NDA 20,210 Review #1

SPONSOR & ADDRESS: Janssen Research Foundation,

Piscataway, New Jersey

REVIEWER: Yash M. Chopra, M.D., Ph.D.,
Pharmacologist

DATE OF REVIEW: July 6, 1992

DATE OF SUBMISSION: Original Submission - August 29, 1991
Amendment - November 27, 1991
Amendment - December 9, 1991
Amendment - December 17, 1991
Amendment - May 28, 1992 ym

HFD-180 RECEIPT DATE: Original Submission - August 30, 1991
Amendment - November 29, 1991
Amendment - December 10, 1991
Amendment - December 18, 1991
Amendment - June 4, 1992 ym

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

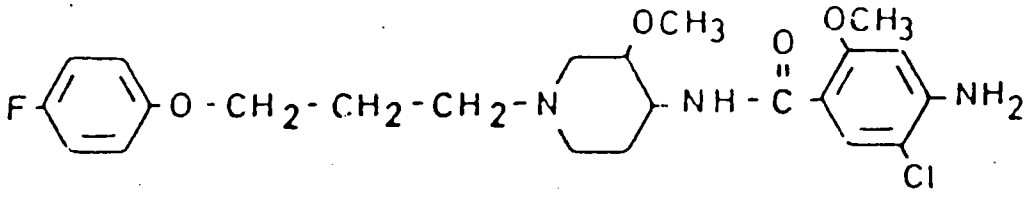
DRUG: Cisapride Monohydrate/Propulsid Tablets

CHEMICAL NAME: (±)-cis-4-amino-5-chloro-N-{1-[3-(4-fluorophenoxy) propyl]-3- methoxy-4-piperidinyl}-2-methoxybenzamide. It is a mixture of (+) and (-) enanticmers and is a white to beige colored powder with no odor. Each 1.04 mg of cisapride monohydrate is equivalent to 1 mg of cisapride.

MOLECULAR WEIGHT: 483.97

MOLECULAR FORMULA: $C_{25}H_{29}ClFN_3O_4 \cdot 4\ H_2O$

STRUCTURAL FORMULA:



NDA 20,210

FORMULATION: Each Propulsid tablet contains 10 or 20 mg of cisapride as a monohydrate. The composition (in mg) of tablets is as below:

Ingredients	Average composition of Tablets	
	10 mg	20 mg
Cisapride Monohydrate	10.39	20.78
Lactose Monohydrate NF		
Corn Starch NF		
Microcrystalline cellulose		
Povidone, USP (K90)		
Magnesium Stearate, NF		
Colloidal silicone dioxide, NF		
Polysorbate 20, NF		
Purified water, USP		

CATEGORY: Gastrointestinal Prokinetic Drug

RELATED INDs No:

MARKETING INDICATION: Cisapride is indicated for gastroesophageal reflux disorders (GERD) characterized by the symptoms of heartburn, regurgitation, esophagitis and epigastric pain.

DOSE: Cisapride is recommended at a dose 0.8 mg/kg/day (based on 50 kg body weight of an adult) orally in 4 divided doses (i.e., 0.2 mg/kg, q.i.d.) and administered at least 15 min before meals and at bedtime. If needed, the dose could be increased to 1.6 mg/kg/day.

PRECLINICAL STUDIES AND TESTING LABORATORIES

Type of Study	Study/Report #	Name of Laboratory	Drug Batch #
I.PHARMACOLOGY	--	--	--
II.ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION:			
1. Single I.V./Oral Dose Absorption and Pharmacokinetics Study in Rat	R 51619/26	Janssen	376 (Radioactive)
2.Absorption,Metabolism and Excretion in Male Dog after an oral Dose	R 51619/28	Janssen	A109 (Radioactive)

