

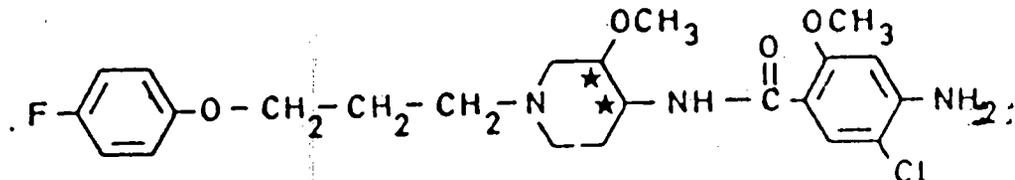
USP
Johnson

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Chemistry Review #1

JUN 25 1992

1. NDA 20-210
2. Chemistry Review: April 24, 1992
3. Type of Submission: original submission and amendments
4. Center's Therapeutic Classification: 1C
5. Status of Application: pending NDA
6. Name of Applicant:
Janssen Research Foundation
Ruth Wasserman, Director Regulatory Affairs
7. Address:
40 Kingsbridge Road
Piscataway, NJ 08855-3998
(908) 524-9170
8. Product Names
(a) Proprietary: Propulsid Tablets
(b) Established: cisapride
USAN:
USP:
(c) Code Name and Number: R51619 (NDS)
9. Dosage Form, Strength, and Route of Administration:
oral tablets, 10 & 20 mg
10. Proposed Marketing Status: Rx
11. Pharmacological Category and Indication: peristaltic stimulant for the treatment of gastroesophageal reflux disorders
12. Structural Formula, Chemical Name, Empirical Formula, Molecular Weight:
(±)-cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate
CAS [81098-60-4]
 $C_{23}H_{29}ClFN_3O_4 \cdot H_2O$
MW = 483.97 monohydrate
= 465.95 anhydrate
1.00 mg anhydrate = 1.0387 mg monohydrate



13. Structural Formulas of Related Compounds:
Metoclopramide: 11th Merck #6063, p 965
Domperidone: 11th Merck #3412, p 537
Clebopride Hydrogen Malate: (Ph)-CH₂-[NCH₂CH₂CHCH₂CH₂]-4-NHC(O)-2-OCH₃, 4-NH₂, 5-Cl-(Ph).malic acid (from DDIR search)
14. Document Dates:
08/29/91 original submission
11/27/91 BP amendment
12/09/91 BZ amendment
03/27/92 AM amendment
15. CDER Date: 08/29/91
16. Division Dates:
08/30/91 original submission
11/29/91 BP amendment
12/10/91 BZ amendment
03/30/92 AM amendment
17. Assigned Dates:
10/17/91 original submission
12/12/91 BP amendment
12/13/91 BZ amendment
04/01/92 BM amendment
18. Supporting Documents:

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19. Related Documents:

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20. Remarks:

Patent 4,962,115 expires 10/09/2007.

The drug product was first approved (04/88) in Sweden and is now approved in 42 countries. Approval has not been refused for safety reasons nor has it been withdrawn from the market.

NDA Section 3: Chemistry, Mfg & Controls

volume 1.1

NDA summary

volume 2.1-3.1

drug substance information

volume 4.1-5.1

drug product information

volume 6.1-7.1

environmental assessment information

volume 8.1

methods validation package

- the NDS page numbering system is 03-xxxx; all page references in this review are for section 03 of the NDA

This drug product was presented to an Advisory Committee on April 13-14, 1992.

21. Conclusions and Recommendations

EER for proposed sites for NDS mfg, tablet mfg, packaging and testing was submitted 10/31/91 and returned 12/18/91. EER was acceptable for all sites.

The Environmental Assessment information (volumes 1.6-1.7) was sent to Dr. Vincent 12/13/91. The review was completed 03/13/92; the EA reviewer's comments were communicated to the firm by the reviewer in a telephone conversation on 03/05/92. This information must be complete prior to NDA approval.

Analytical test methods are not yet ready for evaluation.

