

05 Nov 1992

NDA: 20-210  
CISAPRIDE (PROPULSID<sup>®</sup>) TABLETS  
10 & 20 mg  
Janssen Research Foundation  
40 Kingsbridge Rd, Piscataway, NJ 08855

SUBMISSION DATES:  
10/19/1992

REVIEWER:  
Hisham Y. Abdallah, Ph.D.

TYPE OF SUBMISSION: Response to Biopharmaceutics Comments

**BACKGROUND:**

This submission responds to two letters from the Division of GI and Coagulation Products dated 5/18/92 and 7/29/92 conveying chemistry and biopharmaceutics comments, respectively. The following is a review of the biopharmaceutics part of the submission.

**Comment #1:**

Please include ranges for the excipients. With respect to magnesium stearate, if the range is  $> \pm 10\%$ , present data that at the high end of the range, there is no detrimental effect on *in-vivo* performance of the tablets.

**Janssen Response:**

Ranges are not used for any excipients including magnesium stearate. The exact formula is specified in the batch worksheet and materials are weighed on appropriate balances.

**Comment #2:**

Based on solubility data, "sink conditions" are not achieved in the proposed dissolution method, especially for the 20-mg tablet. Such conditions may be attainable in 0.01N HCl. Please submit dissolution data in 0.01N HCl.

**Janssen Response: (see attachment)**

The firm submitted data on dissolution of the 10-mg and 20-mg tablets in 0.1N and 0.01N HCl as well as equilibrium solubility data in both media. Higher solubility of the drug substance and faster dissolution of the 20-mg tablets were observed in 0.01N HCl compared to 0.1N HCl. The medium used for dissolution testing of both tablet strengths has been revised to 0.01N HCl instead of 0.1N HCl.

**Recommendation:**

This submission (NDA 20-210; submission date 10/19/1992) has been reviewed by the Division of Biopharmaceutics. This firm's response is acceptable.

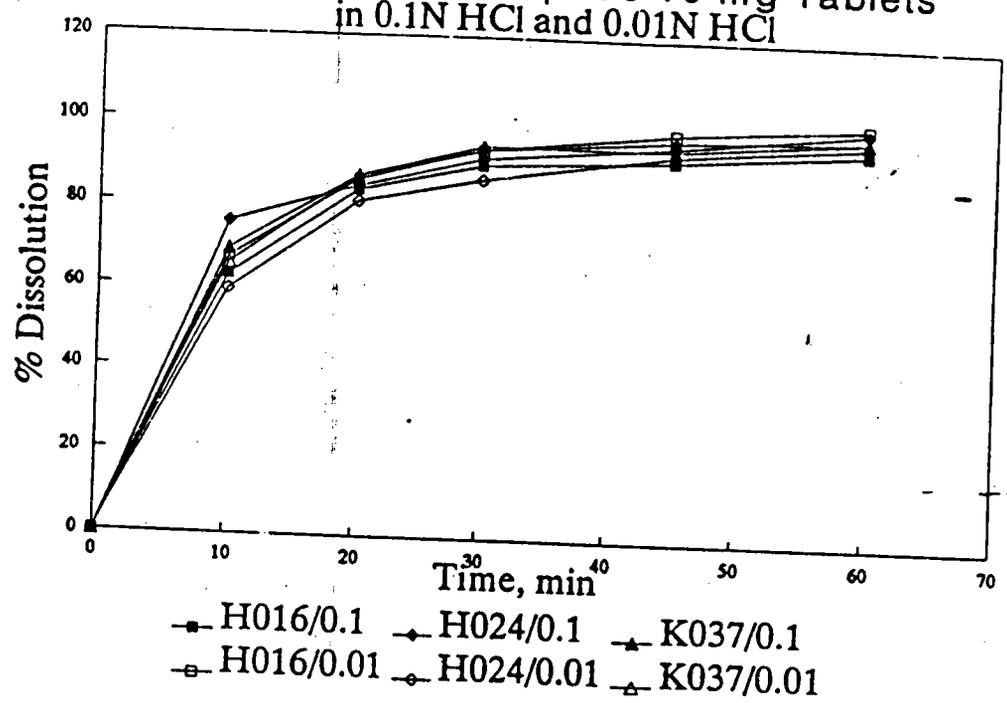
*Hisham Y. Abdallah* 11/3/92  
Hisham Y. Abdallah, Ph.D.  
Pharmacokinetics Review Branch

FT initialled by Nicholas Fleischer, Ph.D.

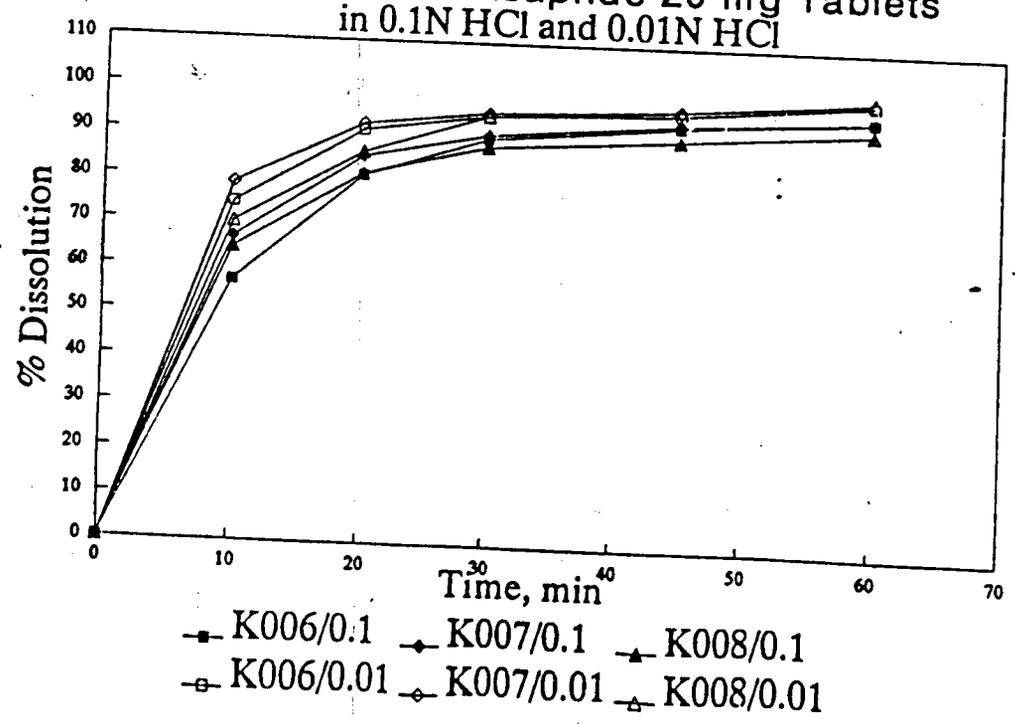
for *Ameeta Parekh*  
*Parekh* 11/3/92  
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cc: NDA 20-210, HFD-180, HFD-426 (Fleischer, Abdallah), Drug, FOI (HFD-19), Chron.

Dissolution of Cisapride 10 mg Tablets  
in 0.1N HCl and 0.01N HCl



Dissolution of Cisapride 20 mg Tablets  
in 0.1N HCl and 0.01N HCl



Solubility of Cisapride Drug Substance (mg/ml)			
0.1N HCl		0.01N HCl	
25°C	37°C	25°C	37°C
0.14	0.37	1.07	2.76

Dissolution in 0.1N HCl and 0.01N HCl (10/19/92)

I. 10 mg Tablets:

T	Lot # 1192H016		Lot # 1192H024		Lot # 1192K037	
	0.1N	0.01N	0.1N	0.01N	0.1N	0.01N
10	62.8	67.2	75.6	59.3	69.1	65.7
20	83.6	86.1	84.5	80.9	87	87.1
30	90.1	93.8	91.6	86.7	94.7	93.8
45	92	98.5	95.4	93.3	94.6	96.9
60	94.9	101	100	96.8	98.1	98.0

II. 20 mg Tablets:

T	Lot # 1192K006		Lot # 1192K007		Lot # 1192K008	
	0.1N	0.01N	0.1N	0.01N	0.1N	0.01N
10	56.9	74.3	66.5	78.7	64.2	69.9
20	80.8	90.8	85.1	92.1	81.2	86
30	89.4	94.3	90.2	95	87.7	94.3
45	92.9	95.7	93.5	96.6	90.1	96.5
60	95.4	99	95.4	99.3	92.8	99.8

0.1 N HCl VS 0.01 N HCl DISSOLUTION DATA					
LOT NO.	TABLET STRENGTH (MGS)	30 MINUTE DATA		45 MINUTE DATA	
		t-VALUE (CALCULATED)*	t-VALUE (TABULATED) CERTAINTY LEVEL**	t-VALUE (CALCULATED)*	t-VALUE (TABULATED) CERTAINTY LEVEL**
1192H016	10	1.61	1.80/90%	4.57	4.44/99.9%
1192H024	10	2.16	2.20/95%	0.991	1.09/70%
1192K037	10	0.453	0.540/40%	1.63	1.80/90%
1292K006	20	4.85	4.44/99.9%	4.39	4.44/99.9%
1292K007	20	5.03	4.44/99.9%	3.47	4.44/99.9%
1292K008	20	7.40	4.44/99.9%	9.07	4.44/99.9%

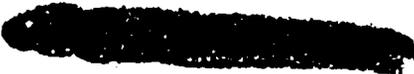
\*For each set of 0.1 N HCl and 0.01 N HCl dissolution data, the t-value was calculated according to the equation:

$$t = \frac{|\bar{d}|}{\frac{SD_{d-1}}{\sqrt{n}}}$$

where:  
 $|\bar{d}|$  - absolute difference in the average of the 12 dissolution values in 0.1 N HCl and 0.01 N HCl  
 $n$  - sample size - 12  
 $SD_{d-1}$  - standard deviation for  $n-1$  (i.e. 11) degrees of freedom

\*\*Those values were taken from standard t-value tables (two-tailed test). The stated certainty levels (in %) represent the probability that a calculated t value less than the tabulated t value is not a random event. Thus, for example, there is about a 90% probability that the dissolution differences observed in 0.1 N HCl and 0.01 N HCl at the 30 minute timepoint for batch 1192H016 is a real event.

**Revised Dissolution Specifications:**

Strengths:	10 mg and 20 mg
Apparatus:	USP II (paddle)
Medium:	0.01N HCl
Volume:	900 ml
Agitation:	50 rpm
Sampling time:	45 min
Assay:	UV absorbance at 274 nm
Specification:	Q = 

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CISAPRIDE (PROPULSID<sup>®</sup>) TABLETS  
10 & 20 mg  
Janssen Research Foundation  
40 Kingsbridge Rd, Piscataway, NJ 08855

SUBMISSION DATES:  
8/29 & 12/4/1991

REVIEWER:  
Hisham Y. Abdallah, Ph.D.

TYPE OF SUBMISSION:

Original NME

### SYNOPSIS:

The pharmacokinetics of cisapride have been studied following single and repeated dosing in young and elderly healthy subjects as well as in patients with GI, hepatic and renal disease. The pharmacokinetic interactions of cisapride with food and selected drugs were also evaluated. The sponsor tested for bioequivalence between the 10-mg and 20-mg tablets.

### Recommendation:

This submission (NDA 20-210; submission dates 8/29 & 12/4/1991) has been reviewed by the Division of Biopharmaceutics. This submission fulfills the biopharmaceutics requirements provided Comments 3-5 and Labeling Comments 6-8 are satisfactorily addressed by the sponsor.

*Comments 1 & 2 for the Medical Division should be reviewed by HFD-180 Medical Officer and appropriately forwarded to the firm.*

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**BACKGROUND:**

The proposed tablet formulations contain Cisapride (CS) as the monohydrate, a GI prokinetic agent intended to be used in GERD. The mechanism of action of CS is primarily through the enhancement of the release of acetylcholine at the myenteric plexus. Chemically, CS consists of the racemate ( $\pm$ )-cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; MW 484; molecular formula  $C_{25}H_{29}ClFN_3O_4 \cdot H_2O$ . The drug is slightly basic, with a primary pKa of 7.9 associated with the piperidinyl nitrogen. CS is practically insoluble in water, sparingly soluble in methanol and soluble in acetone. Water solubility is at its maximum between pH 2 and pH 4 and appears to depend on the ionic strength of the medium and/or the buffer species. CS exists in 2 crystal forms (I&II) with comparable water solubility; the manufacturing process is said to produce only form I. The influence of polymorphism on CS bioavailability is not known.

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The proposed tablets contain the equivalent 10 and 20 mg of CS. The 10-mg tablets will be manufactured at Janssen facilities in Beerse, Belgium and Gurabo, PR. The 20-mg tablets will be manufactured only at Gurabo. The 10 and 20-mg strengths are compositionally proportional and the market formulations are identical to those used in clinical trials. The sponsor tested the bioequivalence of the 20-mg tablets (batch 1298K003, Gurabo; batch size [REDACTED]) to the 10-mg tablets (batch 86E14/F09, Beerse; batch size [REDACTED]). Bioequivalence was concluded.

**Proposed Dosage:** Initially 10 mg qid at least 15 min before meals and at bedtime. Increase to 20 mg qid if needed.  
In patients with hepatic or renal insufficiency, the initial dose should be halved. Subsequently, this dose may be adapted depending on therapeutic response and possible side effects.  
No modification of dosage is necessary for elderly patients.

#### PHARMACOKINETICS IN HEALTHY SUBJECTS:

##### ABSORPTION:

CS is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hr after dosing. The absolute bioavailability of CS is 35-40% following its administration in solution, suspension or tablet form.

Experimentally reduced gastric acidity in fasting subjects caused a marked decrease in the rate and possibly the extent [ $AUC(0-24)$ ] of CS absorption. The combination of food with reduced gastric acidity results in absorption rate and extent similar to those observed under fasting conditions and normal acidity.

##### DISTRIBUTION:

CS binds to an extent of 97.5-98% in plasma. Albumin is the major binding protein, while  $\alpha_1$ -acid glycoprotein and other protein play less important roles. The protein binding is related to plasma CS concentrations; this was especially evident at concentrations exceeding those found following therapeutic doses. Binding of CS to RBC's is lower than its plasma protein binding, hence its blood/plasma concentration ratio of 0.64. The volume of distribution of CS is about 180 L, indicating extensive tissue distribution. Under steady-state conditions, the milk-to-serum concentration ratio was found to be less than 1:20.

##### ELIMINATION:

The total blood clearance of CS is about 200 ml/min, *i.e.*, less than 15% of hepatic blood flow. This suggests the GI lumen and/or wall, but not the liver, as the major site for first-pass elimination. The mean terminal  $t_{1/2}$  reported for CS ranges from 6 to 12 hr; longer half-lives, up to 20 hr, have been reported following i.v. administration.

CS is extensively metabolized; unchanged drug accounts for less than 10% of urinary and

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fecal recovery following oral administration. Norcisapride (NCS), formed by N-dealkylation, is the principal metabolite in plasma, feces and urine. Large number of minor metabolites, including some glucuronides have also been identified.

NCS has a renal clearance of 350 ml/min, indicating active tubular secretion. The plasma concentration and urinary excretion rate profiles of NCS paralleled those of CS, with the terminal slopes of both plasma profiles representing the terminal disposition rate constant of CS.

#### DOSE PROPORTIONALITY:

Following single oral solution doses of 5, 10 and 20 mg,  $C_{max}$  and  $AUC$  increased proportionally with dose. Under steady-state conditions, however,  $C_{max}$  and  $AUC(0-24)$  increased less than proportionally following 10, 20 or 40 mg CS qid, possibly due to a change in plasma protein binding of CS resulting in an increase in clearance, and/or a decrease in the extent of absorption by a reduction in GI transit time at higher doses.

#### REPEATED-DOSE PHARMACOKINETICS:

There was no unexpected drug accumulation due to time- or dose-dependent changes in PK. After cessation of the repeated dosing, the elimination half-lives (8 to 10 hr) were in the same order as after single dosing. Accumulation ratio is about 2.

#### INFLUENCE OF DISEASE ON PHARMACOKINETICS:

Average PK parameters for CS in patients with constipation, hepatic or renal impairment are similar to those observed in normal subjects. Variability, however, is considerably greater in liver cirrhosis patients compared to normal subjects. Renal clearance and the urinary recovery of NCS were decreased in patients with renal insufficiency. In a PK screen, patients with GERD, dyspepsia and constipation showed steady-state plasma levels comparable to those observed in normal subjects.

#### INFLUENCE OF AGE ON PHARMACOKINETICS:

The studies indicated that the PK of CS were not greatly altered in the elderly. Plasma concentrations during repeated administration tend to be higher in the elderly than in young subjects.

#### CONCENTRATION-EFFECT RELATIONSHIP:

No correlation was found between steady-state plasma concentration of CS, measured either immediately before or 1-4 hr after the morning dose, and the global results of the treatment or the occurrence of adverse effects. This was observed in a pharmacokinetic screen using samples (one sample per patient) from 102 patients with GERD, functional dyspepsia or constipation. It should be noted, however, that the results may have been confounded by inter-subject variability in protein binding, since total, and not unbound, CS was measured.