3. Pharmacokinetics after a single I.V.or Oral Dose in Dogs	R 51619/49	Janssen	84G03/F15
4.Absorption and Plasma Levels of Orally Administered Cisapride in Rabbits	R 51619/17	Janssen	81K/9/F02
5. Absorption, Tissue Distribution, Metabolism and Excretion in male rats (Single Vs Multiple Oral Doses)	R 51619/57	Janssen	A109
6.Pharmacokinetics after 1-Month I.V. Repeat Dose Study in Dogs	1097	Janssen	A109
7.Pharmacokinetics after 12-Month Oral Repeat Dose Study in Dogs	1104	Janssen	A109
8.Absorption and Distribution Study in Rats	R 51619/31	Janssen	A109
9.Distribution Study by Autoradiography in Pregnant and Male Rats	R 51619/29	Janssen	A109
10.Absorption and Distribution after a Single Dose of 10,40 or 160 m/kg in rats.	R 51619/35	Janssen	A109
11. Placental Transfer in Rats after an I.V. or an Oral Dose	R 51619/33	Janssen	A109
12.Excretion in Milk in Lactating Dogs	R 51619/32	Janssen	A109 Radioctive
13.In vitro Protein Binding Study in Plasma Samples of Rats, Dogs and Human	R 51619/27	Janssen	A109
14.In vitro,Pure Proteins Binding Studies	R 51619/27	Janssen	A 109
15.Induction of Hepatic Drug Metabolizing enzymes in Male Rats	R 51619/37	Janssen	--

III. TOXICOLOGY:

1. Acute Toxicity Studies:

a. <u>p.o.</u>

Rat	51619/50	Janssen	A201
Newborn Rat	51619/41	Janssen	A2801
Mouse	51619/38	Janssen	A2801
Dog	51619/4	Janssen	A0201
b. i.v.			
Rat	51619/1	Janssen	A201
Mouse	54427/1	Janssen	V860-131
	54432/1	Janssen	A0101
Dog	51619/3	Janssen	A0101
c. i.m.	51619/46	Janssen	AC0101
Rat	51619/48	Janssen	C0101

2. Subacute/Subchronic/Chronic Toxicity Studies:

a. Rat

1-Month I.V. Toxicity Study	1096	Janssen	A0101
3-Month Toxicity Studies:			
(i) by Gavage	1377	Janssen	A2801
(ii) Diet	1111	Janssen	A0501,A0601
(iii) Rectal	1624	Janssen	A3201
6-Month Oral Toxicity Studies:			
(i) In Adult Rat	1150	Janssen	C0101
(ii) Neonate Rat	1771	Janssen	C0101
12-Month Oral Toxicity Study	1667	Janssen	C0101
18-Month Oral Toxicity Study	1151	Janssen	A1601

b. Dog:

1-Month i.v. Study	1097	Janssen	A0201
3-Month Oral Study	1114	Janssen	A0501-A0601
3-Month Rectal Study	1623	Janssen	A3201

12-Month Oral Study	1144	Janssen	A1601
12-Month Oral Toxicity Study in Neonate Dogs	1851	Janssen	C0101

3. Carcinogenicity Studies:

Mice	(Old)	1145	Janssen	C0101
	(New)	1987	Janssen	C0101
Rats	(Old)	1230	Janssen	A2501
	(New)	1952	Janssen	D011-BEA031

5. Reproductive Toxicity Studies:

a. Oral Segment I. Fertility and Reproductive Performance Study in Rats

i)	1166	Janssen	A1301
ii)	2025	Janssen	C0101

b. Oral Segment II. Teratology Study

i) Rats	1141	Janssen	A0601
	1167	Janssen	A1301
ii). Rabbits	1099	Janssen	A0201
	1143	Janssen	A0601
	1578	Janssen	A1301

c. Oral Segment III. Perinatal and Postnatal Study

Rats	1142	Janssen	A1301

IV. MUTAGENICITY:

1. Ames Test (a)	25524		A0501
(b)	2195	Janssen	BEA011

2. In Vitro Chromosomal Aberration Assay:

In Human lymphocytes

(a)	49404	BEA 011
(b)	14276	BEA011

ii) Mouse Lymphoma forward	14265		BEA011
iii) Rat Hepato-UDS Assay	192701		BEA031
iv) Dominant Lethal Test in Male and Female Mice	1148/1154	Janssen	A1301
v) Rat Micronucleus Test	1164	Janssen	A0201
vii) Drosophila Sex Linkage Test	1178	Janssen	A1601

GOOD LABORATORY PRACTICE & QAU REGULATIONS:

Sponsor has included the statements that all preclinical studies were conducted in compliance with GLP and QAU regulations.