The Biopharm consult review has not been received yet, thus an acceptable dissolution Q value has not been established.

A request for consult review of the x-ray diffraction, IR and DSC information was submitted to Tony DeCamp, HFD-520 on 02/11/92. The review was completed 02/19/92; comments to the firm are proposed (addendum).

The NDS is NOT APPROVABLE in that it lacks adequate information regarding the synthesis and stability of the drug substance and the manufacture and stability of the drug product.

22.

Mike Adams 6/25/92

Mike Adams, HFD-180
Review Chemist

23.

~~John J. Gibbs~~ 6/25/92

John J. Gibbs, Ph.D.
Supervisory Chemist

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

JUL 21 1993

NDA 20-210

CHEM.REVIEW #5

REVIEW DATE: 07/13/93

SUBMISSION TYPE:
BC AMENDMENT

DOCUMENT DATE
07/01/93

CDER DATE
07/02/93

ASSIGNED DATE
07/02/93

NAME & ADDRESS OF APPLICANT:

Janssen Research Foundation
1125 Titusville-Harbourton Road
Titusville, NJ 08560-0200

DRUG PRODUCT NAME

PROPRIETARY: Propulsid
NONPROPRIETARY/USAN: Cisapride Tablets
CODE NAME/#: R51619 (NDS)
THERAPEUTIC CLASS: 1-S

PHARMACOLOGICAL CATEGORY/INDICATION:

Peristaltic stimulant for the treatment of GERD

DOSAGE FORM: uncoated tablets

STRENGTHS: 10 & 20 mg

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: see Chem Review #1

SUPPORTING DOCUMENTS: see Chem Review #1

RELATED DOCUMENTS: see Chem Review #1

CONSULTS:

Biopharm, completed 11/05/92
Environmental Assessment, 03/31/93 amendment is under review

REMARKS/COMMENTS: none

CONCLUSIONS & RECOMMENDATIONS:

The firm has failed to provide complete responses to our 06/30/93 AE letter. The missing information should be requested from the firm in another AE letter; item I of this review is a draft letter.

The application is APPROVABLE (AE) pending submission of further chemistry information, acceptance by the Environmental Assessment reviewer, and cGMP clearance.

Mike Adams 07/21/93

Mike Adams
Chemist, HFD-180

John J. Gibbs 7/21/93

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-80

cc:
NDA 20,210
HFD-180/division file
HFD-180/MAdams (N20210.R5)
HFD-181/KJohnson
R/D Initial: JGibbs/07-14/93
MA/dob DRAFT 07-14-93/F/T 7-21-92
Filename: c:\wp51\chem\N\20210307.5MA

JUL 21 1993

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA 20-210 CHEM.REVIEW #6 REVIEW DATE: 07/19/93

SUBMISSION TYPE: DOCUMENT DATE CDER DATE ASSIGNED DATE
AC AMENDMENT 07/14/93 07/15/93 07/19/93

NAME & ADDRESS OF APPLICANT:
Janssen Research Foundation
1125 Titusville-Harbourton Road
Titusville, NJ 08560
(609) 730-3077

DRUG PRODUCT NAME
PROPRIETARY: Propulsid
NONPROPRIETARY/USAN: Cisapride Tablets
CODE NAME/#: R51619 (NDS)
THERAPEUTIC CLASS: 1

PHARMACOLOGICAL CATEGORY/INDICATION:
Peristaltic stimulant for the treatment of GERD

DOSAGE FORM: uncoated tablets

STRENGTHS: 10 & 20 mg tablets

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: see Chem Review #1

SUPPORTING DOCUMENTS: see Chem Review #1

RELATED DOCUMENTS: see Chem Review #1

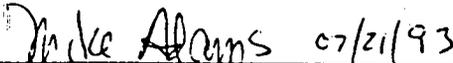
CONSULTS:

 Biopharm, completed 11/05/92
 Environmental Assessment, completed 07/15/93
 Follow/Up EIR for cGMP clearance made 06/17/93 has received no response; inquiry has been made.