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### DRUG INTERACTIONS

*Antacids* (Maalox) did not affect the absorption of cisapride. CS accelerated the absorption of *cimetidine*, while cimetidine increased  $C_{max}$  and  $AUC(0-24)$  but did not alter  $T_{max}$  of CS. *Ranitidine* had no effect on the rate or extent of CS absorption; CS reduced the  $T_{max}$  and  $AUC(0-8)$ , with no effect on  $C_{max}$ , of ranitidine. CS produced a 20 % decrease in *digoxin*  $C_{max}$  and, interestingly, reduced its renal clearance by 27%. No PK or clinical interaction was found between *propranolol* and CS in patients with mild hypertension.

CS significantly prolonged the coagulation time in patients treated with *acenocoumarol*. It also shortened the  $T_{max}$  but did not influence either  $C_{max}$  or  $AUC$  of *phenprocoumon* in healthy volunteers. No significant interactions were found between CS and *warfarin*. CS increased the absorption rate of ethanol with an increase in the impairment of reaction time caused by the latter. I.v. CS increased the absorption rate, but not extent of *diazepam*. Gastric emptying of a *diazepam* solution was accelerated by CS. These changes in *diazepam* PK were associated with a lowered reaction-time response during the first 45 min after *diazepam* dosing, but did not alter self-rated sedation. *Morphine*-induced delay in gastric emptying was prevented by i.m. CS. CS had no influence on antipyrine kinetics in healthy volunteers.

The *in-vitro* plasma protein binding of CS was not influenced by high therapeutic concentrations of imipramine, propranolol, diazepam, tolbutamide, cimetidine, indomethacin, phenytoin or sulfamethazine. High concentrations of warfarin increased the unbound fraction of CS by 33%. CS did not affect the *in-vitro* plasma protein binding of imipramine, propranolol, phenytoin, diazepam or warfarin.

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### COMMENTS TO THE MEDICAL DIVISION:

1. There is some indication that exposure may be higher in the elderly; however, the data submitted are not conclusive. It is recommended that this observation be considered along with safety data in designing dosing regimens for elderly patients.
2. Phase 4 Commitments:
  - a. The influence of crystal polymorphism on bioavailability needs to be investigated.
  - b. Although the major metabolite, NCS, is found in much lower concentrations in plasma compared to CS, its unbound levels may reach 60% those of CS. It is recommended, therefore, that the activity and toxicity of this metabolite as well as its potency ratio relative to CS be further elucidated.

### COMMENTS TO THE SPONSOR:

3. In the information submitted on formulation, no ranges are given for the various ingredients. This is especially important in case of magnesium stearate. The sponsor should

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specify the range of this ingredient and, if such range is wide ( $> \pm 10\%$ ), present data that at the high end of the range, there is no detrimental effect on *in-vivo* performance of the tablets.

4. Based on solubility data, "sink conditions" are not achieved in the proposed dissolution method, especially for the 20-mg tablets. Such conditions may be attainable in 0.01N HCl. The sponsor is requested to submit dissolution data in 0.01N HCl. (Note Supervisor's Comment on p. 8.) am
5. The data submitted cannot unequivocally substantiate complete absorption of CS following oral dosing. In absence of fecal excretion data following i.v. dosing, it is not clear whether metabolites excreted in the feces are formed systemically or locally in the GI lumen. (see Labeling Comment #1).

**LABELING COMMENTS:**

6. The section entitled "Pharmacokinetics" should be re-written as follows:  
*"PROPULSID<sup>™</sup> is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hr after dosing. The absolute bioavailability of PROPULSID<sup>™</sup> is 35-40%, possibly due to pre-systemic elimination in the gastrointestinal tract and liver. Experimentally reduced gastric acidity in fasting subjects caused a marked decrease in the rate and possibly the extent of PROPULSID<sup>™</sup> absorption. PROPULSID<sup>™</sup> binds to an extent of 97.5-98% to plasma proteins, mainly to albumin. The volume of distribution of PROPULSID<sup>™</sup> is about 180 L, indicating extensive tissue distribution.*

*The plasma clearance of PROPULSID<sup>™</sup> is about 100 ml/min. The mean terminal half-life reported for PROPULSID<sup>™</sup> ranges from 6 to 12 hr; longer half-lives, up to 20 hr, have been reported following i.v. administration. PROPULSID<sup>™</sup> is extensively metabolized; unchanged drug accounts for less than 10% of urinary and fecal recovery following oral administration. Norcisapride, formed by N-dealkylation, is the principal metabolite in plasma, feces and urine. Large number of minor metabolites, including some glucuronides have also been identified.*

*There was no unusual drug accumulation due to time-dependent or non-linear changes in PK. After cessation of the repeated dosing, the elimination half-lives (8 to 10 hr) were in the same order as after single dosing.*

*There is some evidence that the degree of accumulation of PROPULSID<sup>™</sup> and/or its metabolites may be higher in patients with hepatic or renal impairment as well as in elderly patients compared to young healthy volunteers."*

7. Under "Drug Interactions", the fourth paragraph should read:

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*"Cimetidine coadministration leads to an increased peak plasma concentration and AUC of PROPULSID™; there is no effect on PROPULSID™ absorption when coadministered with ranitidine. The gastrointestinal absorption of cimetidine and ranitidine is accelerated when coadministered with PROPULSID™."*

8. Under "Nursing Mothers", labeling should read:  
*"Cisapride is excreted in human milk at concentrations approximately one twentieth of those observed in plasma. Caution should..."*

*Hisham Y. Abdallah* 6/22/92

Hisham Y. Abdallah, Ph.D.  
Pharmacokinetics Review Branch

Biopharm Day: 6/8/92 (Collins, Ludden, Malinowski, Fleischer, Parekh)

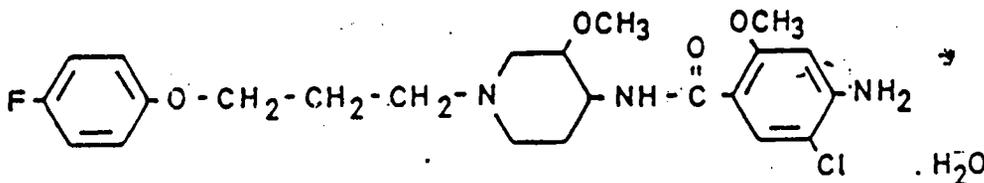
FT initialled by Nicholas Fleischer, Ph.D.

*Ameeta Parekh*  
*for Nick Fleischer*

cc: NDA 20-210, HFD-180, DI, F, A, RI, HFD-426 (Fleischer, Abdallah), Drug, FOI (HFD-19), Chron.

Cisapride, 10&20 mg Tablets  
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 Biopharm Day 6/8/92

### CHEMICAL STRUCTURE



**m.p:** 118°C  
**pKa:** 7.9 (piperidine)  
**stability:** stable to light and alkali, slowly hydrolyzes in acid  
**pH and solubility:**

medium	Sol., mg/ml
0.1N HCl	0.04
0.01N HCl	0.4
citrate pH 2	0.05
citrate pH 4	0.1
citrate pH 6	<0.01
borate pH 8	<0.01
borate pH 10	<0.01
0.1N NaOH	<0.01

**polymorphism:** exists in 2 forms with comparable solubility  
**ln P<sub>ed/w</sub>:** 4.2 (pH 10); 4.0 (pH 8); 1.2 (pH 2&4)

1 Page(s)

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## ASSAY METHODOLOGY

### I. HPLC METHOD FOR THE DETERMINATION OF CISAPRIDE IN PLASMA SAMPLES.

**Study ID:** N46969, Ser. # R51619/42  
**Reference:** Vol 41., p. 6-87  
**Date:** January 1986  
**Investigators:** F Van Rompaey, R Woestenborghs, W Lorreyne, J Heykants  
**Site:** Dpt. of Drug Metab. and PK, Janssen, Beerse, Belgium.

#### Procedure:

#### Recovery:

CS: 71-77%  
IS: 79%

#### Specificity:

CS and IS peaks were well-resolved from each other and from major fecal and urinary metabolites added to the samples and from other extraneous peaks.

#### Stability:

Up to 9 months

#### Linearity:

ng/ml

#### Sensitivity:

ng/ml

**Accuracy and Precision:**

Nominal Concentration ng/ml	Observed Concentration, ng/ml			
	n	Mean ± SD	%CV	%Dev
	2		4.2	+0.5
	5		6.0	+6.0
	7		10.8	-2.4
	6		5.6	-3.7
	7		2.4	-2.4
	7		6.2	-4.2

Back-calculated standard curves (n=16) produced %CV of less than 8% for CS concentrations ██████ ng/ml.

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**II. DETERMINATION OF CISAPRIDE IN PLASMA AND ANIMAL TISSUES BY HPLC.**

**Study ID:** N56474  
**Reference:** Vol 41., p. 6-111  
*J. Chromatog., 424, 195-200 (1988)*  
**Investigators:** R Woestenborghs, W Lorceyne, F. Van Rompaey, J Heykants  
**Site:** Dpt. of Drug Metab. and PK, Janssen, Beerse, Belgium.

**Procedure:**  
**Recovery:**  
**Specificity:**

Identical to assay I

**Stability:**  
**Linearity:**  
**Sensitivity:**  
**Accuracy and Precision:**

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**III. SIMULTANEOUS HPLC DETERMINATION OF CISAPRIDE AND ITS N-DEALKYLATED METABOLITE IN PLASMA AND URINE SAMPLES.**

**Study ID:** N36552, Ser. # R51619/25  
**Reference:** Vol 41., p. 6-73A  
**Date:** January 1984  
**Investigators:** R Woestenborghs, W Lorreyne, J Heykants  
**Site:** Dpt. of Drug Metab. and PK, Janssen, Beerse, Belgium

**Procedure:**

**Recovery:**

NCS: 74%  
CS: 80%  
IS: 72%

**Specificity:**

CS, NCS and IS peaks were well-resolved from each other and from other components.

**Linearity:**

CS: [redacted] ng/ml (low curve); [redacted] ng/ml (high curve)  
NCS: [redacted] ng/ml (low curve); [redacted] ng/ml (high curve)

All correlation coefficients were > 0.99.

**Sensitivity:**

CS: [redacted] ng/ml  
NCS: [redacted] ng/ml

**Precision and Accuracy:**

Nominal Concentration ng/ml	Observed NCS Concentration, ng/ml		
	n	%CV	%Dev
	3	7.6	-8.0
	3	10.9	+3.2
	3	3.5	+7.6
	3	6.9	+1.0
	3	3.4	-6.0
	3	4.0	+5.6
	3	2.5	+6.0

No validation data for CS.

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**IV. HPLC DETERMINATION OF CISAPRIDE IN PLASMA SAMPLES.**

**Study ID:** N31584, Ser. # R51619/19  
**Reference:** Vol 41., p. 6-117  
**Date:** March 1983  
**Investigators:** R Woestenborghs, W Lorreyne, L Embrechts, J Heykants  
**Site:** Dpt. of Drug Metab. and PK, Janssen, Beerse, Belgium.

**Procedure:**

**Recovery:**

CS: 87%

IS: 84%

**Specificity:**

CS and IS peaks were well-resolved from each other and from extraneous peaks.

**Linearity:** 1-250 ng/ml

**Sensitivity:** 1 ng/ml

**Accuracy and Precision:**

Nominal Concentration ng/ml	Observed Concentration, ng/ml			
	n	Mean ± SD	%CV	%Dev
	4		16.3	+6.5
	8		9.8	+3.4
	8		8.6	+4.9
	8		3.7	+1.1
	7		5.0	-2.9
	7		5.3	-3.5
	5		3.7	+3.1
	4		4.9	-2.2

V. GC DETERMINATION OF NORCISAPRIDE IN PLASMA AND URINE SAMPLES

Study ID: N49613, Ser. # R51619/54  
Reference: Vol 39, p. 234-44  
Date: April 1986  
Investigators: R Woestenborghs, C Pauwels, W Lorreyne *et al.*  
Procedure:

Plasma or urine (1 ml) was spiked with 0.05 or 0.5  $\mu\text{g}$  of the internal standard (IS), R57024, alkalized with 0.5 ml of 2.5M NaOH and extracted twice with benzene. The residue after evaporation was dissolved in benzene and derivatized with heptafluorobutyric anhydride (HFBA), evaporated, redissolved in 0.05M  $\text{H}_2\text{SO}_4$ , extracted with benzene, evaporated and dissolved finally in benzene. 2  $\mu\text{l}$  was injected into the chromatograph.

Separation was achieved on a 200 x 0.3 cm glass column packed with 3% SP-2250 DB on 100-120 mesh Supelcoport. The temperatures of the column, injector and detector were 250°C, 260°C and 270°C, respectively. The carrier gas ( $\text{N}_2$ ) flow rate was 70 ml/min and detection was achieved by a  $^{63}\text{Ni}$  electron-capture detector. Under these conditions, IS and NCS eluted at 4.3 and 5.7 min, respectively.

Recovery: 85-90%  
Specificity:

NCS and IS peaks were well-resolved from each other and from extraneous peaks.

Linearity: [redacted] ng/ml (PHR) and [redacted] ng/ml (PAR) for plasma  
[redacted] ng/ml (PHR) and [redacted] ng/ml (PAR) for urine

Sensitivity: [redacted] ng/ml

Accuracy and Precision:

1. Plasma:

Nominal Concentration ng/ml	Observed Concentration, ng/ml			
	n	Mean $\pm$ SD	%CV	%Dev
	3		10.0	0.0
	3		3.0	-3.3
	3		3.1	-0.7
	3		1.5	+1.7
	3		3.3	-1.8
	3		4.8	+2.4

Cisapride, 10&20 mg Tablets  
NDA 20-210; 8/29/92; 12/4/91

Assay Validation, Avi

2. Urine:

Nominal Concentration ng/ml	Observed Concentration, ng/ml			
	n	Mean±SD	%CV	%Dev
	3		10.3	+16.0
	3		4.2	-6.5
	3		7.5	+1.7
	3		3.7	-1.6
	3		2.2	-7.3
	3		3.2	-2.1
	3		6.2	+1.7
	3		8.6	+8.6
	3		4.0	+4.9

## PHARMACOKINETIC STUDIES

### I. ABSORPTION, METABOLISM AND EXCRETION OF CISAPRIDE IN VOLUNTEERS AFTER ORAL ADMINISTRATION.

**Study ID:** N40274; Ser. # R51619/29  
**Reference:** Vol. 41, p. 6-128  
**Date:** July 1984  
**Investigators:** W Meuldermans, A Van Peer, J Henderickx *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt. Clin. Res. and Devel., Janssen, Beerse, Belgium.

#### Objective:

To characterize the absorption, metabolism and excretion of <sup>14</sup>C-cisapride (CS) following a single oral solution dose in healthy male volunteers.

#### Dosage Forms:

\* <sup>14</sup>C-CS (labeled at the C=O group), batch # A109, specific activity 16.7  $\mu$ Ci/mg "base" and a radiochemical purity of 96%, diluted with non-radioactive CS, Batch # A1301, to a specific activity of 7.7  $\mu$ Ci/mg.

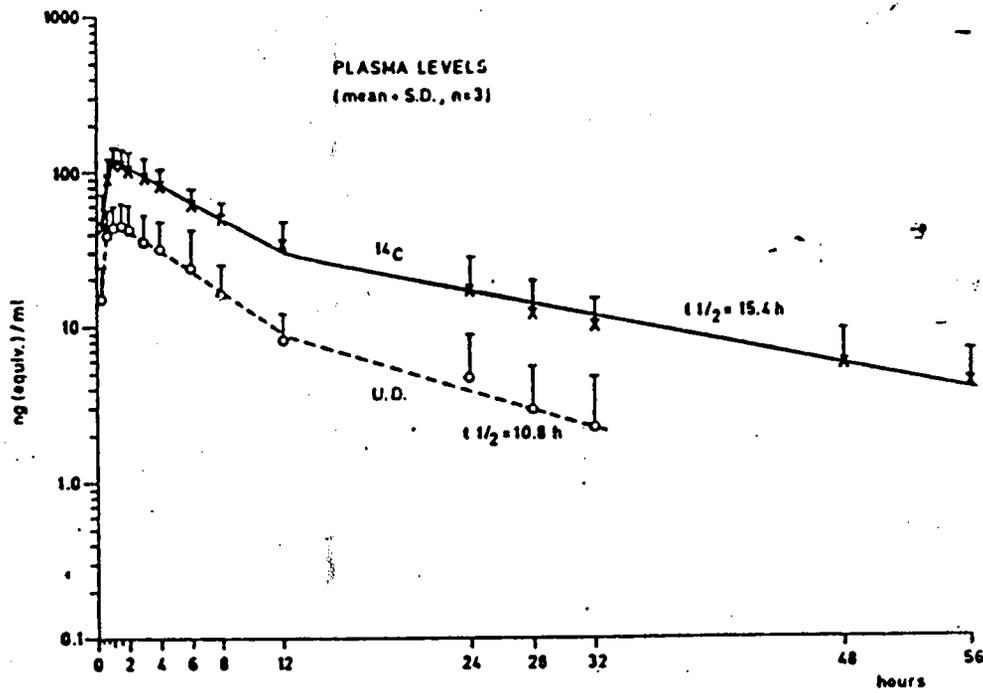
#### Study Design:

Three healthy male volunteers (29-40 yr; 68-72 kg) participated in this single-dose study. After an overnight fast, each subject received 5 ml (10 mg) CS solution followed by 100 ml water. A light breakfast was served 2 hr after dosing. Blood samples were drawn into heparinized tubes at 0, 20 and 40 min and 1, 1.5, 2, 3, 4, 6, 12, 24, 28, 32, 48 and 56 hr post-dosing. Urine was collected at intervals for 96 hr. The first six stools after dosing were also collected.

