling as at least one paper demonstrates that rechallenge precipitated relapse, and because there is a pharmacological basis for this effect. However, the risk seems very low when considering the large number of patients who have been treated worldwide. The neurological adverse effects should also be mentioned in the labeling, although the patients who experienced these complications had multiple diseases and were taking several medication that could be responsible for the events. The observation of drug-drug interactions reported in the NDA should also be discussed, as cisapride is a gastrokinetic agent which may increase the bioavailability of several medications, and this may require adjustment of any polypharmacology. Finally, cisapride should be administered with caution in patients with hepatic and liver insufficiency.



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