REMARKS/COMMENTS: none

CONCLUSIONS & RECOMMENDATIONS:

The NDA is APPROVABLE pending final cGMP clearance.
The proposed test methods should be submitted for FDA validation.

 07/21/93

Mike Adams
Review Chemist, HFD-180

 7/21/93

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
NDA 20,210
HFD-180/Division File
HFD-180/MAdams
HFD-181/KJohnson
R/D Initial: JGibbs/7-20-93
MA/dob DRAFT 7-20-93/F/T7-21-93
Filename: c:\wp51\chem\N\20210307.6MA

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

029
J. L. Jones
FEB 12 1993

NDA 20,210

CHEM.REVIEW #3

REVIEW DATE: 02/03/93

<u>SUBMISSION TYPE:</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AC AMENDMENT	09/18/92	N/A	09/22/92
AC AMENDMENT	10/19/92	N/A	10/23/92
AC AMENDMENT	02/01/93	N/A	02/04/93

NAME & ADDRESS OF APPLICANT:

Janssen Research Foundation
1125 Titusville-Harbourton Road
Titusville, NJ 08560
(609) 730-3077

DRUG PRODUCT NAME

PROPRIETARY: Propulsid
NONPROPRIETARY/USAN: Cisapride Tablets
CODE NAME/#: R51619 (NDS)
THERAPEUTIC CLASS: 1C

PHARMACOLOGICAL CATEGORY/INDICATION:

Peristaltic stimulant for the treatment of GERD

DOSAGE FORM: uncoated tablets

STRENGTHS: 10 & 20 mg tablets

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR

WEIGHT: see Chemistry Review #1

SUPPORTING DOCUMENTS: see Chemistry Review #1

RELATED DOCUMENTS: see Chemistry Review #1

CONSULTS:

Biopharm, completed 11/05/92

Environmental Assessment, requested 02/03/93; under review

REMARKS/COMMENTS:

The specifications and methods for NDS and drug product release have not been finalized. The manufacturing process and controls still need minor revision. The proposed packaging has been revised to include a sample blister package and a different 325 cc bottle.

Review of the stability data will be made after the Q values for each dissolution medium and the drug product controls have been established. The firm's statistical analysis of their stability studies was submitted to the Statistician on 02/03/93.

A request for a commitment from the firm to work with HFD-180 to complete methods validation has been included in the IR letter.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is APPROVABLE pending submission of further chemistry information

Mike Adams 02/12/93

Mike Adams
Review Chemist, HFD-180

John J. Gibbs 2/12/93

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
NDA 20,210
HFD-180/Division File
HFD-181/KJohnson
HFD-180/MAdams
R/D Initial:JGibbs/2-11-93 Filename: c:\chem\N\20210302.3MA
MA/dob DRAFT 2-9-93/F/T 2-11-93

OK
Johnson

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls JUN 29 1993

NDA 20-210 CHEM. REVIEW #4 REVIEW DATE: 06/18/93

<u>SUBMISSION TYPE:</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
BC AMENDMENT	03/31/93	N/A	04/06/93
BC AMENDMENT	04/30/93	N/A	05/05/93

NAME & ADDRESS OF APPLICANT:
Janssen Research Foundation
1125 Titusville-Harbourton Road
Titusville, NJ 08560
(609) 730-3077

DRUG PRODUCT NAME
PROPRIETARY: Propulsid
NONPROPRIETARY/USAN: Cisapride Tablets
CODE NAME/#: R51619 (NDS)
THERAPEUTIC CLASS: 1-S

PHARMACOLOGICAL CATEGORY/INDICATION:
Peristaltic stimulant for the treatment of GERD

DOSAGE FORM: uncoated tablets

STRENGTHS: 10 & 20 mg tablets

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: see Chem Review #1

SUPPORTING DOCUMENTS: see Chem Review #1

RELATED DOCUMENTS: see Chem Review #1

CONSULTS:
Biopharm, completed 11/05/92
Environmental Assessment, await completed review of 03/31/93 amendment

REMARKS/COMMENTS:
The acceptable dissolution spec is Q= in 45 minutes for product release and stability.
Based on the submitted stability data and acceptable dissolution spec, the acceptable expiration dates are 36M for 10 mg tablets in bottles, 18M for 10 mg tablets in blisters, 24M for 20 mg tablets in bottles, and 36M for 20 mg tablets in blisters.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is APPROVABLE pending submission of further chemistry information.