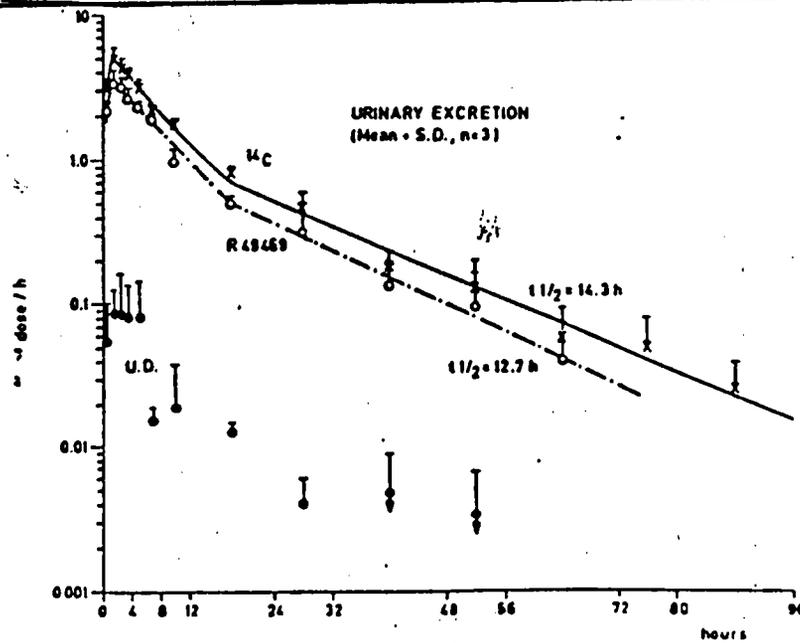
#### Analytical Methodology:

Total radioactivity was determined by liquid scintillation. Plasma and urine CS and NCS were measured by HPLC (see *Analytical Methodology*, method III). Mass balance of metabolites in urine and feces was assessed by radio-HPLC [REDACTED]

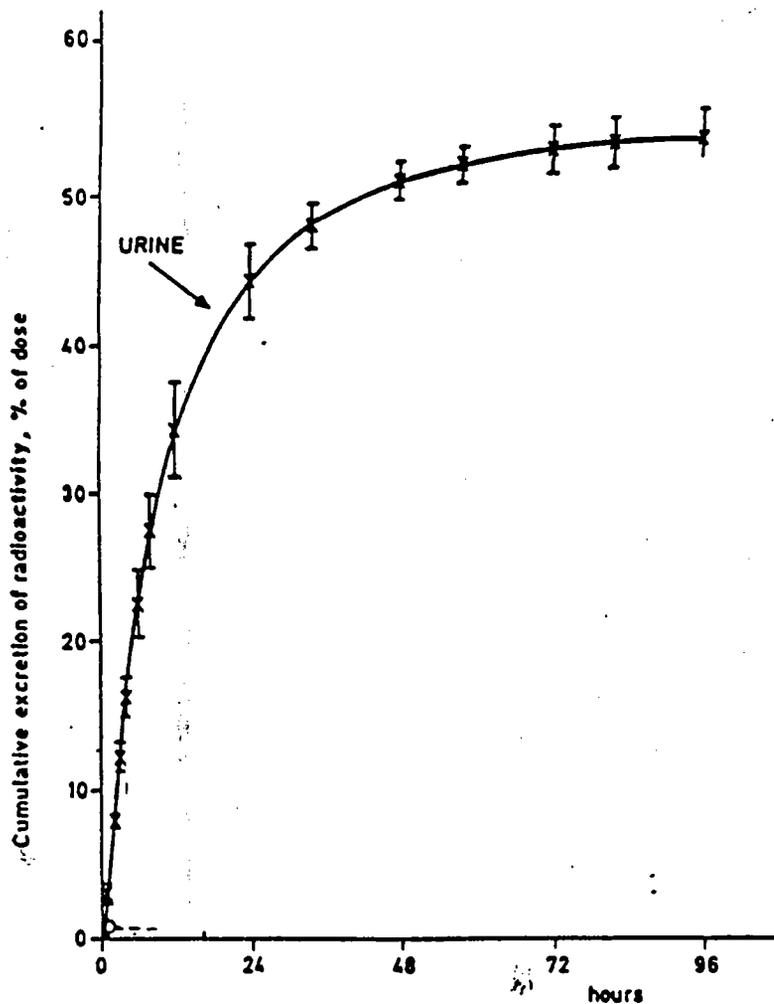
Results:



Mean plasma concentrations of unchanged CS (U.D.) and total radioactivity



Mean urinary excretion rate of NCS (R49469) and total radioactivity



Mean urinary and individual fecal excretion of radioactivity

Parameter	CS	NCS	Total RA
$C_{max}$ , ng/ml	$46.7 \pm 15.5^a$	--	$127.1 \pm 10.3$
$T_{max}$ , hr	$1.4 \pm 0.7$	--	$1.2 \pm 0.3$
$t_{1/2}$ , hr	$10.7 \pm 1.7$	$12.2 \pm 3.2$	$16.6 \pm 2.2$

Parameter	CS	NCS	Total RA
$AUC(0-\infty)$	431±283	--	1409±561
$Cl_o$ , ml/min	488±233	--	--
$Cl_{renal}$ , ml/min	3.49±0.99	--	--
$(X^\infty)_{urine}$ , %	--	--	53.9±1.86
$(X^\infty)_{feces}$ , %	--	--	48.4±2.90
$(X^\infty)_{total}$ , %	--	--	102.3±1.18

Mean ± S.D.  
From urine data

## II. PHARMACOKINETICS OF CISAPRIDE AND THE METABOLITE NORCISAPRIDE IN PLASMA AND URINE AFTER A SINGLE ORAL DOSE OF CISAPRIDE TO HEALTHY VOLUNTEERS.

**Study ID:** N49710; Ser. # R51619/77  
**Reference:** Vol. 41, p. 6-181  
**Date:** May 1986  
**Investigators:** A Van Peer, R Gasparini, R Woestenborghs *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt. Clin. Res. and Devel., Janssen, Beerse, Belgium.

**Objective:**

To characterize the plasma and urine PK of CS and NCS using a GC assay sensitive to 1 ng/ml.

**Dosage Forms:**

\* 10 ml of a 1 mg/ml solution (lot # 86A06)

**Study Design:**

This was a single-dose study in 6 healthy male volunteers (28-39 yr; 63-72 kg). Subjects fasted overnight and received a standard breakfast of ham, cheese, bread and jelly 2 hr post-dosing. Blood samples were taken at 0, 0.5, 1, 2, 3, 4, 6, 8, 24 and 32 hr.

**Analytical Methodology:**

CS was measured by HPLC (method IV). NCS was measured by a GC assay (Method V).

**Results:**

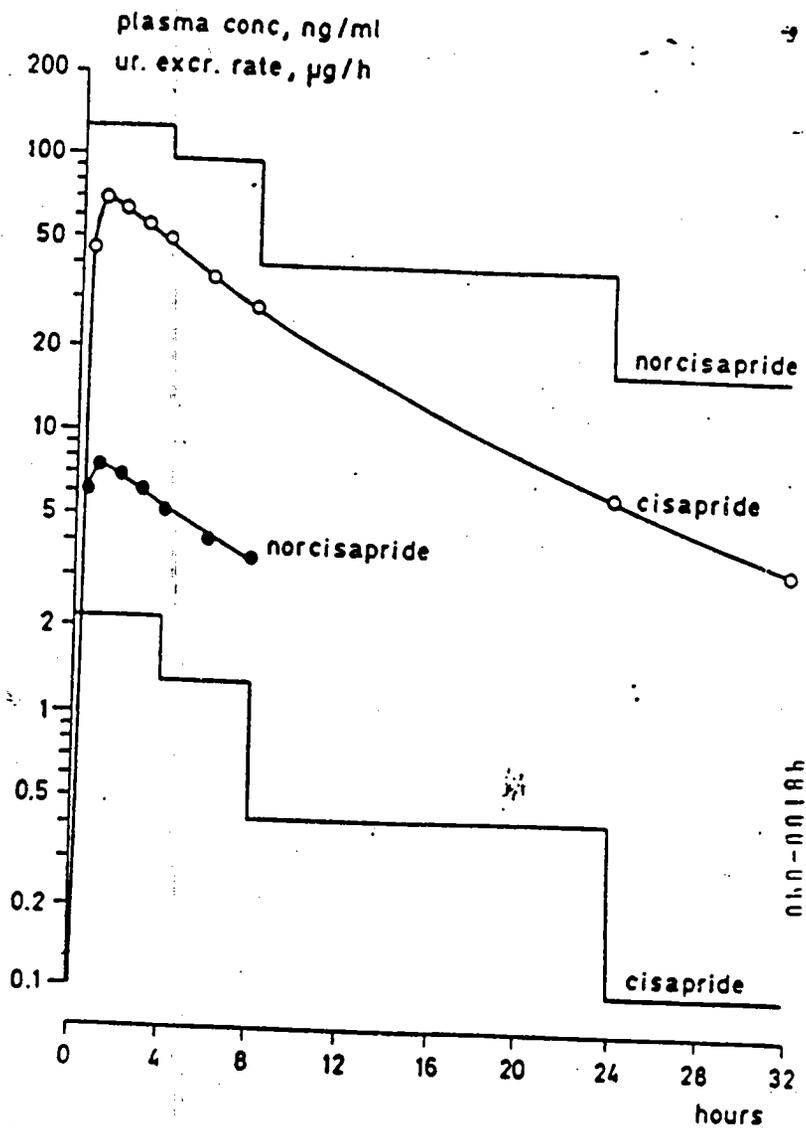


Figure 1: Semilogarithmic plot of the mean plasma concentrations and urinary excretion rates of cisapride and norcisapride after a single 10 mg oral dose of cisapride to six healthy volunteers.

Parameter	CS	NCS
$T_{max}$ , ng/ml	1.2±0.4*	1.3±0.8
$C_{max}$ , hr	69.5±12.6	7.5±1.7
$\beta$ , hr <sup>-1</sup>	0.092±0.013	0.089±0.021
$t_{1/2}$ , hr	7.7±1.0	8.2±1.8
$AUC(0-\infty)$	719±135	88.1±24.0
$AUC\ Ratio\ (NCS/CS)$	0.13±0.04	
$Cl_{renal}$ , ml/min	0.53±0.18	347±78
$(X^{\infty})_{urine}$ , %	0.23±0.10	25.9±3.2

Mean ± S.D.

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### III. PHARMACOKINETICS OF CISAPRIDE AND ITS BIOAVAILABILITY AFTER ORAL AND RECTAL ADMINISTRATION IN SIX HEALTHY MALE VOLUNTEERS.

**Study ID:** N30670; Ser. # R51619/3  
**Reference:** Vol. 41, p. 6-191  
**Date:** October 1982  
**Investigators:** A Van Peer, L Embrechts, R Woestenborghs *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt. Clin. Res. and Devel., Janssen, Beerse, Belgium.

#### Objective:

To characterize the PK and BA of CS following i.v., p.o. and rectal dosing.

#### Dosage Forms:

- \* 4 ml of a 1 mg/ml i.v. solution (lot # 82A15/F04)
- \* 2.5 ml of a 4 mg/ml solution (lot # 81K19/F02)
- \* 10 mg tablet (lot # 82C25/G01). *Non-Clinical*
- \* 10 mg suspension (strength not given; lot # 82C18/G02)
- \* 30 mg suppository (lot # 82B22/G01).

**Study Design:**

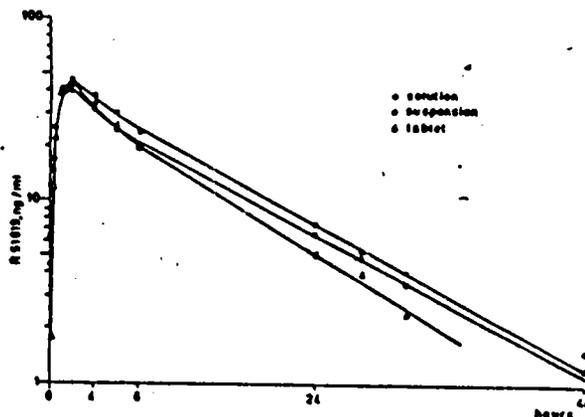
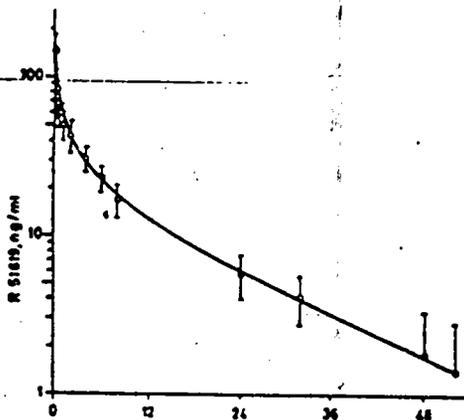
This was a single-dose cross-over study in 6 healthy male volunteers (31-50 yr; 68-83 kg; 2 smokers). Subjects fasted overnight and received a breakfast of ham, cheese, bread, butter and coffee 2 hr post-dosing. Blood samples were taken at the following times:

- \* *i.v.*: 0, 2, 5, 10, 15, 30 min and 1, 2, 4, 6, 8, 24, 32, 48 and 52 hr.
- \* *Oral*: 0, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 32, 48 and 52 hr.
- \* *Rectal*: 0, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 32, 48 and 52 hr.

**Analytical Methodology:**

CS was measured by HPLC (method IV).

**Results:**



Parameter	I.V. 4 mg	Solution 10 mg	Suspension 10 mg	Tablet 10 mg	Suppository 30 mg
$C_{max}$ , ng/ml	--	48 ± 12 <sup>a</sup>	42 ± 12	49 ± 11	28 ± 11
$T_{max}$ , hr	--	2 ± 1	1.5 ± 0.5	1.5 ± 0.5	6 ± 3
$t_{1/2}$ , hr	19.4 ± 11.3	11.4 ± 4.5	11.0 ± 2.6	8.4 ± 2.5	9.7 ± 4.6
$AUC(0-\infty)$	606 ± 87	641 ± 195	547 ± 210	515 ± 92	508 ± 238
$Cl/F$ , ml/min	112 ± 14	292 ± 128	343 ± 127	333 ± 67	--
$V_c$ , L	27 ± 13	--	--	--	--
$V_{area}$ , L	183 ± 109	--	--	--	--
$F_{abs}$	--	0.42 ± 0.11	0.37 ± 0.17	0.34 ± 0.06	0.11 ± 0.06
$F_{rel}$	--	--	0.88 ± 0.26	0.86 ± 0.24	0.26 ± 0.14

Mean ± S.D.

#### IV. DETERMINATION OF THE DOSE-PROPORTIONALITY OF CISAPRIDE IN MAN

**Study ID:** N49136  
**Reference:** Vol. 41, p. 6-245  
**Date:** September 1985  
**Investigators:** A Van Peer, R Woestenborghs J Heykants *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt. Clin. Res. and Devel., Janssen, Beerse, Belgium.

#### Objective:

To Investigate the dose-proportionality of single oral solution doses of 5, 10 and 20 mg of CS in healthy male volunteers.

#### Dosage Forms:

\* 5, 10 or 20 ml of a 1 mg/ml solution (lot # 84C20/F27) with 200 ml of water, 15 min before breakfast.

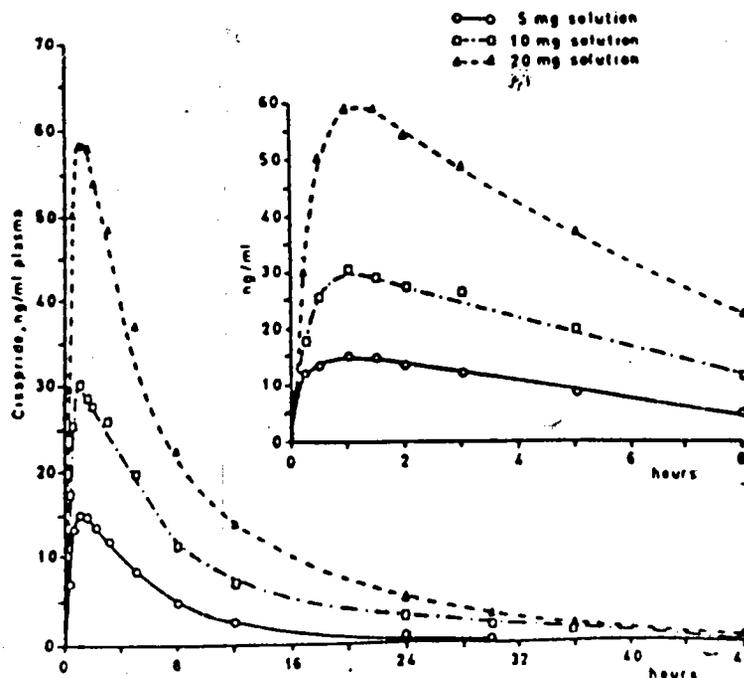
#### Study Design:

This was a single-dose, randomized, cross-over study in 12 healthy male volunteers (23-39 yr; 63-92 kg). Subjects fasted overnight and received a standard breakfast of 4 oz orange juice, 1.25 oz dry cereal, 4 oz skim milk, 2 slices of white toast and 0.5-1 oz jelly. Lunch and dinner were served 4 and 9 hr post-dose. Blood samples were taken at 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 30, 36 and 48 hr.