PHARMACOLOGY:

Cisapride a gastroprokinetic agent, is claimed to stimulate gastrointestinal tract motility by facilitating postganglionic cholinergic nerves neurotransmission in myenteric plexus and increasing acetylcholine release in stomach, small intestines and colon. It exerts only an insignificant effect on the gastro-intestinal secretions and other non-cholinergic receptors. The pharmacology of the compound is discussed below:

Primary Pharmacology

1. Effects on Gastrointestinal Motility:

(a) In vitro Studies: Cisapride (10^{-9} to 10^{-6} M), increased the motility of isolated tissue preparations of esophagus, stomach, small intestines and large intestine of rat, dog, cat, rabbit and opossum. It (10^{-9} M) also enhanced the motility of isolated strips of human intestines, colon and large intestines in tissue preparations. The higher concentrations of the compound (10^{-6} M) produced an inhibition in the motility of esophagus, stomach, small and large intestines of rat, dog, cat, rabbit and opossum thus produced a U-shaped dose response curve. Cisapride induced increase in motility was mediated by cholinergic nerves and release of acetylcholine, as these responses were blocked by atropine and not by an antihistaminic (H_1 or H_2)-, adrenergic blocking drugs (α_1, α_2, β)-, dopaminergic blocking agents (D_1 and

NDA 20,210

LABELLING:

The draft labelling of cisapride conforms to the format specified under CFR 21, subpart B, 201.50 to 201.57 dated April 1991.

RECOMMENDATIONS:

1. From preclinical standpoint, the application is approvable.

7.13.1992.

Yash, M. Chopra, M.D., Ph.D
Pharmacologist, HFD-180

PHARMACOLOGY/TOXICOLOGY REVIEW

HFD-180

NDA# 20,210
IND#
INDICATIONS: Gastroprokinetic
SPONSOR: Janssen

DRUG NAME: Cisapride (Propulsid)
OTHER NAMES:

STEREOISOMER? yes___ no_X__
DELIVERY SYSTEM? yes___ no_X__

Toxicology Studies Included in this Review:

	Mouse	Rat	Rabbit	Dog	Other
Single Dose					
Intravenous	X	X		X	
Identify route (p.o)	X	X		X	
Newborn		X		X	
Repeat Dose					
14 day		X i.v.		X(i.v)	
28 day (1 mo)		X gavage,		X p.o,	
90 day (3 mo)		X diet, Rectal		X, Rectal	
180 day (6 mo)		X Adult, diet X Neonates			
1 year (12 mo)		X Diet		X Neonates X Adult	
18 Month Carcinogenicity	X	X Diet X			
Reproductive Tox					
Segment I		X,2 studies			
Segment II		X 2,studies	X,3 Stud.		
Segment III		X			
Dermal Toxicity					
Ocular Toxicity					
Genotoxicity					

1. Ames Tests - 2 2. Chromosomal Aberration Test 3. Mouse lymphoma forward 4. Rat UDS Assay 5. Rat Micronucleus Test 6. Dominent lethal Test in male and female rats. 7. Drosophillia Sex linkage Test

Pharmacology Studies Included in this Review:

	Mouse	Rat	Rabbit	Dog	Primate	Human
Pharmacokinetics (Single and repeat dose)		X	X	X(p.o & i.v.)		X
Protein binding		X		X		X
Placental Transfer		X				
Lactating				X		

Pharmacologic Effects	Mouse	Rat	Rabbit	Dog	Primate	In vitro
1.Gastrointestinal Motility (isolated Prepn)		X		X	X	X
2.Gastrointestinal (In vivo)				X	X(cat & ferret)	X
3.Gastrointestinal secretions		X	X		X (guinea pig)	X
4.Mechanism of prokinetic effect				X		
5.cardiovascular						
6.Neuromuscular junction & CNS	X					

Conclusions
1. IND: No objection ____ Objection _____
NDA: No objection X Objection _____

2. Tumorigen? yes__ no_X Neurotoxic? yes__ no_X Immunotoxic? yes__ no_X

3. Put an asterisk by the studies that were conducted using the final formulation!

4. Inactive ingredient or metabolite concerns? No

Reviewer: Yash M. Chopra Date: July 1, 1992

YMC/haw/1/28/92
J:Pharm\Forms\Rev.2