Mike Adams 6/29/93

Mike Adams
Review Chemist, HFD-180

for Arthur B. Shaw 6/29/93
John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:

NDA 20-210

HFD-180/Division File

HFD-180/MAdams

HFD-181/KJohnson

R/D Initial:JGibbs/6-21-93 Filename: WP: c:\chem\N\20210306.4MA

MA/dob DRAFT 6/24/93/F/T 6-29-93

C. J. Johnson

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

Propulsid

(Cisapride)

Tablets (10mg & 20mg)

NDA 20-210

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

21

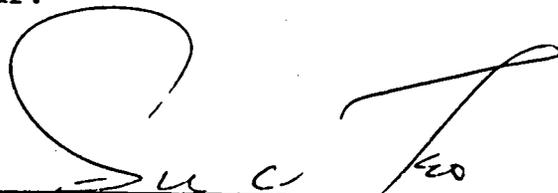
FINDING OF NO SIGNIFICANT IMPACT

NDA 20-210

Janssen Research Foundation has submitted an environmental assessment to support a new drug application dated January 29, 1993 . The application was submitted in pursuant to section 505 of the Food, Drug, and Cosmetic Act for Propulsid (cisapride), 10 mg & 20 mg Tablets

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered all the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their application, the firm has prepared a environmental assessment according to 21 CFR 25.31a(a) which evaluates the environmental impacts of the manufacture and use of the drug products. The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the finished products are expected to minimize occupational exposures and environmental release. Any residues of the drug substance and its major metabolites entering the environment as a result of administering the drug to humans are expected to strongly adsorbed by soils. In addition, no wetland areas, significant cultural resources or endangered species, air quality, fish and wildlife resources, environmentally significant habitats, and water quality would be significantly affected, and no significant land use changes would occur.



Prepared by Su C. Tso, Ph.D.

7/15/93

Date 7/15/93



Phillip G. Vincent, Ph.D.
Environmental Assessment Officer

7/15/93

Date

cc: Original: NDA 20-210
HFD-362/Chao HFD-102/Kumkumiam
HFD-520/SCTso HFD-102/PVincent
HFD-180/Johnson FONSI file: NDA 20-210

ENVIRONMENTAL ASSESSMENT.

1. DATE.

January 29, 1993

2. NAME OF APPLICANT.

Janssen Pharmaceutica N.V. on behalf of Janssen Research Foundation, Titusville,
New Jersey.

3. ADDRESS.

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
2340 Beerse
Belgium

4. DESCRIPTION OF THE PROPOSED ACTION.

a. Brief description of requested approval.

The purpose of this NDA application is to request approval from FDA to market PROPULSID® (cisapride) 10 mg and 20 mg tablets, a new drug for use in the treatment of gastroesophageal disorders characterized by the symptoms of heartburn, regurgitation and epigastric pain or endoscopic evidence of esophagitis.

b. Need for the action.

Gastroesophageal reflux disorder is a chronic condition which is very common in the US; it is estimated that 40% of adult Americans suffer from heartburn (the most commonly encountered symptom of reflux) at least once a month. [1]

Cisapride is a safe and efficacious synthetic gastrointestinal prokinetic agent which affects the pathophysiological mechanisms of reflux disease. [2] This includes increasing pressure in the lower esophageal sphincter, promoting esophageal peristalsis, and accelerating gastric emptying. These mechanisms are not shared by most currently available drug therapies, which exert their action by neutralization of gastric acid.

The drug substance is formulated into a tablet dosage form for oral administration.

00-00022

c. Location where product is produced.