#### Analytical Methodology:

CS was measured by HPLC (method I).

#### Results:



Parameter	5 mg	10 mg	20 mg
$C_{max}$ , ng/ml	16.4±4.6*	32.7±10.1	64.1±15.4
$T_{max}$ , hr	1.3±0.5	1.4±0.9	1.0±0.5
$t_{1/2}$ , hr	8.8±3.0	10.9±3.0	10.4±3.4
AUC(0-48)	121±51	294±134	569±156

Mean ± S.D.

$C_{max}$  and AUC increased proportionally; no significant difference in dose-normalized parameters. Within-subject correlation coefficients were 0.905 - 1.000.

V. THE DOSE PROPORTIONALITY (AND PHARMACOKINETIC LINEARITY) OF CISAPRIDE IN HEALTHY VOLUNTEERS

Study ID: JRD 51,619/1001  
Date: October 1990 (study performed 10-12/1989)  
Reference: Vol. 43, p. 6-559  
Investigators: J Barone, R Bierman  
Hurtado Rutgers Student Health Services, New Brunswick, NJ

Objective:

To determine the steady-state dose proportionality of cisapride in healthy volunteers.

Dosage Form:

Cisapride (10 mg), batch # 86E14/F09, exp. May 1991

Study Design:

This was a randomized, double-blind cross-over study in 24 healthy, non-smoking male volunteers (18-30 yr, 53-95 kg). Volunteers received orally 10 mg (1 CS+3 placebo), 20 mg (2 CS+2 placebo) or 40 mg (4 CS) qid in the form of 10 mg tablets, 30 min before each meal and at bedtime for 5 days. Each treatment phase was separated by a minimum of a nine-day washout phase. On Day 1 of each period, after an overnight fast, each subject received his first morning dose of cisapride (7 am).

Pre-morning dose blood samples were taken on Days 2-4. On the evening of Day 4, volunteers returned to the health center, were given a standardized dinner and remained cloistered until 7 am on Day 6. Blood samples were taken on Day 5 before and at 1, 2, 3, 5 (pre-dose 2), 6, 7, 10 (pre-dose 3), 11, 12, 15 (pre-dose 4), 16, 17, 24, 39, 48, 72 and 96 hr after the morning dose. The above outlined procedure was repeated in periods 2 (Days 15-23) and 3 (Days 29-37) until each volunteer had received all three dosages of CS.

**Plasma Protein Binding:**

Pre-dose plasma samples and samples taken 1 hr after the third dose on Day 5 were used for analysis. Binding was determined using equilibrium dialysis with <sup>3</sup>H-cisapride.

**Results:**

**I. Achievement of Steady State:**

This was tested by multivariate ANOVA. There were statistically significant ( $p \leq 0.03$ ) differences in  $C_{min}$  on Days 3, 4, 5 and 6. However, the differences in mean  $C_{min}$  were small.

Dose	$C_{min}$ , ng/ml				$\Delta C_{ss}^a$	$(C_{av})_{ss}$ ng/ml	$\frac{\Delta C_{ss}}{(C_{av})_{ss}}$ , %	
	Day 3	Day 4	Day 5	Day 6				
10 mg	Mean	27.9	28.3	32.3	32.8	4.9	30.3	16
	S.D.	15.0	14.6	16.4	15.3			
	%C.V.	54	52	51	47			
20 mg	Mean	48.4	51.3	55.7	54.9	6.9	52.7	13
	S.D.	25.8	27.4	27.7	24.0			
	%C.V.	53	53	50	44			
40 mg	Mean	77.8	79.6	86.6	84.8	8.8	82.2	11
	S.D.	38.8	38.8	39.9	47.5			
	%C.V.	50	49	46	56			

$$^a C_{max} - C_{min}$$

**2. Pharmacokinetic parameters:**

Parameter	10 mg	20 mg	40 mg	
$AUC(0-24)$ Unadjusted ng hr/ml	1193 ± 397	1925 ± 656	2978 ± 1127	
	Adjusted	962 ± 328	744 ± 282	
	90% CI	(75.4 - 85.9)	(57.1 - 67.6)	
	Ratio of Means	--	80.6%	62.4%
$C_{max}$ Unadjusted ng/ml	75.7 ± 23.1	115.1 ± 31.5	190.4 ± 55.8	
	Adjusted	57.5 ± 15.8	47.6 ± 13.9	
	90% CI	--	(69.9 - 82.1)	(56.8 - 69.0)
	Ratio of Means	--	76.0%	62.9%
$T_{max}$ , hr	1.50 ± 0.88	1.33 ± 0.48	1.13 ± 0.34	
	90% CI	--	(68.3 - 109.4)	(54.4 - 95.6)
	Ratio of Means	--	88.9%	75.0%

Parameter	10 mg	20 mg	40 mg
$AUC(0-\infty)$ Unadjusted ng hr/ml	1580 ± 659	2677 ± 1244	4284 ± 2216
Adjusted	--	1339 ± 622	1071 ± 554
90% CI	--	(78.8 - 90.6)	(61.9 - 73.7)
Ratio of Means	--	84.7%	67.8%
$C_{min}$ Unadjusted ng/ml	32.3 ± 16.4	55.7 ± 27.7	86.6 ± 39.9
Adjusted	--	27.8 ± 13.9	21.7 ± 10.0
90% CI	--	(78.0 - 94.2)	(59.0 - 75.1)
Ratio of Means	--	86.1%	67.0%
$\beta$ , hr <sup>-1</sup>	0.10 ± 0.02	0.08 ± 0.02	0.07 ± 0.02
90% CI	--	(79.0 - 95.1)	(68.9 - 84.7)
Ratio of Means	--	87.1%	76.8%
$t_{1/2}$ , hr	7.77 ± 2.46	8.98 ± 3.13	9.76 ± 2.41
90% CI	--	(106.6 - 129.3)	(118.0 - 140.2)
Ratio of Means	--	118.0%	129.1%
$Cl_r/F$ , ml/min	612.14 ± 178.5	758.3 ± 213.9	994.9 ± 324.9
90% CI	--	(113.7 - 134.1)	(152.3 - 172.8)
Ratio of Means	--	123.9%	162.5%

There were no significant sequence effects with any of the parameters. There were, however, significant ( $p \leq 0.03$ ) phase effects with the two  $AUC$  parameters and the trough plasma level. The first phase had the lowest and the third had the highest values, except for trough plasma concentration, for which the second and third phases had about the same values.

### 3. Plasma Protein Binding:

% Free Cisapride			
Pre-treatment	10 mg QID	20 mg QID	40 mg QID
2.8 ± 0.2	3.25 ± 0.29	3.60 ± 0.33	3.95 ± 0.37

Drug binding was reduced at higher dosages.

The pharmacokinetic parameters  $AUC(0-24)$ ,  $AUC(0-\infty)$  and  $Cl_r/F$  were recalculated on the basis of free drug concentration.

Parameter		10 mg	20 mg	40 mg
<i>AUC</i> (0-24) ng hr/ml	Unadjusted	38.89 ± 12.21	68.83 ± 22.63	117.99 ± 47.58
	Adjusted	---	34.42 ± 11.32	29.50 ± 11.89
	90% CI		(82.9 - 96.0)	(70.1 - 83.2)
	Ratio of Means		89.5%	76.7
<i>AUC</i> (0-∞) ng hr/ml	Unadjusted	51.52 ± 20.17	95.85 ± 43.97	169.58 ± 91.14
	Adjusted	---	47.93 ± 21.99	42.40 ± 22.79
	90% CI		(86.8 - 102.6)	(75.8 - 91.6)
	Ratio of Means		94.7	83.7
<i>Cl<sub>r</sub>/F</i> , ml/min		18761 ± 5661	21140 ± 5961	25521 ± 8917
	90% CI		(101.2 - 119.7)	(124.1 - 142.6)
	Ratio of Means		110.5	133.4

There were no significant sequence effects on the pharmacokinetic parameters due to phase or sequence. As with the *AUC* using total plasma concentrations, there were at least marginal ( $p \leq 0.08$ ) phase effects with the first phase having the lowest values and the last phase having the highest.

The apparent increase in clearance may be explained by a change in the plasma protein binding of cisapride, resulting in a faster clearance of the drug and decrease in the expected plasma concentrations. The increased gastric motility at these high cisapride doses may also have affected its absorption by accelerating transit through the gastrointestinal tract.

#### VI. SECRETION OF CISAPRIDE IN HUMAN MILK.

**Study ID:** N45342  
**Reference:** Vol. 43, p. 6-809  
**Investigators:** GJ Hofmeyer, EWW Sonnendecker  
**Site:** Dpt. Ob. Gyn., Johannesburg Hospital  
**Objective:** To investigate the secretion of CS in human milk.  
**Dosage Forms:** 20 mg CS t.i.d. for 4 days (no further information)  
**Study Design:**

This was a multiple-dose trial in 10 lactating women ( $25 \pm 1$  yr). Milk samples (5 ml) were taken before and 1 hr after the midday dose of CS. On day 4, blood was drawn at the time of the second milk sampling.

**Results:**

CS concentration in milk was  $6.2 \pm 1.3$  ng/ml on day 4, compared with  $137 \pm 8.1$  ng/ml in serum.

## BIOAVAILABILITY/BIOEQUIVALENCE STUDIES

### I. BIOAVAILABILITY OF THREE ORAL DOSAGE FORMS OF CISAPRIDE IN MAN.

**Study ID:** N49446; Ser # R51619/43  
**Reference:** Vol. 42, p. 6-324  
*Clinical Pharmacy, 6, 640-5 (1987)*  
**Date:** April-May 1984  
**Investigators:** A Van Peer, R Woestenborghs, J Heykants *et al.*  
**Site:** Hurtado Rutgers Student Health Services, New Brunswick, NJ.

#### Objectives:

- \* To determine the bioavailability of a suspension and two tablet formulations (5 and 10 mg) relative to an aqueous-solution.

#### Drug Dosage Forms:

*Treatment A:* two 5-mg tablets, lot # 84B28/F10, with 200 ml water

*Treatment B:* one 10-mg tablet, lot # 84A31/F09, with 200 ml water

*Treatment C:* 10 ml of 1 mg/ml suspension, lot # 83K04/F22, with 200 ml water

*Treatment D:* 10 ml of 1 mg/ml solution, lot # 84C20/F27, with 200 ml water.

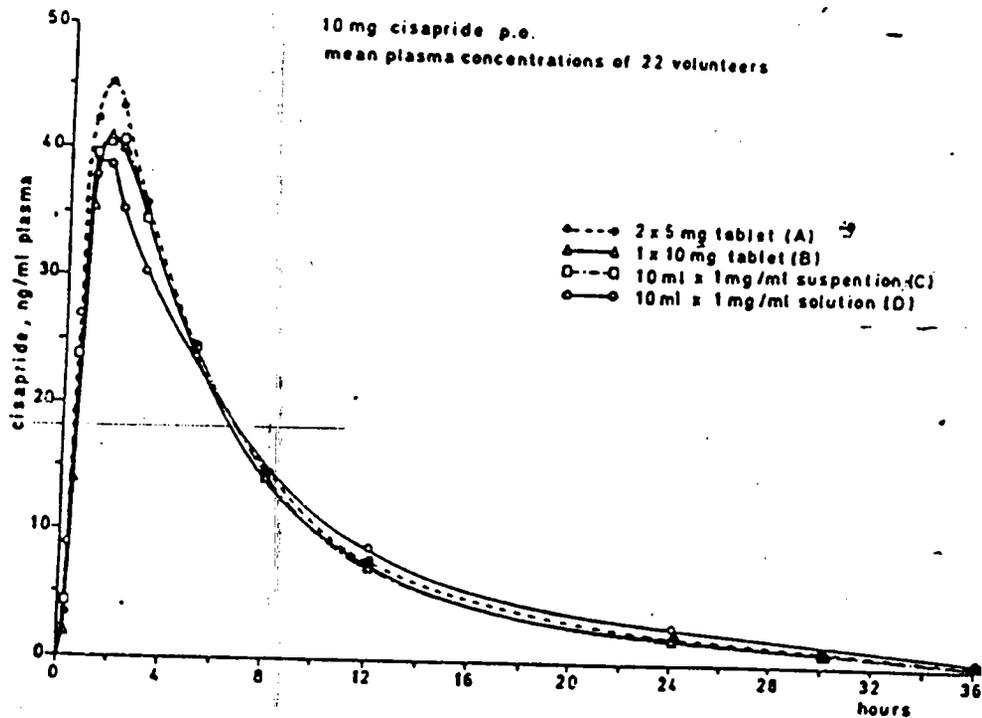
#### Study Design:

This was a randomized, cross-over study in 22 non-smoking, healthy male volunteers (18-30 yr, 62-81 kg). Subjects reported to the facility on the evening before each study day and fasted for at least 12 hr. Fifteen min after dosing, subjects received a standardized low-fat breakfast of 4 oz orange juice, 1.25 oz dry cereal, 2 slices white toast, 1 oz jelly, 4 oz skim milk. Lunch was given 4 hr post-dose. Subjects' movement was not restricted. Blood samples were collected at 0, 0.25, 0.5, 1.0, 1.5, 2, 3, 5, 8, 12, 24, 30, 36 and 48 hr.

#### Analytical Methodology:

CS was measured by HPLC (method I)

Results:



Parameter	2x5 mg Tab	1x10 mg Tab	10 mg Susp	10 mg Sol
$T_{max}$ , hr	1.5±0.5	1.7±0.5	1.7±0.7	1.3±0.5
$C_{max}$ , ng/ml	48.8±12.8	45.0±15.2	43.7±13.7	41.6±10.6
$AUC(0-48)$	345±134	325±117	326±118	344±131
$\beta$ , hr <sup>-1</sup>	0.105±0.019	0.103±0.021	0.112±0.030	0.096±0.022
$t_{1/2}$ , hr	6.80±1.28	7.03±1.62	6.61±1.69	7.62±2.01
$F_{rel}/Sol$	103.5±27.5	99.3±31.3	97.6±24.8	--

Mean ± S.D.

II. THE BIOEQUIVALENCE OF CISAPRIDE 20 MG TABLET AND SUSPENSION COMPARED TO TWO STANDARD 10 MG TABLETS IN HEALTHY VOLUNTEERS

Date: February-March 1990  
Study ID: JRD 51,619/1002  
Reference: Vol. 42, p. 6-400  
Investigators: J Barone and R Bierman  
Coll. Pharm, Rutgers Univ.; Hurtado Rutgers Student Health Service,  
New Brunswick, NJ.

Objective:

To determine the bioequivalence of both a 20 mg tablet and suspension of cisapride compared to two 10 mg tablets in healthy volunteers.

Dosage Forms:

- \* Treatment A: 10 ml suspension (2 mg/ml sorbitol base, Lot # 1699J001, mfg 8/89) followed by 190 ml water;
- \* Treatment B: one 20-mg tablet (Batch # 1298K003, mfg 11/89; batch size 267,600; Gurabo, PR) with 200 ml water
- \* Treatment C: two 10-mg tablets (Batch # 86E14/F09, exp 5/91; batch size 600,00; Beerse, Belgium) with 200 ml water

Study Design:

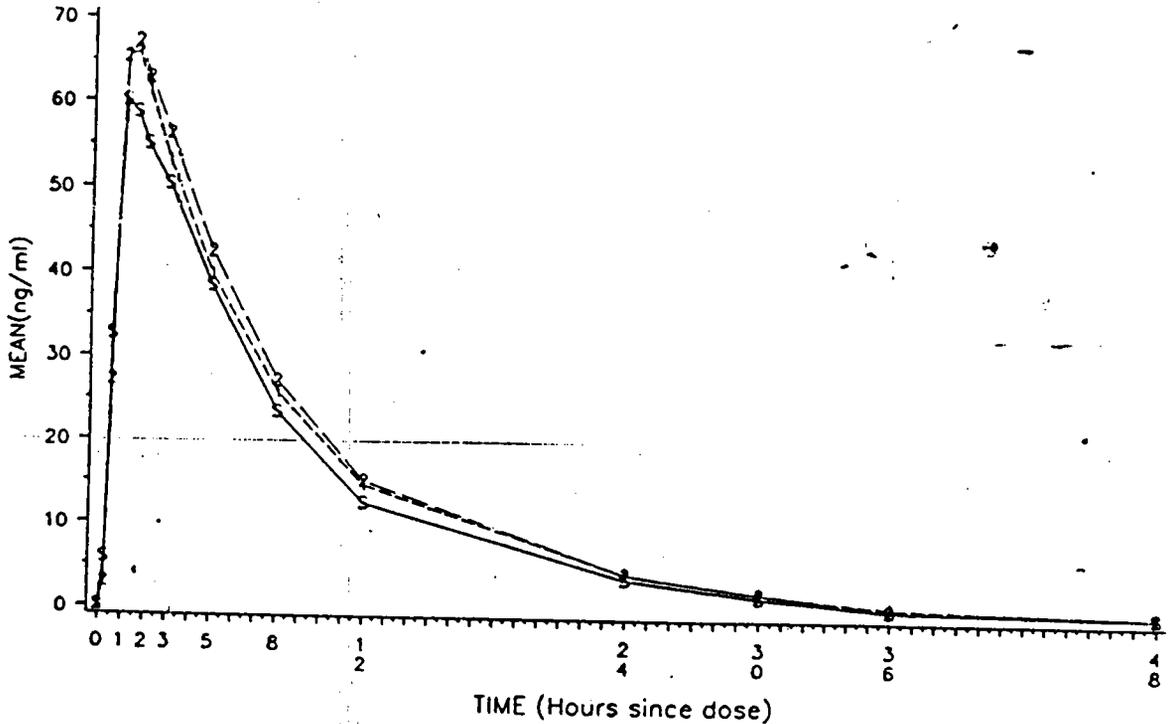
This was a randomized, single-dose, open, cross-over study in 27 healthy, non-smoking, male volunteers (23 White, 2 Oriental, 2 Asian Indians; 19-30 yr; 60-100 kg). Volunteers received either a single dose of two 10 mg cisapride tablets, one 20 mg cisapride tablet or 10 ml cisapride suspension (2 mg/ml). Each one-day treatment phase was separated by a six-day washout phase. Volunteers were admitted to the testing facility and cloistered overnight prior to dosing. After a supervised fast of at least 12 hr, the volunteers received one of the above treatments. Volunteers were permitted to drink water *ad libitum* except for two hr pre-dosing until 15 min post-dosing. A standardized breakfast consisting of 4 oz orange juice, 2.5 oz dry cereal, 2 slices of white toast with  $\leq 1$  oz jelly and 4 oz skim milk was served 15 min after dosing. From the time of dosing until the standard lunch was served (4 hr post-dose), the volunteers were requested to sit or stand. They were not permitted to lie down. Volunteers were permitted to resume normal eating habits 12 hr post-dose. They could leave the testing facility after 24 hr post-dose, but had to return for the 30-, 36- and 48-hr blood draws.

