NDA 20,210

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

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

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: Cisapride Monohydrate/Propulsid Tablets

CHEMICAL NAME: (+)-cis-4-amino-5-chloro-N-[(3-(4-fluorophenoxy) propyl)-3- methoxy-4-piperidinyl]-2-methoxybenzamide. It is a mixture of (+) and (-) enantiomers 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_{23}H_{29}ClFN_{3}O_{4} \cdot 4 \text{H}_2\text{O}

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

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Average composition of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg</td>
</tr>
<tr>
<td>Cisapride Monohydrate</td>
<td>10.39</td>
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<tr>
<td>Lactose Monohydrate NF</td>
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<tr>
<td>Corn Starch NF</td>
<td></td>
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<tr>
<td>Microcrystalline cellulose</td>
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<tr>
<td>Povidone, USP (K90)</td>
<td></td>
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<tr>
<td>Magnesium Stearate, NF</td>
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<tr>
<td>Colloidal silicone dioxide, NF</td>
<td></td>
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<tr>
<td>Polysorbate 20, NF</td>
<td></td>
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<tr>
<td>Purified water, USP</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study/Report #</th>
<th>Name of Laboratory</th>
<th>Drug Batch #</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. PHARMACOLOGY</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>II. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Single I.V./Oral Dose Absorption and Pharmacokinetics Study in Rat</td>
<td>R 51619/26</td>
<td>Janssen</td>
<td>376 (Radioactive)</td>
</tr>
<tr>
<td>2. Absorption, Metabolism and Excretion in Male Dog after an oral Dose</td>
<td>R 51619/28</td>
<td>Janssen</td>
<td>A109 (Radioactive)</td>
</tr>
</tbody>
</table>
3. Pharmacokinetics after a single I.V. or Oral Dose in Dogs

4. Absorption and Plasma Levels of Orally Administered Cisapride in Rabbits

5. Absorption, Tissue Distribution, Metabolism and Excretion in male rats (Single Vs Multiple Oral Doses)

6. Pharmacokinetics after 1-Month I.V. Repeat Dose Study in Dogs

7. Pharmacokinetics after 12-Month Oral Repeat Dose Study in Dogs

8. Absorption and Distribution Study in Rats

9. Distribution Study by Autoradiography in Pregnant and Male Rats

10. Absorption and Distribution after a Single Dose of 10, 40 or 160 m/kg in rats.

11. Placental Transfer in Rats after an I.V. or an Oral Dose

12. Excretion in Milk in Lactating Dogs

13. In vitro Protein Binding Study in Plasma Samples of Rats, Dogs and Human


15. Induction of Hepatic Drug Metabolizing enzymes in Male Rats

III. TOXICOLOGY:

1. Acute Toxicity Studies:

   a. p.o.
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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. 1096 Janssen A0101
Toxicity Study

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
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12-Month Oral Study

12-Month Oral Toxicity Study in Neonate Dogs

3. Carcinogenicity Studies:

Mice (Old) 1145 Janssen A1601
(New) 1987 Janssen CO101

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 CO101

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
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ii) Mouse Lymphoma 14265 forward

iii) Rat Hepato- UDS Assay

iv) Dominant Lethal 1148/1154 Test in Male and Female Mice Janssen BEA031

v) Rat Micronucleus 1164 Test 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 gastrointestinal 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 10^4 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 (10^4 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
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.

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

7,13, 1992
### Pharmacology/Toxicology Review

**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:

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

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

#### Pharmacology Studies Included in this Review:

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Mouse</th>
<th>Rat</th>
<th>Rabbit</th>
<th>Dog</th>
<th>Primate</th>
<th>Human</th>
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</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
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<tr>
<td>(Single and repeat dose)</td>
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<tr>
<td>Protein binding</td>
<td></td>
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<td>X</td>
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<tr>
<td>Placental Transfer</td>
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<td>X</td>
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<tr>
<td>Lactating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Pharmacologic Effects</td>
<td></td>
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<tr>
<td>1. Gastrointestinal Motility (isolated Prepn)</td>
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<tr>
<td>2. Gastrointestinal (in vivo)</td>
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<tr>
<td>3. Gastrointestinal secretions</td>
<td></td>
<td>X</td>
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<tr>
<td>4. Mechanism of prokinetic effect</td>
<td></td>
<td>X</td>
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<tr>
<td>5. Cardiovascular junction &amp; CNS</td>
<td></td>
<td>X</td>
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</tbody>
</table>

Conclusions:

1. IND: no objection
2. NDA: no 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