Cisapride *drug substance* may be produced by:

Janssen Pharmaceutica
Turnhoutseweg 30
2340 Beerse, Belgium.

Additionally, some of the *intermediates* used in the synthesis of cisapride drug substance may be produced by:

Janssen Pharmaceutica
Janssen Pharmaceuticaaan 3
2440 Geel, Belgium.

A table which provides a scheme of intermediates and drug substance synthesized at each of the above sites is provided in Confidential Appendix A.

The *drug product* (PROPULSID 10 mg and 20 mg tablets) will be produced by:

00-00023

d. **Locations where product will be used and disposed of.**

Use of drug product

The use of the drug product, PROPULSID tablets, is limited to patients being treated for gastroesophageal reflux disorders. Treatment will occur in patients located throughout the USA. The drug product will be available for use only by prescription. A draft of the labeling is in Appendix 1.

Disposal of Drug Substance and Drug Product

Waste resulting from manufacture, testing and packaging in Beerse and Geel of drug substance, or from rejected or outdated drug substance, will be transported from Beerse and Geel to the following licensed waste processor:

Indaver N.V.
Poldervlietweg
2030 Antwerp, Belgium

Waste resulting from manufacture, testing and packaging in _____ of drug substance and drug product, or from rejected or outdated drug substance, will be transported from _____ to the following licensed waste processors:

Waste resulting from rejected, returned or outdated drug product will be transported to the following licensed waste processor:

Rollins Environmental Services
PO Box 337
Bridgeport, New Jersey

00-00024

e. **Types of environments present at and adjacent to those in (d).**

Manufacturing Sites

Janssen Pharmaceutica Beerse is located on a parcel of 148 acres. The site is surrounded with residential type housing and has its primary access from state road No. N 14 connecting Antwerp to Turnhout. The terrain is flat and the climate is temperate.

Janssen Pharmaceutica Geel is located on a parcel of 99 acres in the Geel industrial area. The industrial area is bounded to the north by the channel "Albertkanaal" and to the south by highway E313 connecting Antwerp to Achen. The terrain is flat and the climate is temperate.

Waste Processing Sites

Indaver n.v., Antwerp, Belgium, is located on a parcel of about 100 acres in a rural environment. There is possibility both for incineration of the waste and landfilling. The terrain is flat and the climate is temperate.

Rollins Environmental Services, Bridgeport, New Jersey is located on a parcel of about 250 acres in a rural environment. The site is located about one-half mile to the south of US Route 322, one-half mile to the west of US Route I-295, and one-half mile to the east of Bridgeport, NJ. The terrain is flat and the climate is temperate.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION.

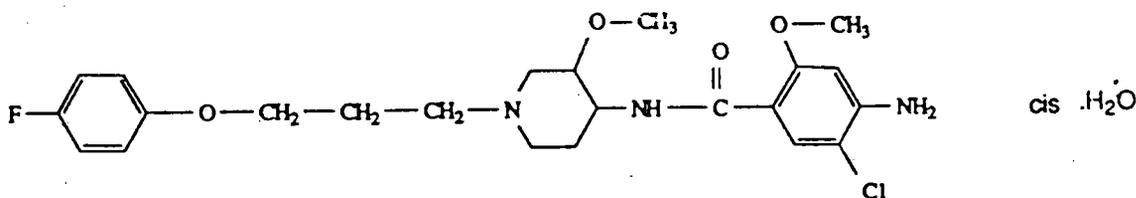
5.1 Drug Substance: R 51619: Cisapride

Complete nomenclature: (\pm)-*cis*-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate.

CAS Registration number: 81098-60-4

Molecular weight: 483.97

Structural formula:



Physical description: Cisapride is a white to slightly beige odorless powder.

Water solubility (25°C): 1.66 ppm (1.66×10^{-3} g/l)

Octanol/Water Partition coefficient log P = 1.69 (pH 5.1), 2.86 (pH 6.8),
3.32 (pH 7.1), 4.23 (pH 9.0)

Vapor pressure (20°C): ca. 7.57×10^{-16} Pa (7.47×10^{-21} atm)

Dissociation constants: pKa1 = 7.73 (piperidine moiety)
pKa2 < 2 (aniline moiety)

Melting range: 115.4 °C - 134.5 °C

Density/relative density (24°C): 1.317×10^3 kg/m³

Impurities and Additives: Information is available in Confidential Appendix A.