Blood for plasma level determinations was drawn at 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 30, 36 and 48 hr after dosing.

Analytical Methodology:

HPLC (method I).

Results:



Parameter		10 mg Tab (Ref)	20 mg Tab	Suspension
$T_{max}$ , hr	Mean $\pm$ SD	1.33 $\pm$ 0.46	1.35 $\pm$ 0.50	1.46 $\pm$ 0.96
	90% CI	--	79.0-123.8	87.3-132.1
$C_{max}$ , ng/ml	Mean $\pm$ SD	69.27 $\pm$ 14.84	71.20 $\pm$ 17.82	64.67 $\pm$ 16.22
	Geo. Mean	67.76	69.07	78.43
	90% CI	--	97.1-108.5	87.7-99.1
	90% CI (log-trans)	--	96.0-108.4	86.9-98.1
$AUC(0-48)$ ng hr/ml	Mean $\pm$ SD	572.9 $\pm$ 199.5	592.1 $\pm$ 223.3	519.3 $\pm$ 184.4
	Geo. Mean	544.3	559.2	489.4
	90% CI	--	97.1-109.6	84.4-96.9
	90% CI (log-trans)	--	95.8-110.2	83.8-96.5
$\beta$ , hr <sup>-1</sup>	Mean $\pm$ SD	0.12 $\pm$ 0.03	0.12 $\pm$ 0.04	0.13 $\pm$ 0.04
	90% CI	--	92.9-113.2	96.6-116.8
$AUC(0-\infty)$ ng hr/ml	Mean $\pm$ SD	573.9 $\pm$ 202.7	593.9 $\pm$ 229.5	520.7 $\pm$ 189.2
	Geo. Mean	544.7	559.9	490.0
	90% CI	--	97.2-109.8	84.5-97.0
	90% CI (log-trans)	--	95.8-110.3	83.9-96.5

Both the 20 mg tablet and the suspension were bioequivalent to the 2x10 mg tablets with all the parameters except for  $T_{max}$ .

The only sequence effect of at least marginal significance was for  $\log C_{max}$  ( $p=0.08$ ). The  $C_{max}$  ( $p=0.01$ ) and  $\log C_{max}$  ( $p=0.01$ ) values in phase I were significantly larger (about 6.5 ng/ml, on average) than in the other two phases.

## INFLUENCE OF AGE ON PHARMACOKINETICS

### I. SINGLE AND REPEATED-DOSE PHARMACOKINETICS OF CISAPRIDE IN HEALTHY ELDERLY VOLUNTEERS.

**Study ID:** N49639; Ser # R51619/75  
**Reference:** Vol. 43, p. 6-894  
**Date:** March 1986  
**Investigators:** H Burmeister, A Van Peer, R Gasparini *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt Clin. Res. and Devel., Janssen, Beerse, Belgium.

#### Objective:

To characterize CS pharmacokinetics in the elderly following single and repeated dosing with 5 mg.

#### Study Design:

The study was performed in 12 healthy elderly volunteers (7M, 5F; 68-77 yr; 55-94 kg).

#### 1. Single-dose phase:

Subjects received a 5 mg tablet of CS 30 min before breakfast. Blood samples were taken at 0, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hr after dosing.

#### 2. Multiple-dose phase:

One week after phase 1, subjects received 5 mg CS t.i.d. 30 min before meals for 13 days. On day 13, samples were taken before and at 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hr after the morning dose.

#### Assay:

CS was measured in serum by HPLC (method I).

#### Results:

Parameter	Mean $\pm$ SD	
	5 mg single dose <sup>1</sup>	5 mg tid steady state
$C_{predose}$ , ng/ml	--	25.4 $\pm$ 14.4
$C_{max}$ , ng/ml	25.1 $\pm$ 9.0	59.4 $\pm$ 33.2
$T_{max}$ , hr	2.7 $\pm$ 2.6	
$C_{24}$ , ng/ml	--	28.6 $\pm$ 15.5
$t_{1/2}$ , hr	12.9 $\pm$ 4.7	15.8 $\pm$ 3.4
$AUC(0-24)$ , ng·hr/ml	269 $\pm$ 111	1052 $\pm$ 456
$AUC(0-\infty)$ , ng·hr/ml	392 $\pm$ 246	
$C_{av}$ , ng/ml	--	43.8 $\pm$ 19.0

CS kinetics not different from young adults.

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II. REPEATED-DOSE PHARMACOKINETICS OF CISAPRIDE 10 MG TID IN THE ELDERLY

**Study ID:** N49640; Ser # R51619/76  
**Reference:** Vol. 43, p. 6-906  
**Date:** March 1986  
**Investigators:** F Fraschini, A Van Peer, R Gasparini *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt Clin. Res. and Devel., Janssen, Beerse, Belgium.

**Objective:**

To characterize CS kinetics following repeated oral dosing with 10 mg in healthy elderly volunteers.

**Study Design:**

The study was performed in 10 healthy male elderly volunteers (65-80 yr; 65-96 kg). Subjects received 10 mg CS t.i.d. 15 min before meals for 6 days. The last dose was taken in the morning on day 7. Blood samples were taken for 8 hr following the first dose on day 1. On day 7, samples were taken before and at 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 hr after dosing.

**Assay:**

CS was measured in serum by HPLC (method I).

**Results:**

Parameter	Mean $\pm$ SD	
	First Dose	Last Dose
$C_{min}$ , ng/ml	--	47.8 $\pm$ 21.0
$C_{max}$ , ng/ml	69.3 $\pm$ 12.2	105.4 $\pm$ 35.3
$T_{max}$ , hr	3.2 $\pm$ 1.7	--
$C_{12hr}$ , ng/ml	--	47.2 $\pm$ 20.3
$t_{1/2}$ , hr	7.8 $\pm$ 3.3	9.9 $\pm$ 3.7
$AUC(0-12)$ , ng·hr/ml	--	878 $\pm$ 315
$AUC(0-\infty)$ , ng·hr/ml	775 $\pm$ 240	--

CS kinetics not different from young adults.

## INFLUENCE OF DISEASE ON PHARMACOKINETICS

### I. THE PHARMACOKINETICS OF CISAPRIDE IN CONSTIPATED PATIENTS. -

Study ID: N46536  
Reference: Vol. 43, p. 6-817  
Date: August 1983  
Investigators: H Courtois  
Site: CRH of Rouen, 76000 Bois-Guillame, France

#### Objective:

To investigate the PK of CS in constipated patients.

#### Study Design:

This was a single-dose trial in 9 constipated patients (6M, 3F;  $63 \pm 18$  yr;  $66 \pm 17$  kg) who had less than 3 stools per week and who presented for various illnesses and were on a variety of other medications, but were considered in a stable condition. CS (10 mg tablet) was administered 15 min before breakfast which was the same for all patients (no further info). Blood samples were taken at 0, 0.25, 0.5, 0.75, 1.5, 2, 3, 4, 6, 8, 24, 28 and 32 hr post-dose.

#### Assay:

CS was measured in serum by HPLC (method I).

#### Results:

Parameter	Overall Mean $\pm$ SD	32-62 yr (n=5) Mean $\pm$ SD	76-90 yr (n=4) Mean $\pm$ SD
$C_{max}$ , ng/ml	$54.6 \pm 18.3$	$63.3 \pm 18.1$	$47.5 \pm 17.9$
$T_{max}$ , hr	$1.40 \pm 0.78$	$1.40 \pm 0.95$	$1.06 \pm 0.51$
TBC/F, ml/min/kg	$3.6 \pm 1.0$	$3.6 \pm 1.1$	$3.4 \pm 1.3$
$V_{area}/F$ , L/kg	$4.4 \pm 1.5$	--	--
$t_{1/2}$ , hr	$15.2 \pm 6.5$	$14.3 \pm 6.2$	$17.5 \pm 6.5$
AUC(0- $\infty$ )	$794 \pm 171$	$823 \pm 213$	$762 \pm 127$

No effect of constipation or age is evident from the results of this study.

II. THE PHARMACOKINETICS OF CISAPRIDE AFTER ORAL ADMINISTRATION TO CIRRHOTIC PATIENTS.

Study ID: N46952  
Reference: Vol. 43, p. 6-839  
Date: January 1986  
Investigators: D Dhumeaux, J Scemma-Clergue  
Site: INSERM U 99, Henri Mondor Hospital, 94010 Creteil, France.

Objective:  
To investigate the PK of CS in cirrhotic patients.

Study Design:

This was a single-dose trial in 8 cirrhotic patients (5F, 3M;  $53 \pm 16$  yr;  $67 \pm 15$  kg). Seven patients had alcoholic cirrhosis while one had hepatitis B. Seven patients received 10 mg tablets of CS 15 min before breakfast, while one received 10 mg i.v. over 1 min. Blood samples were taken at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 24, 28 and 32 hr after oral dosing and 0; 2, 5, 10, 15, 30 min, 1, 2, 4, 6, 8, 24, 28 and 30 hr after i.v. dosing.

Assay:  
CS was measured in serum by HPLC (method I).

Results:

Parameter	Oral 10 mg (n=7) Mean $\pm$ SD (range)	i.v. 10 mg (n=1)
$C_{max}$ , ng/ml	$36.0 \pm 20.9$ (10.6-69.3)	--
$T_{max}$ , hr	$3.46 \pm 2.65$ (1-8)	--
$t_{1/2}$ , hr	$18.1 \pm 10.0$ (8.1-36.2)	6.05
$AUC(0-\infty)$ , ng·hr/ml	$777 \pm 467$ (113-1331)	1223
$V_{area}$ , L/kg	--	0.78
TBC, ml/min/kg	--	1.49

No obvious difference in mean PK parameters compared to normals. Variability is higher.

### III. CISAPRIDE PHARMACOKINETICS IN RENAL INSUFFICIENCY

**Study ID:** N49228  
**Reference:** Vol. 43, p. 6-855  
**Date:** December 1985  
**Investigators:** M De Broe, G Verpooten, A Van Peer *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt Clin. Res. and Devel., Janssen, Beerse, Belgium.

#### Objective:

To characterize plasma concentration and urinary excretion of CS and NCS after single and repeated oral dosing in patients with renal insufficiency.

#### Study Design:

The study was performed in 5 patients with severe renal insufficiency (4F, 1M; 48-64 yr; 35-85 kg;  $Cl_{creatinine}$  6-17 ml/min).

##### 1. Single-dose phase:

Patients received a 10 mg tablets of CS 15 min before breakfast. Blood samples were taken at 0, 0.5, 1, 2, 4, 8, 12, 24, 32 and 48 hr after dosing.

Urine was collected over intervals up to 60 hr post-dosing.

##### 2. Multiple-dose phase:

Two weeks after phase 1, patients received 10 mg CS t.i.d. 15 min before meals for 7 days. Blood samples were taken before the morning dose on days 1, 2, 4, and 6. On day 7, samples were taken before and 1 hr after each dose and at 24, 28, 32, 36 and 48 hr after the morning dose.

Urine was collected at intervals for 60 hr after the morning dose on day 7.

#### Assay:

CS was measured in serum by HPLC (method). NCS was determined by GC (no description).

**Results:**

**1. Single Dose:**

Parameter	CS Mean±SD	NCS Mean±SD
$C_{max}$ , ng/ml	37.4±19.5	44.6±5.8
$T_{max}$ , hr	1.4±0.6	1.4±3
$\beta$ , hr <sup>-1</sup>	0.050±0.018	0.029±0.012
$t_{1/2}$ , hr	15±5	27±10
$AUC(0-\infty)$ , ng·hr/ml	503±248	569±272
$TBC/F$ , ml/min	422±250	--
$Cl_{renal}$ , ml/min	1.3±1.0	28±26
$X_u^\infty$ , % of dose	0.3±0.3	9.8±2.5

**2. Steady State:**

Parameter	CS Mean±SD	NCS Mean±SD
$C_{min}$ , ng/ml	33.5±29.7	64.5±4.5
$C_{24}$ , ng/ml	27.2±16.1	64.6±11.4
$C_{av}$ , ng/ml	50.5±28.6	72.5±9.2
$\beta$ , hr <sup>-1</sup>	0.054±0.011	0.020±0.007
$t_{1/2}$ , hr	13±3	40±19
$AUC(0-24)$ , ng·hr/ml	1212±687	1739±220
$TBC/F$ , ml/min	547±321	--
$Cl_{renal}$ , ml/min	1.1±1.0	21±3
$X_u^{24h}$ , % of dose	0.2±0.2	11.1±2.6

CS kinetics not different from normal. NCS more slowly eliminated.

IV. PHARMACOKINETIC SCREEN ON PLASMA CISAPRIDE IN PATIENTS

Study ID: N49718; R51619/79  
Reference: Vol. 44, p. 6-917  
Date: May 1986  
Investigators: A De Dier, J Peeters, A Van Peer *et al.*  
Site: Dpt. Drug Metab. and PK; Dpt Clin. Res. and Devel., Janssen, Beerse,

Objective:

To screen for potential unanticipated problems associated with CS therapy by examining a small number of plasma concentrations in a relatively large sample of patients of different age, sex and weight.

Study Design:

The study examines steady-state plasma concentrations from 8 studies including 102 adult patients (34M, 68F) with GERD, dyspepsia or constipation and 25 infants (13M, 11F, 1 not reported; 1 wk-1.25 yr) with excessive regurgitation. Samples examined were restricted to:

1. Samples taken either immediately before the morning dose or at 1-4 hr after the morning dose.
2. Samples with detectable CS levels; samples with CS levels < MQC were excluded because of possible patient non-compliance. This restriction was not applied to pediatric samples.
3. Samples from commonly used dosage regimens (4, 5 or 10 mg t.i.d.; 0.2 mg/kg for infants)

Results:

1. Effect of CS dose:

Dose Regimen	Samples before 1st dose		Samples 1-4 hr after 1st dose	
	n	Mean±SD	n	Mean±SD
4 mg tid	--	--	7	9.0±7.0
5 mg tid	15	12.3±9.34	--	--
10 mg tid	40	25.5±22.2	2	58.3±4.74
0.2 mg/kg	--	--	25	28.4±24.5

Pre-dose levels appear to be related to dose and comparable to corresponding values in normal subjects.

*Cisapride, 10&20 mg Tablets*  
*NDA 20-210; 8/29/92; 12/4/91*

*Influence of Disease, A31*

**2. Effect of duration of treatment:**

No evidence of systematic change.

**3. Effect of age, sex and body weight:**

No correlation observed.

**4. Global results of treatment:**

No correlation observed.

**5. Occurrence of adverse effects:**

No correlation observed.

## INFLUENCE OF FOOD ON PHARMACOKINETICS

### I. INFLUENCE OF FOOD AND REDUCED GASTRIC ACIDITY ON THE ORAL BIOAVAILABILITY OF A 10 MG CISAPRIDE TABLET IN MAN.

**Study ID:** N34451; Ser. # R51619/19  
**Reference:** Vol. 41, p. 6-231  
**Date:** June 1983  
**Investigators:** A Van Peer, R Woestenborghs, J Heykants *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt. Clin. Res. and Devel., Janssen, Beerse, Belgium.

**Objective:**

To investigate the influence of food and experimentally induced gastric acidity on the oral bioavailability of CS in healthy male volunteers.

**Dosage Forms:**

\* 10 mg CS tablets (lot # 82E06/F09)

**Study Design:**

This was a single-dose cross-over study in the same 6 healthy male volunteers (31-50 yr; 69-83 kg; 2 smokers) who participated in study N30670 (see under *PHARMACOKINETICS*).

**Phase I: Reduced Acidity/Fasting:**

Subjects received 400 mg cimetidine 2 hr pre-dose and 100 ml of 0.5% NaHCO<sub>3</sub> solution immediately following dose. Breakfast was served 2 hr post-dose.

**Phase II: Reduced Acidity/Fed:**

Subjects received 400 mg cimetidine 2 hr pre-dose and 100 ml of 0.5% NaHCO<sub>3</sub> solution and breakfast immediately following dose.

**Phase III: Food:**

Subjects received breakfast immediately following dose.

Breakfast consisted of 4 slices of bread, 20 g butter, 1 slice cheese, 1 slice ham, 2 cups coffee. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, 28 and 32 hr post-dose.

**Analytical Methodology:**

Method IV.

Results:

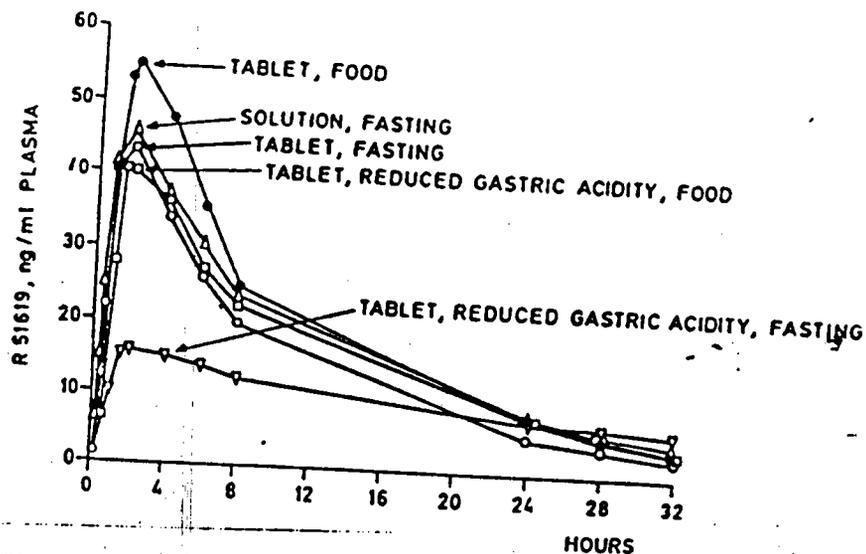


FIGURE 1: Time course in volunteers of the mean plasma levels of cisapride following oral administration of 10 mg in solution and in tablet under various conditions of food intake and reduction in gastric acidity.

Note: The tablet used in study 30670 is a non-clinical formulation while this study used a clinical formulation.

Parameter	Solution <sup>a</sup> Fasting	Tablet <sup>a</sup> Fasting	Tablet Food	Tablet/Fasting Red. Acid.	Tablet/Food Red. Acid.
$C_{max}$ , ng/ml	48 ± 12 <sup>b</sup>	49 ± 11	60 ± 7	17.6 ± 8.4	42.9 ± 13.0
$T_{max}$ , hr	2 ± 1	1.5 ± 0.5	2.0 ± 1.0	6.9 ± 8.5	2.2 ± 0.9
$AUC(0-24)$	518 ± 167	443 ± 92	571 ± 81	270 ± 69	467 ± 124
$AUC(0-\infty)$	643 ± 193	508 ± 99	673 ± 110	540 ± 277	576 ± 122
$F_{rel, 0-24h}/Sol$	--	--	1.19 ± 0.33	0.56 ± 0.23	0.95 ± 0.33
$F_{rel, 0-\infty}/Sol$	--	--	1.11 ± 0.28	0.83 ± 0.28	0.95 ± 0.15
$F_{rel, 0-24h}/Tab$	--	--	1.32 ± 0.19	0.62 ± 0.18	1.07 ± 0.29
$F_{rel, 0-\infty}/Tab$	--	--	1.35 ± 0.19	1.05 ± 0.43	1.15 ± 0.25

<sup>a</sup> Data from study 30670 in the same subjects  
<sup>b</sup> Mean ± S.D.

## DRUG INTERACTIONS

### I. UNALTERED ORAL ABSORPTION OF CISAPRIDE ON COADMINISTRATION OF ANTACIDS.

**Study ID:** N49374; Ser. # R51619/69  
**Reference:** Vol. 42, p. 6-544  
**Date:** February 1986  
**Investigators:** M Verinden, A Van Peer, R Gasparini, *et al.*  
**Site:** Dpt. Drug Metab. and PK; Dpt. Clin. Res. and Devel., Janssen, Beerse  
**Objective:**

To investigate the influence of antacids on the oral absorption and bioavailability of CS.

**Dosage Forms:**

- \* 10 mg of CS (no further information) t.i.d. 15 min before meals for 4 days (days 1-4)
- \* 10 mg of CS (no further information) t.i.d. 15 min before meals; 2 Maalox tablets (0.2 g Mg(OH)<sub>3</sub>, 0.4 g Al<sub>2</sub>O<sub>3</sub> per tablet) 1 and 3 hr after meals (6 times daily) for 4 days (days 5-8).

**Study Design:**

The study was performed in 6 healthy male volunteers (29-39 yr; 63-72 kg). On days 4 and 8, blood samples were taken just prior and 1 hr after each dose. Blood samples were also taken before the morning doses on days 5 and 9.

**Analytical Methodology:**

CS was measured by HPLC (method not specified).

**Results:**

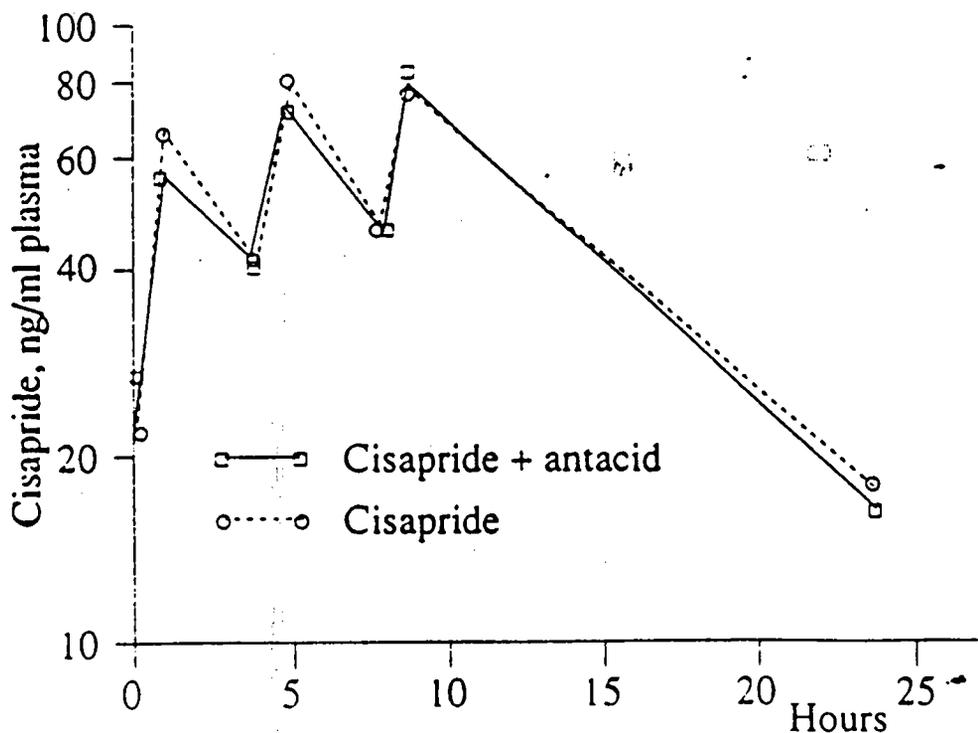


Table 1: Steady-state pharmacokinetic parameters of cispripide following cispripide 10 mg t.i.d., and on coadministration of antacids.

Parameter	AL	CF	GO	HV	JP	RR	Mean $\pm$ S.D.
<u>Cispripide 10 mg t.i.d.</u>							
C <sub>predose</sub> ng/ml							22.0 $\pm$ 6.7
C <sub>24 h</sub> ng/ml							17.9 $\pm$ 7.4
C <sub>max</sub> ng/ml							78.9 $\pm$ 31.1
AUC <sub>0-24 h</sub> ng/ml.h							1244 $\pm$ 406
C <sub>average</sub> ng/ml							52 $\pm$ 17
<u>Cispripide 10 mg t.i.d. and coadministration of antacids</u>							
C <sub>predose</sub> ng/ml							28.0 $\pm$ 14.5
C <sub>24 h</sub> ng/ml							16.8 $\pm$ 3.8
C <sub>max</sub> ng/ml							82.4 $\pm$ 17.7
AUC <sub>0-24 h</sub> ng/ml							1237 $\pm$ 237
C <sub>average</sub> ng/ml							52 $\pm$ 10

## II. CISAPRIDE-CIMETIDINE INTERACTION: ENHANCED CISAPRIDE BIOAVAILABILITY AND ACCELERATED CIMETIDINE ABSORPTION.

**Study ID:** N45340  
**Reference:** Vol. 42, p. 6-552  
*Ther. Drug Monit.*, **11**, 411-4 (1989)  
**Investigators:** W Kirch, HD Janisch, EE Ohnhaus, A Van Peer  
**Site:** Dpt. Drug Metab. and PK, Janssen, Beerse, Belgium.

### Objective:

To investigate the influence of CT and CS on the PK of each other.

### Dosage Forms:

- \* **Phase I:** 10 mg of CS (not specified) tid 30 min before meals for 7 days
  - \* **Phase II:** 10 mg of CS (not specified) tid 30 min before meals; 400 mg CT (not specified) tid with meals for 7 days.
  - \* **Phase III:** 400 mg CT (not specified) tid with meals for 7 days.
- Phases were separated by three-week drug-free washout periods.

### Study Design:

The study was performed in 8 healthy volunteers (5M, 3F;  $25 \pm 2$  yr;  $70 \pm 4$  kg). During each phase, blood samples were taken just prior and 1 hr after the morning dose on days 1, 2, 3 and 6. The last dose of each phase was administered on the morning of day 7; following this dose, blood samples were taken at 0, 0.5, 1, 2, 4, 8, 12, 24, 32 and 48 hr post-dose.

### Analytical Methodology:

CS was measured by HPLC (method II); CT was measured by HPLC (Randolphi *et al.*, *J. Pharm. Sci.*, **66**, 1148-50 (1977)).

### Results:

#### 1. Influence of CT on CS:

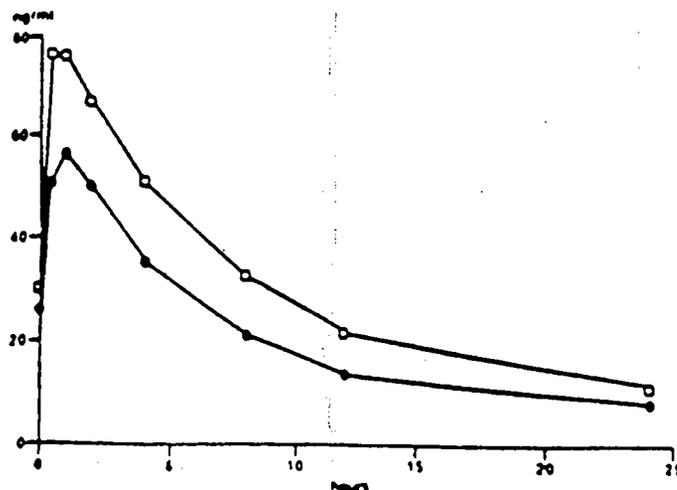


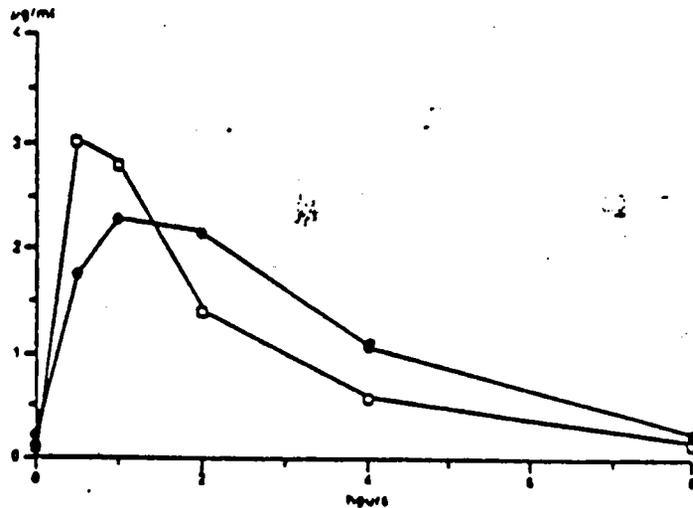
FIG. 1. Mean cisapride concentrations after the last 10-mg dose in the control state and during cimetidine coadministration. (●), Cisapride monotherapy; (□), cisapride plus 400 mg cimetidine three times daily.

Parameter	CS alone	CS/CT	p <sup>a</sup>
$C_{min}$ , ng/ml	26.7±16.0 <sup>a</sup>	30.7±10.2	0.15
$C_{max}$ , ng/ml	57.6±25.0	83.8±18.6	0.01
$T_{max}$ , hr	0.9±0.3	1.1±0.6	0.68
$AUC(0-8)$	302±104	425±77	0.01
$AUC(0-24)$	509±289	738±148	0.02
$t_{1/2}$ , hr	8.1±2.5	9.6±2.5	0.17
$Cl_o$ , ml/min	631±205	105±83	0.01
$Cl^{ren}$ , ml/min	1.4±0.8	1.3±0.7	0.70

<sup>a</sup> paired.t test  
<sup>b</sup> Mean ± S.D.

2. Influence of CS on CT:

FIG. 2. Mean cimetidine plasma concentrations after the last 400-mg dose in the control state and during cimetidine coadministration. (●), Cimetidine monotherapy; (□), cimetidine plus 10 mg cisapride three times daily.



Parameter	CS alone	CS/CT	p <sup>a</sup>
$C_{min}$ , ng/ml	0.23±0.17 <sup>a</sup>	0.13±0.07	0.17
$C_{max}$ , ng/ml	2.79±0.43	3.50±1.17	0.09
$T_{max}$ , hr	1.3±0.6	0.6±0.2	0.005
AUC(0-8)	9.6±1.7	8.0±1.7	0.03
AUC(0-24)	11.0±2.3	9.0±2.0	0.05
$t_{1/2}$ , hr	1.96±0.12	1.95±0.22	0.85
$Cl_o$ , ml/min	712±135	870±179	0.02
$Cl^{cr}$ , ml/min	288±139	286±135	0.98

<sup>a</sup> paired t test  
<sup>b</sup> Mean ± S.D.

### III. CISAPRIDE-RANITIDINE INTERACTION

**Study ID:** N49638; R51619/74  
**Reference:** Vol. 44, p. 6-1079  
**Investigators:** G Castelli, A Van Peer, R Gasparini *et al.*  
**Site:** Dpt. Drug Metab. and PK, Janssen, Beerse, Belgium.  
**Objective:**

To investigate the influence of RT and CS on the PK of each other.

**Dosage Forms:**

- \* **Treatment A:** A single dose of 150 mg RT (Zantac<sup>(R)</sup>)
- \* **Treatment B:** A single dose of 10 mg CS (not specified)
- \* **Treatment C:** Concurrent dosing with the above

Treatments were separated by one-week drug-free washout periods.

**Study Design:**

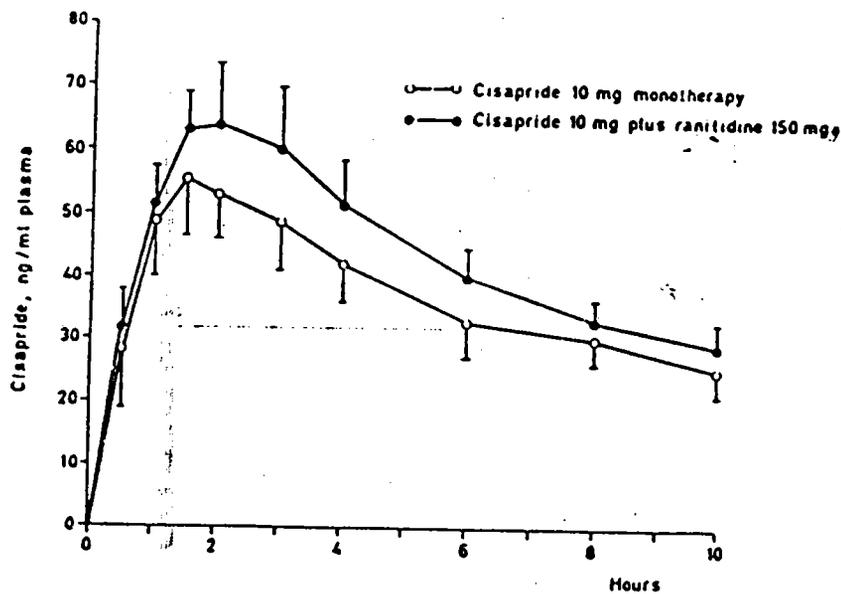
The study was performed in 5 healthy male volunteers (30-45 yr; 68-80 kg) in a randomized cross-over design. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 hr post-dose.