More information on the drug substance is available in the Confidential Appendix A and in Item 7.

00-00026

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION. (CONT'D.)

Information about the synthesis of cisapride is available in Confidential Appendix A. The synthesis of cisapride consists of a number of chemical reactions. A flowchart describing the synthetic processes is given in Figure 5.1. In this flowchart the releases into the environment are also given, which relates to Item 6 of this EA.

5.2 Synthesis starting materials and Intermediates of the synthesis

Detailed information on the synthesis starting materials and the intermediates, as well as Material Safety Data Sheets for most of these substances, is provided in Confidential Appendix A.

00-00027

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION.(CONT'D.)

5.3 Drug Product.

The drug product will be manufactured at the

Composition of Cisapride 10 mg and 20 mg oral tablets:

	mg per 10 mg tablet	mg per 20 mg tablet
Cisapride Monohydrate	10.39	20.78
Lactose Monohydrate, NF		
Starch, NF (Corn)		
Microcrystalline cellulose, NF		
Povidone, USP (K90)		
Magnesium stearate, NF		
Colloidal Silicon Dioxide, NF		
Polysorbate 20, NF		
FD&C Blue No. 2 Aluminum Lake (13%)		
Nominal weight		

The 10 mg tablets are white, circular and biconvex and slightly arched tablets, with "P/10" inscription on one side and "JANSSEN" inscription on the other side.

The 20 mg tablets are slightly mottled blue, oval shaped, biconvex tablets, with "P/20" inscription on one side and "JANSSEN" on the other side.

00-00029

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

Items 6a-6d are presented below for each site which produces drug substance and/or drug product.

The expected concentrations of substances expected to enter the environment as a result of use and/or disposal is discussed in Item 6e, which follows 6a-6d.

6.1. JANSSEN PHARMACEUTICA - BEERSE - BELGIUM.

This production site will produce the drug substance at the chemical production unit. This synthesis consists of a number of chemical reactions including using various raw materials.

As mentioned in Item 4.c, several intermediates will be produced in Geel; however, Beerse is treated as if it were manufacturer of all the intermediates. In this manner, we take into account the worst-case scenario (i.e. total synthesis of cisapride).

6.1.1. Waste water.

A. List of substances to be emitted:

All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.

The water layer originated from the synthesis process is lead to the central waste water treatment plant, where all waste waters from the site are assembled.

The aqueous layers with high B.O.D./ C.O.D. content from "drug substance" production have a B.O.D.(Biological Oxygen Demand) range of 2500-4000 mg/l and a C.O.D. (Chemical Oxygen Demand) range of 5000-9000 mg/l.

Detailed information on the introduction of substances into the environment is available in the Confidential Appendix C.

B. The controls exercised

All waste water is channelled through a system of sewers to a central two stages biological waste water treatment plant. No water is pumped into the environment untreated, whether it is industrial waste water or sewage from the normal sanitary facilities.

Description of the Waste Water Treatment Plant

The waste water treatment plant (WWTP) at Beerse has a population equivalent of 43,000; this means that it has sufficient capacity (2340 kg. B.O.D./day) to process the waste water of 43,000 inhabitants.

Certain types of waste water, which would otherwise disturb the normal biological process, are pre-treated (oxidation, sedimentation, adsorption on activated charcoal, ion exchange) before entering the main treatment plant, or are transported to another company for special treatment (solidification, incineration).

00-00030

The waste water (after pre-treatment, if necessary) first undergoes physicochemical treatment, which makes subsequent biological processing possible. This consists of breaking down the organic substances in two steps by aerobic degradation. In the tertiary treatment stage, the last remaining impurities are filtered out.

The solid residue is transported to specialized waste disposal companies. Here, too, a preventive approach is adopted. The cooling water which is needed for the production of chemicals is not discharged into the sewers but is recycled in cooling towers. Inside the towers the water is cooled to ambient air temperature so that it can be reused in the production process.

A more detailed description of the WWTP is available in Appendix 3.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

The effluent from the WWTP is discharged in compliance with the requirements set forth in the Janssen Pharmaceutica-Beerse "Waste water discharge permit," Ref to Appendix 4. The permit is obtained from the Flemish regional authorities "Vlaamse Maatschappij voor Waterzuivering." dated December 14, 1984.

Major requirements :

- Flow rate 7000 m³/day
- pH 6.5 - 9.0
- B.O.D. 15 mg/l
- C.O.D. 150 mg/l
- Suspended solids 60 mg/l

D. The effect of approval upon compliance with current emission requirements at the production site

The proposed action is not expected to adversely affect the waste water treatment plant efficiency and is not expected to have impact on compliance with current waste legislation or to violate the current permit.

6.1.2 Air Emissions.

A. List of substances to be emitted:

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

Emissions from "drug substance" production containing organic - Volatile Organic Compound (VOC) - and Inorganic emissions, are discharged to the atmosphere through a scrubber system. In addition, all reactors are equipped with their own cooler condensing system.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO₂ is absorbed with NaOH.

Description of the VOC Abatement Emission Control system.

In the near future the V. O. C. from the "drug substance" production will be controlled with a two stage activated carbon adsorption system (similar to the system which is planned at Geel; see Item 6.2.2.). The basic engineering is completed and the installation of the system is planned for 1993.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Air emissions are in compliance with the requirements set forth in the Janssen Pharmaceutica-Beerse "Permit to operate," Ref to Appendix 4. The permit is obtained from the Flemish regional authorities "Administratie voor Ruimtelijke Ordening en Leefmilieu." and is dated April 23, 1987. Major requirements : Ref to Appendix 4.

D. The effect of approval upon compliance with current emission requirements at the production site

The proposed action is not expected to have impact on compliance with the current waste legislation or to violate the current permit.

00-00032

6.1.3. Solid Waste

A. List of substances to be emitted:

The sludge obtained by the waste water treatment and the filter cake generated after filtration (drug substance) account for the majority of the solid waste that will be incinerated. Process solvents will either be recuperated or incinerated depending on their composition.

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

No waste treatment is done at the site. Waste is temporarily stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator. A manifest system is used.

Recuperation takes place at third-party facilities; however, some solvent recuperation will be done at the distillation unit at Janssen-Beerse.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Waste treatment is done in compliance with the Flemish regional waste legislation. Since no treatment takes place at the site no special permit for treatment is required. However monthly and yearly reports to the authorities are required.

D. The effect of approval upon compliance with current emission requirements at the production site

The synthesis of the drug substance cisapride at the production site at Janssen Pharmaceutica Beerse will have no impact on compliance with current waste legislation.

00-00033

6.2. JANSSEN PHARMACEUTICA - GEEL - BELGIUM.

This production site will produce some of the intermediates at the chemical production unit. We take into account the worst case, being total synthesis of the drug substance cisapride. This synthesis consists of a number of chemical reactions including using various raw materials or intermediates.

6.2.1. Waste water.

A. List of substances to be emitted:

All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.

The water layer originated from the synthesis process is lead to the central waste water treatment plant, where all waste waters from the site are assembled.

The aqueous layers with high B.O.D./ C.O.D. content from "drug substance" production have a B.O.D.(Biological Oxygen Demand) range of 2500-4000 mg/l and a C.O.D. (Chemical Oxygen Demand) range of 5000-9000 mg/l.

Detailed information on the introduction of substances into the environment is available in the Confidential Appendix C.

B. The controls exercised

All waste water is channelled through a system of sewers to a central two-stage biological waste water treatment plant. No water is pumped into the environment untreated, whether it is industrial waste water or sewage from the normal sanitary facilities.