**Analytical Methodology:**

CS was measured by HPLC (method I); RT was measured by RIA (Jenner *et al.*; *Life. Sci.*, 28, 1323-9 (1981).

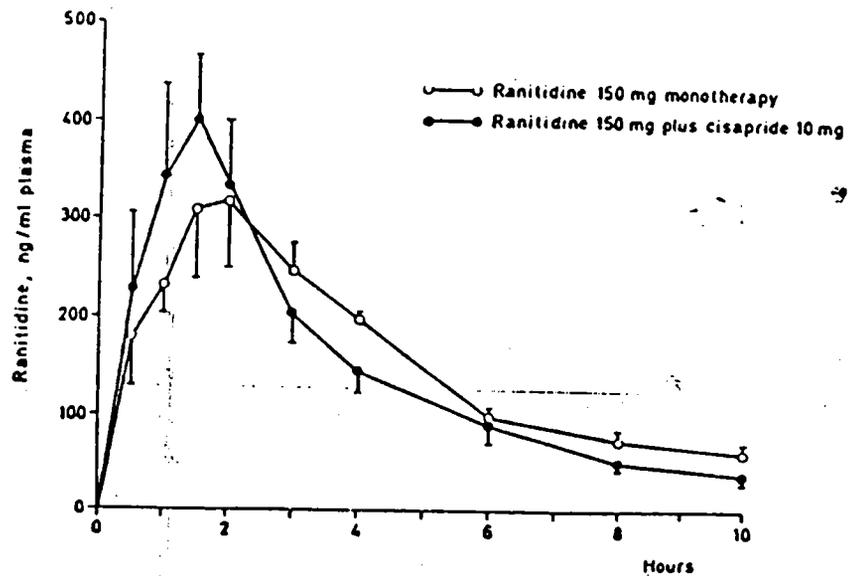
Results:

1. Influence of RT on CS:



Parameter	CS alone	CS/RT
$T_{max}$ , hr	1.7±0.4	1.7±0.3
$C_{max}$ , ng/ml	59.5±21.6	68.9±20.8
$AUC(0-10)$	368±125	432±109
$AUC(0-\infty)$	668±229	833±278
$\beta$ , hr <sup>-1</sup>	0.093±0.038	0.082±0.030
$t_{1/2}$ , hr	8.3±2.7	9.3±2.6

2. Influence of CS on RT:



Parameter	RT alone	RT/CS
$T_{max}$ , ng/ml	$1.6 \pm 0.2$	$1.2 \pm 0.4$
$C_{max}$ , hr	$343 \pm 155$	$450 \pm 159$
$AUC(0-10)$	$1451 \pm 289$	$1504 \pm 457$
$AUC(0-\infty)$	$1735 \pm 294$	$1548 \pm 440$
$\beta$ , $hr^{-1}$	$0.26 \pm 0.09$	$0.28 \pm 0.07$
$t_{1/2}$ , hr	$2.92 \pm 0.99$	$2.64 \pm 0.72$

ANOVA did not reveal any significant differences in the PK of either drug.

#### IV. CISAPRIDE-RANITIDINE INTERACTION

Study ID: N73165  
Reference: Vol. 44, p. 6-1094  
Investigators: DJ Rowbotham, WS Nimmo  
Site: Dpt. Anaesthesia, Sheffield University Medical School, UK  
Objective:

To investigate the influence of RT and CS on the PK of each other.

**Dosage Forms:**

- \* Treatment A: 150 mg RT + 10 mg CS (lot # 86C20/F09)
- \* Treatment B: 150 mg RT
- \* Treatment C: 10 mg CS

Treatments were separated by one-week drug-free washout periods.

**Study Design:**

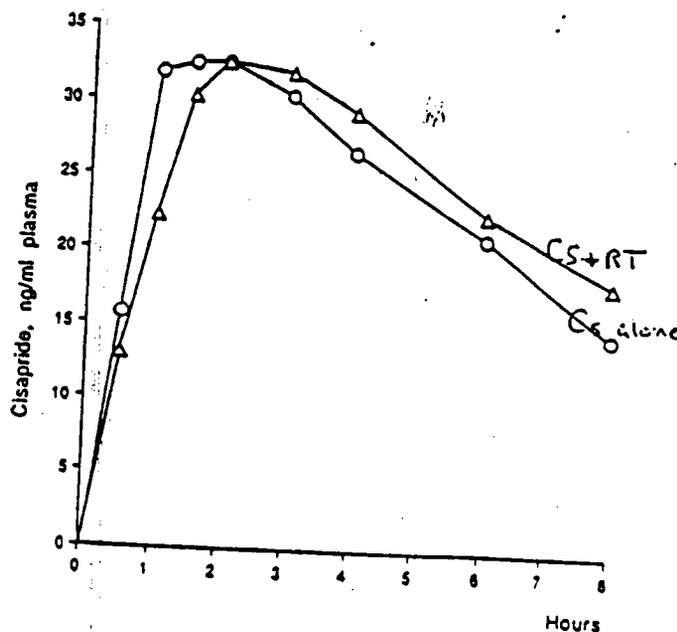
The study was performed in 12 healthy male volunteers (18-55 yr; within  $\pm 15\%$  of normal BW) in a randomized cross-over design. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hr post-dose.

**Analytical Methodology:**

CS was measured by HPLC (method II); RT was measured by HPLC (Carey *et al.*, *J. Liq. Chromatog.*, 2, 1391-1303 (1979)).

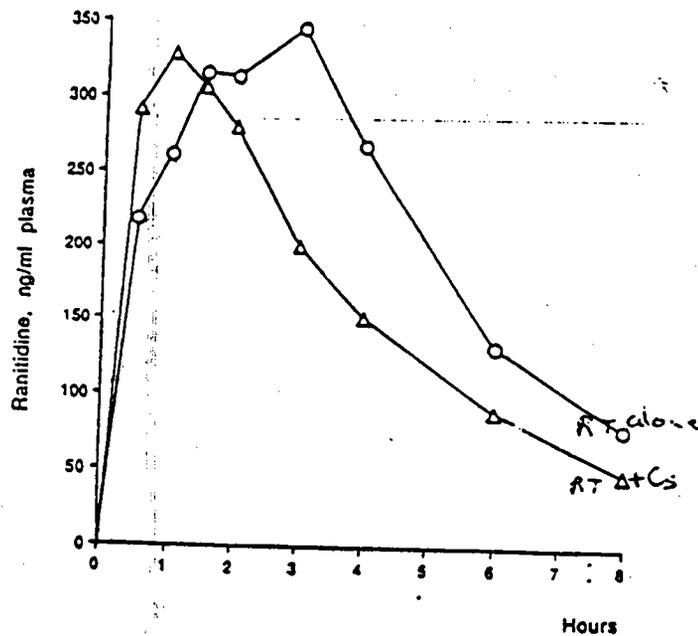
**Results:**

**1. Influence of RT on CS:**



Parameter	CS alone	CS/RT
$T_{max}$ , ng/ml	2.1±1.6	2.3±1.6
$C_{max}$ , hr	36.3±11.7	36.6±12.8
$AUC(0-8)$	191±60	196±57

2. Influence of CS on RT:



Parameter	RT alone	RT/CS
$T_{max}$ , ng/ml	2.1±1.2	1.0±0.5 <sup>a</sup>
$C_{max}$ , hr	438±101	434±138
$AUC(0-8)$	1725±241	1325±403 <sup>a</sup>

<sup>a</sup> p < 0.05 (ANOVA)

V. INFLUENCE OF METOCLOPRAMIDE AND CISAPRIDE ON DIGOXIN BIOAVAILABILITY

Study ID: N38913  
Reference: Vol. 44, p. 6-1113  
Investigators: W Kirsch, HD Janisch, U Dührsen *et al.*  
Site: Medical Dpt., Univ. Essen; GE Dpt., Klinikum Charlottenburg, Berlin, FRG.

Objective:

To investigate the influence of metoclopramide and CS on the bioavailability of DG in healthy volunteers.

Dosage Forms:

- \* Phase A: 0.5 mg DG bid for 3 days followed by 0.25 mg bid for 7 days.
- \* Phase B: 0.5 mg DG bid for 3 days followed by 0.25 mg bid + 10 mg metoclopramide tid for 7 days.
- \* Phase C: 0.5 mg DG bid for 3 days followed by 0.25 mg bid + 10 mg CS tid for 7 days.

In all phases, the last dose of DG was given in the morning on day 10. Phases were separated by "adequate" drug-free washout periods.

Study Design:

The study was performed in 6 non-smoking, healthy volunteers (4M, 2F;  $31 \pm 8$  yr;  $71 \pm 10$  kg). During each phase, blood samples were taken on days 4, 5, 6 and 9 before and 2 hr after the morning dose. After the last DG dose, blood samples were taken at 2, 4, 6, 12, 24, 48, 72, 96, 120, 168 and 240 hr post-dose.

Urine was collected

Analytical Methodology:

DG was measured by RIA ( $^{125}\text{I}$ -digoxin-RIA, Diagnostic Products Corp., Los Angeles).

Results:

Parameter	DG alone	DG/CS	DG/MCP
$T_{max}$ , hr	$1.72 \pm 0.16^a$	$2.21 \pm 0.14$	$2.22 \pm 0.05^b$
$C_{max}$ , ng/ml	$1.56 \pm 0.16$	$1.26 \pm 0.12$	$1.06 \pm 0.08^b$
$AUC(0-12)$	$736 \pm 73$	$605 \pm 34$	$636 \pm 32$
$X_r(0-12)$ , $\mu\text{g}$	$65.3 \pm 13.9$	$45.9 \pm 11.2$	$59.6 \pm 9.8$
$Cl_{ren}$ , ml/min	$106.2 \pm 19.2$	$77.3 \pm 7.1^b$	$100.9 \pm 8.1$

<sup>a</sup> Mean  $\pm$  SEM

<sup>b</sup>  $p < 0.05$  compared with DG monotherapy

VI. INFLUENCE OF CISAPRIDE ON PROPRANOLOL PLASMA CONCENTRATIONS AND BLOOD-PRESSURE LOWERING

Study ID: N46957; R51619/23-NL  
Reference: Vol. 44, p. 6-1124  
Investigators: B Hazelhoff, E van der Kleijn  
Site: Radboud Hospital, Nijmegen, The Netherlands

Objective:

To investigate the influence of CS on the plasma concentration and clinical blood-pressure lowering of a delayed-release formulation of PR.

Dosage Forms:

- \* Phase A: After a three-week placebo run-in period, subjects were administered a long-acting oral PR formulation (Inderal Retard®), 160 mg once daily at bedtime for 2 weeks.
- \* Phase B: CS 10 mg tid was concomitantly administered for one week, 15 min before meals.

Study Design:

Nine patients with mild hypertension (3M, 6F; 34-71 yr; 54-106 kg) participated in the study. Blood samples were taken on days 7 and 14 of Phase A and on day 7 of Phase B. Blood pressure (supine, upright) was measured before and during medication.

Results:

Time of Day	PR alone	PR/Cs	p value <sup>a</sup>
8:30 am	38.8±35.3	43.9±32.9	0.84
11:30 am	36.3±33.1	38.5±23.6	0.81
2:30 pm	37.5±29.7	26.4±24.1	0.15
5:30 pm	39.1±35.3	26.1±23.7	0.19

<sup>a</sup> two-tailed Wilcoxon signed rank test (n=8)

No pharmacokinetic or clinical interaction was found between PR and CS. There was no difference between the supine or upright systolic and diastolic blood pressures between the two-week PR and the one-week PR treatment blocks. CS did not influence the plasma PR concentrations and CS pre-dose plasma levels ( $25.2 \pm 14.4$  ng/ml) were similar to those found in volunteers in earlier studies.

VII. EFFECT OF CISAPRIDE ON ANTICOAGULANT TREATMENT WITH ACENOCOUMAROL

Study ID: N45574; R51619/14-NL  
Reference: Vol. 44, p. 6-1137  
Investigators: HJM Staal, JJC Jonker  
Site: St. Trombosediensten Artsenlaboratorium, Rotterdam, NL

**Objective:**

To investigate the influence of CS on anticoagulant treatment with acenocoumarol.

**Study Design:**

This was a placebo-controlled cross-over study in 22 patients who had been treated for at least six months with this anticoagulant. CS (10 mg tid) was administered for 3 weeks. The coagulation time and mean coagulation (thrombotest) values were determined.

**Results:**

Mean coagulation (thrombotest) values were 135 and 160 seconds for the placebo-CS sequence, and 165 and 115 seconds for the CS-placebo sequence.

Even though the clinical effect of CS on acenocoumarol was considered to be minor, it was recommended that thrombotest values be checked one week after the start or discontinuation of CS treatment in these patients in order to properly adjust acenocoumarol dosages.

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VIII. PHARMACOKINETICS OF PHENPROCOUMON ON SIMULTANEOUS INTAKE OF METOCLOPRAMIDE OR CISAPRIDE.

Study ID: N73359  
Reference: Vol. 44, p. 6-1145  
Investigators: D Wesemeyer, T Gaska, S Mausch *et al.*  
Site: Janssen Research Foundation, Neuss

**Objective:**

To investigate the influence of CS on the pharmacokinetics of phenprocoumon.

**Summary:**

The effects of metoclopramide and CS on the pharmacokinetics of phenprocoumon were evaluated in 24 healthy male and female volunteers. Phenprocoumon was given at a single oral dosage of 0.22 mg/kg alone and on Day 4 of a 10-day dosing regimen of either CS 10 mg QID or metoclopramide 10 mg TID. Metoclopramide significantly decreased the AUC of

phenprocoumon and significantly decreased the  $t_{1/2}$  from  $132 \pm 29$  hr to  $111 \pm 16$  hr. CS had no significant effect on either parameter, although a decreased bioavailability was observed in some individuals. The  $C_{max}$  was unaffected by either drug and the  $T_{max}$  was shortened by both drugs from 2.4 to 1.2 hr.

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**IX. EFFECT OF CISAPRIDE ON ANTICOAGULANT TREATMENT WITH WARFARIN**

**Study ID:** N73423  
**Reference:** Vol. 44, p. 6-1153  
**Investigator:** T Daneshmend  
**Site:** Dpt Therapeutics, University Hospital, Nottingham, UK.

**Objective:**

To investigate the influence of single and repeated-dose CS on warfarin anticoagulation in healthy volunteers.

**Summary:**

The interaction between a single dose of CS 10 mg or placebo and warfarin was evaluated in 12 healthy male volunteers. The volunteers were given warfarin over a period of 29 days at a dose that maintained the international normalized ratio (INR) between 1.30 and 1.66 (equal to a prothrombin time of 16 to 23 seconds). On Days 24 and 27, they were given a single dose of either CS 10 mg or placebo in a double-blind, randomized cross-over manner. After a five-day washout, the volunteers were given CS 10 mg QID for four days, then warfarin was administered and adjusted to give an INR between 1.30 and 1.66. There were no statistically significant interactions found between CS and warfarin. CS had no effect on the total warfarin dose required to maintain the INR between 1.30 and 1.66, nor did it affect warfarin blood levels.

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**X. AN EVALUATION OF POSSIBLE INTERACTIONS BETWEEN ETHANOL AND CISAPRIDE**

**Study ID:** N49087  
**Reference:** Vol. 44, p. 6-1200  
**Investigator:** C Idzikowski, P welburn  
**Site:** Clin. Pcol. Unit, Janssen Pharmaceutical Ltd., Grove, Wantage, UK

**Objective:**

To examine the psychomotor effects and pharmacokinetics of CS alone or in combination with a moderate dose of ethanol.

XI. THE ACTION OF CISAPRIDE ON GASTRIC EMPTYING AND THE PHARMACODYNAMICS AND PHARMACOKINETICS OF ORAL DIAZEPAM

Study ID: N49026  
Reference: Vol. 44, p. 6-1233  
*Eur J Clin Pharmacol*, 30, 205-8 (1986)  
Investigator: DN Bateman  
Site: Wolfson Unit of Clin Pcol, The University of Newcastle upon Tyne, UK

Objective:

To investigate the effect of i.v. CS (8 mg) on the absorption and CNS effects of oral diazepam.

Summary:

The actions of 8 mg i.v. CS on gastric emptying and oral absorption of diazepam were investigated in eight healthy volunteers. The rate of gastric emptying of 500 ml liquid containing 10 mg diazepam was assessed by direct measurement of the gastric volume using ultrasound.

CS increased the peak concentration of diazepam by 17.6% from  $369 \pm 18$   $\mu\text{g/ml}$  to  $434 \pm 20$   $\mu\text{g/ml}$ . It also shortened the time to the peak concentration from  $46 \pm 6$  min to  $33 \pm 4$  min. The  $AUC(0-1)$  was increased, but the bioavailability  $AUC(0-48)$  was not altered. Gastric emptying of the diazepam liquid was accelerated by CS ( $t_{1/2}$  placebo  $14.9 \pm 1.34$  min, CS  $7.4 \pm 0.4$  min). These changes in diazepam pharmacokinetics were associated with a lowered reaction-time response during the first 45 min after diazepam dosing, but did not alter self-rated sedation. There were no differences in reaction time after one hr.

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**XII. EFFECT OF CISAPRIDE ON MORPHINE-INDUCED DELAY IN GASTRIC EMPTYING**

**Study ID:** N46949  
**Reference:** Vol. 44, p. 6-1237  
*Br J Anaesth*, 59, 536-9 (1987)  
**Investigator:** DJ Rowbotham, WS Nimmo  
**Site:** Dpt Anaesth, Sheffield University Medical School, UK

**Objective:**

To investigate the effect of i.m. CS (4 mg) on the gastric emptying in patients after premedication with morphine

**Summary:**

The effect of intramuscularly injected CS on morphine-induced delayed gastric emptying was assessed in preoperative patients using the rate of oral acetaminophen absorption as a measure of the rate of gastric emptying. Forty patients randomly received one of four intramuscular premedications: 1) placebo only, 2) 10 mg morphine, 3) 10 mg morphine plus 10 mg CS, and 4) 10 mg morphine plus 4 mg CS. The morphine only group and the morphine plus 4 mg CS group showed delayed gastric emptying compared to the placebo group. The morphine-induced delay in gastric emptying was prevented by 10 mg CS as there was no difference in gastric emptying between this group and the placebo group.

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**XIII. CISAPRIDE AND ANTIPYRINE KINETICS**

**Study ID:** N45270  
**Reference:** Vol. 44, p. 6-1241  
**Investigator:** D Davies, FJ Mills, E Hughes  
**Site:** Dpt Clin Pcol, Hammersmith Hospital, London, UK

**Objective:**

To investigate the possibility of hepatic microsomal oxidative enzyme induction by CS using antipyrine as a marker.

**Summary:**

Antipyrine was orally administered to 14 healthy volunteers to investigate whether chronic administration of CS might induce or inhibit hepatic microsomal oxidation in man. Subjects were given 10 mg CS tid for 28 days, 15 to 30 min before meals. A single oral dose of 600 mg antipyrine was given five days before the CS treatment started, and again on Days 8 and 28 to assess the single-dose antipyrine kinetics.

There were no significant changes in antipyrine clearance or half-life by the one-week or four-week CS treatment compared to the pretreatment values. The volume of distribution was not significantly changed in the female volunteers (n=7), while a small, but statistically significant, increase occurred in the male volunteers and in the total group (Table 9). Liver function tests revealed no significant changes in alkaline phosphatase, gamma-glutamyl transpeptidase, SGOT or bilirubin during the study.

Parameter	Day 0	Day 8	Day 28
<i>TBC</i> , ml/min	50.4±3.4	52.0±4.6	49.7±3.1
All (n=14)	45.7±3.9	44.6±1.4	46.1±4.5
7 F	55.1±5.3	59.4±8.3	53.2±4.2
7 M			
<i>t</i> <sub>1/2</sub> , h			
All (n=14)	10.88±0.68	10.78±0.69	11.62±0.71
7 F	9.90±0.55	10.09±0.63	10.67±0.67
7 M	11.86±1.18	11.47±1.22	12.57±1.21
<i>V</i> , L			
All (n=14)	44.6±2.9	46.5±2.6	48.5±2.5*
7 F	35.5±1.8	38.7±2.0	41.4±2.5
7 M	53.7±2.3	54.2±2.3	55.6±2.1*

Mean±SEM  
 \* p<0.05

## PLASMA PROTEIN BINDING

### I. THE PLASMA PROTEIN BINDING OF CISAPRIDE AND ITS DISTRIBUTION IN BLOOD.

Study ID: N38637; Ser. # R51619/27  
Reference: Vol. 43, p. 6-770  
Date: April 1984  
Investigators: W Meuldermans, J Van Houdt, J Heykants *et al.*  
Site: Dpt. Drug Metab. and PK, Janssen, Beerse, Belgium.

#### Objective:

To characterize the plasma protein binding and distribution in blood of CS *in vitro*.

#### Drugs Used:

- \* <sup>3</sup>H-CS (labeled at position 2 of the fluorobenzoyl moiety), batch # 395, specific activity 181  $\mu$ Ci/mg and a radiochemical purity of 99.6%,
- \* Non-radioactive CS, Batch # A2801
- \* Non-radioactive NCS, diazepam and cimetidine

#### Procedure:

Equilibrium dialysis against suitable buffers.

#### Analytical Methodology:

Liquid scintillation spectrometry.

#### Results:

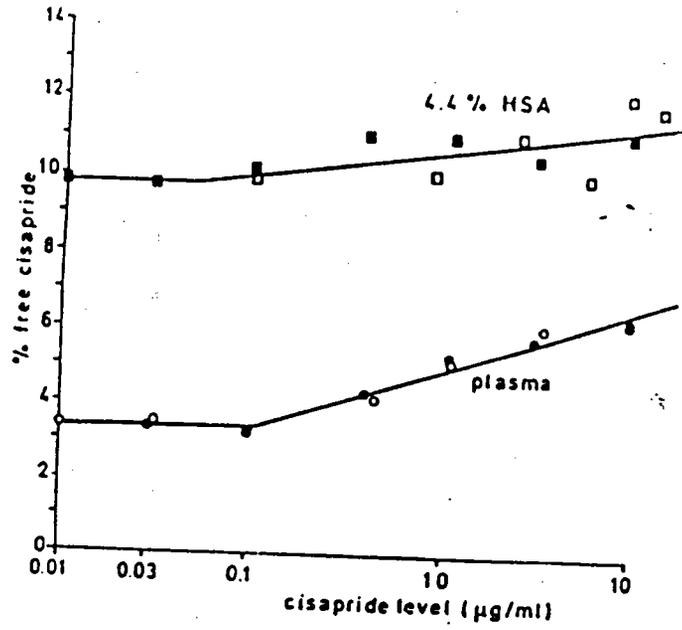
##### 1. Blood Distribution:

Parameter	Mean $\pm$ S.D.
<i>Hematocrit</i>	0.44 $\pm$ 0.01
<i>Fraction bound in plasma</i>	0.9748 $\pm$ 0.0020
<i>Fraction dist. to plasma water in blood</i>	0.0193 $\pm$ 0.0013
<i>Fraction bound to plasma proteins in blood</i>	0.8500 $\pm$ 0.0222
<i>Fraction dist. to cells in blood</i>	0.1308 $\pm$ 0.0212
<i>Fraction dist. to cells in cell suspension</i>	0.9068 $\pm$ 0.0052
<i>Blood/plasma concentration ratio</i>	0.6444 $\pm$ 0.0142

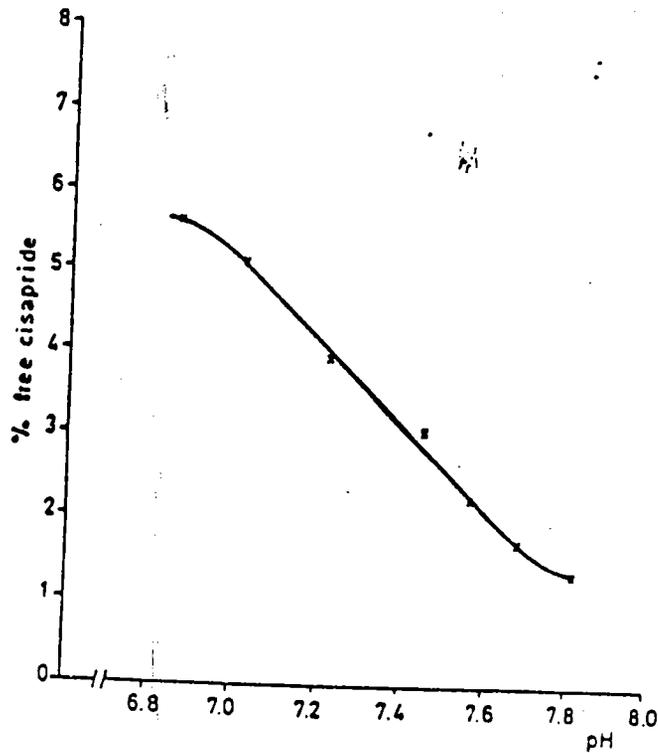
##### 2. Influence of other drugs:

The addition of NCS, diazepam or cimetidine in concentrations normally achieved under therapeutic regimens did not alter the plasma protein binding of CS.

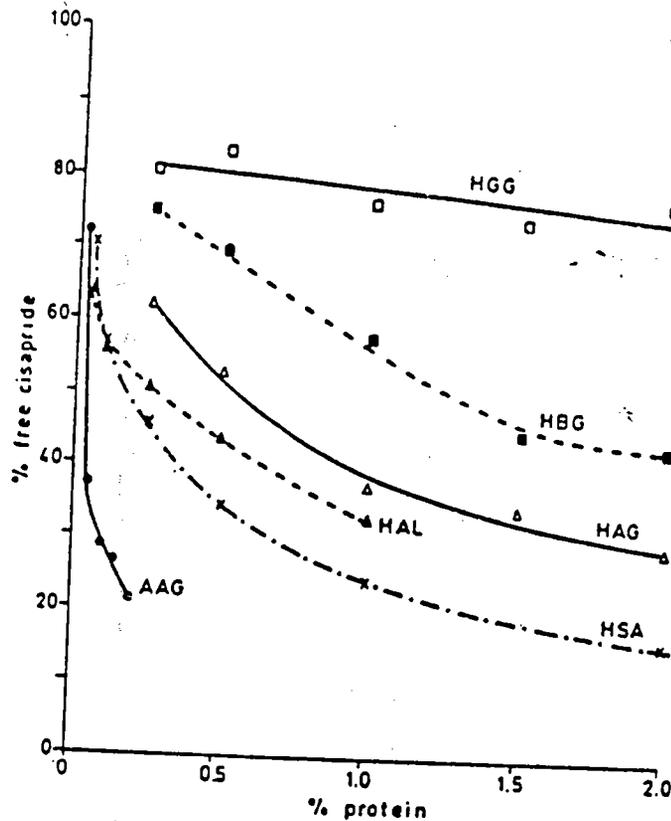
3. CS concentration:



4. Influence of pH:



5. Protein Concentration:



II. FURTHER STUDIES ON THE PLASMA PROTEIN BINDING OF CISAPRIDE: IN-VITRO PROTEIN BINDING INTERACTIONS. IN-VITRO AND EX-VIVO PLASMA PROTEIN BINDING IN HEALTHY SUBJECTS AND IN PATIENTS WITH RENAL INSUFFICIENCY.

Study ID: N49177; Ser. # R51619/51  
Reference: Vol. 43, p. 6-792  
Date: February 1986  
Investigators: W Meuldermans, E Mostmans, A Van Peer, J Heykants  
Site: Dpt. Drug Metab. and PK, Janssen, Beerse, Belgium.

Abstract:

The plasma protein binding of CS at 100 ng/ml was not influenced by high therapeutic concentrations of imipramine, propranolol, diazepam, tolbutamide, cimetidine, indomethacin and sulfamethazine. High concentrations of phenytoin (20 µg/ml) and warfarin (10 µg/ml) caused a relative increase of the free fraction of CS of 8% and 33%, respectively.

CS, at 100 ng/ml, did not influence the plasma protein binding of imipramine, propranolol, diazepam, phenytoin or warfarin.

In healthy subjects *in-vitro* and *ex-vivo* binding was identical (98.0%) under single-dose conditions. At steady-state, however, *ex-vivo* binding was significantly lower (97.3%), probably due to non-linearity of binding.

In patients with renal insufficiency, protein binding decreased to 97.1% *in vitro* and 96.6% *ex vivo* at steady state.

Plasma protein binding of total radioactivity in healthy subjects following the administration of a single oral dose of  $^{14}\text{C}$ -CS was < 85%.

Changes in plasma protein binding of CS are not expected to be of clinical importance due to its large volume of distribution.

## IN-VITRO DISSOLUTION

### Proposed Dissolution Method:

Strengths: 10 mg and 20 mg  
Apparatus: USP II (paddle)  
Medium: 0.1N HCl  
Volume: 900 ml  
Agitation: 50 rpm  
Sampling time: 45 min  
Assay: UV absorbance at 274 nm  
Specification: Q = [REDACTED]  
Q = [REDACTED]

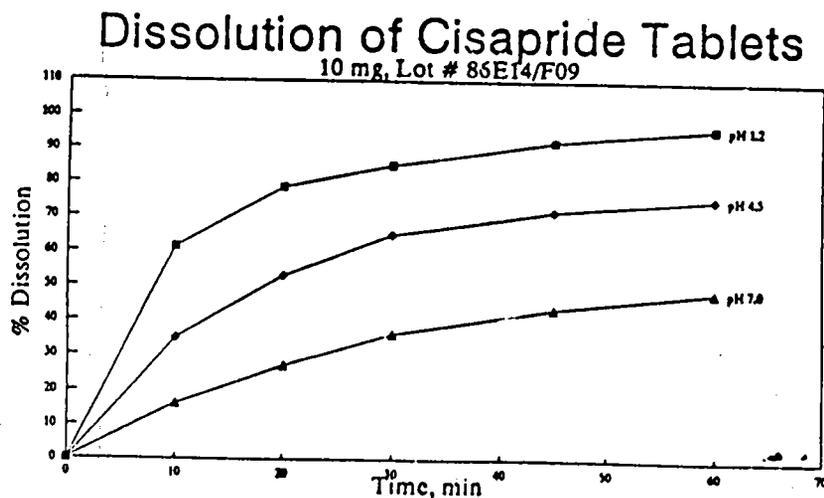
### Dissolution Studies:

Dissolution was tested on 6 tablets using the above method at 37°C in media of varying pH:

- \* 0.1N HCl, pH 1.2
- \* Water, pH 7.0
- \* citrate-phosphate buffer, pH 4.5
- \* phosphate buffer, pH 7.5

The results are summarized below:

1. 10-mg Tablets: Batch # 86E14/F09

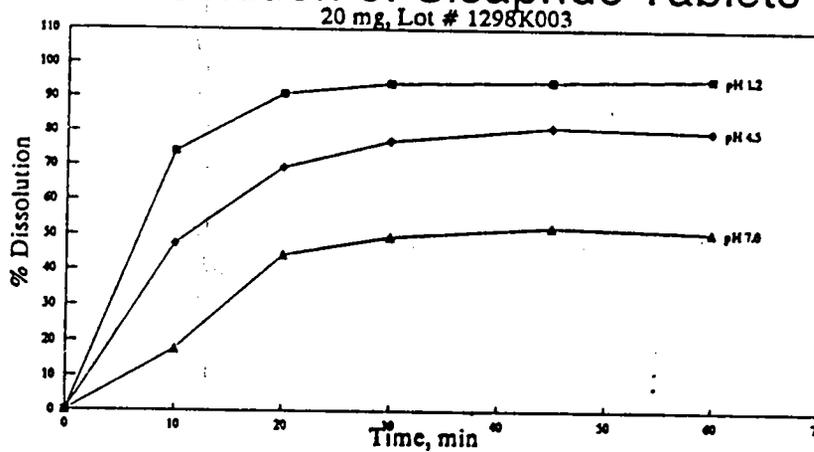


Time, min	pH 1.2	pH 4.5	pH 7.0	pH 7.5
10	61.4±7.37 <sup>a</sup>	35.0±6.78	16.3±3.55	-- <sup>b</sup>
20	78.7±10.1	53.0±9.38	27.4±4.47	--
30	85.3±9.98	64.9±9.28	36.3±7.00	--
45	92.3±6.37	71.9±6.11	43.6±8.15	--
60	96.3±2.02	75.6±4.83	48.8±8.39	--

<sup>a</sup>, % dissolved, Mean ± SD; <sup>b</sup>, No drug detected

2. 20-mg Tablets: Batch # 1298K003

Dissolution of Cisapride Tablets



Time, min	pH 1.2 <sup>a</sup>	pH 4.5	pH 7.0	pH 7.5
10	74.0±5.92 <sup>b</sup>	47.4±5.69	17.6±12.1	-- <sup>c</sup>
20	90.9±3.42	69.4±5.34	44.1±21.5	--
30	93.9±3.00	77.1±3.24	49.5±26.0	--
45	94.5±2.36	81.3±3.58	52.4±27.7	--
60	95.4±3.43	80.1±1.20	50.8±28.4	--

<sup>a</sup>, 12 tablets; <sup>b</sup>, % dissolved, Mean ± SD, <sup>c</sup>, No drug detected

Dissolution of both tablet strengths was most complete and least variable at pH 1.2.

Time Profile Dissolution Data on Cisapride 10 mg Tablets 2

	10 Min	20 Min	30 Min	45 Min	60 Min
Vessel 1	88.6%	96.2%	92.7%	94.8%	95.9%
Vessel 2	76.5%	89.2%	97.9%	98.3%	98.3%
Vessel 3	69.2%	92.3%	98.6%	99.0%	99.0%
Vessel 4	79.6%	97.2%	95.8%	97.2%	96.9%
Vessel 5	83.0%	95.5%	92.4%	93.1%	92.8%
Vessel 6	84.8%	91.3%	95.8%	96.2%	95.9%
Vessel 7	86.8%	96.5%	97.9%	98.3%	95.3%
Vessel 8	86.8%	98.6%	99.3%	100.0%	100.0%
Vessel 9	87.5%	94.4%	95.1%	95.8%	95.8%
Vessel 10	79.9%	93.7%	94.7%	95.8%	95.8%
Vessel 11	59.0%	72.4%	82.5%	84.6%	86.4%
Vessel 12	85.1%	95.1%	95.5%	96.2%	96.5%
Average	80.6%	92.7%	94.9%	95.8%	96.0%
%RSD	10.9%	7.4%	4.7%	4.2%	3.7%

7 Page(s)

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