Description of the Waste Water Treatment Plant

The waste water treatment plant (WWTP) has a population equivalent of 52,000; this means that it has sufficient capacity (2840 kg. B.O.D./day) to process the waste water of 52,000 inhabitants.

Certain types of waste water, which would otherwise disturb the normal biological process, are pre-treated (oxidation, sedimentation, adsorption on activated charcoal, ion exchange) before entering the main treatment plant, or are transported to another company for special treatment (solidification, incineration).

The waste water (after pre-treatment, if necessary) first undergoes physicochemical treatment, which makes subsequent biological processing possible. This consists of breaking down the organic substances in two steps by aerobic degradation. In the tertiary treatment stage the last remaining impurities are filtered out.

The solid residue is transported to specialized waste disposal companies. Here, too, a preventive approach is adopted. The cooling water which is needed for the production of chemicals is not discharged into the sewers but is recycled in cooling towers. Inside the towers the water is cooled to ambient air temperature so that it can be re-used in the production process.

A more detailed description of the WWTP is available in Appendix 3.

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The WWTP has been extended and now has a capacity of 6000 kg B.O.D./day (population equivalent of 110,000). The extension consisted of an extra equalization unit, an activated sludge unit, a trickling filter, a final settling unit, a sludgehandling unit, thickeners and a compressor building.

In order to minimize offensive emissions for the local residents the trickling filter, the equalization unit, the neutralization unit and the sludgehandling unit were covered over. The installation has been in use since September 1992.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

The effluent from the WWTP is discharged in compliance with the requirements set forth in the Janssen Pharmaceutica-Geel "Environmental permit," Ref to Appendix 5. The permit is obtained from the Flemish regional authorities "Provinciebesuur Antwerpen." dated October 1, 1992.

Major requirements :

- Flow rate 3000 m³/day
- pH 6.0 - 9.5
- B.O.D. 950 mg/l
- C.O.D. 1950 mg/l
- Suspended solids 1000 mg/l

D. The effect of approval upon compliance with current emission requirements at the production site

The proposed action is not expected to adversely affect the waste water treatment plant efficiency and is not expected to have impact on compliance with current waste legislation or to violate the current permit.

00-00035

6.2.2 Air Emissions.

A. List of substances to be emitted:

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

Emissions from "drug substance" production containing organic - Volatile Organic Compound (VOC) - and inorganic emissions, are discharged to the atmosphere through a scrubber system. In addition all reactors are equipped with their own cooler condensing system.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO₂ is absorbed with NaOH.

Description of the VOC Abatement Emission Control system.

V. O. C. from the "drug substance" production will be controlled with a two stage activated carbon adsorption system. The basic engineering is completed and the installation of the system is planned for 1993.

The VOC Abatement Emission Control system consists of the following major components:

- The *preconditioning unit* with three Solvent Loaden Air (SLA) blower assemblies, steam reheat coils and relative humidity controls.
- The activated carbon *Adsorption Unit* with adsorbers, related equipment, initial charge of activated carbon, fully-automatic controls and inlet and exhaust analyzers.
- The *Steam Regeneration Unit*: The Carbon Adsorption System will include a Steam Regeneration Unit with heat exchanger, pump, tanks, steam regenerator, automatic controls and related components for revaporization and closed loop recycling of the water layer to produce low pressure steam for regeneration of the carbon beds.
- A *common Distillation Unit* to process the combined decanter water phases from the carbon adsorption systems. The Distillation System includes heat exchangers, tanks, pumps, column, automatic controls and related equipment for the removal and concentration of the solvents contained in the water layer.

The solvents contained in the water layer will either be recuperated by third parties, either be incinerated by a licensed high temperature waste incinerator.

00-00036

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Air emissions are in compliance with the requirements set forth in the Janssen Pharmaceutica-Geel "Permit to operate," Ref to Appendix 5.
The permit is obtained from the Flemish regional authorities "Administratie voor Ruimtelijke Ordening en Leefmilieu." and is dated November 26, 1987.
Major requirements : Ref to Appendix 5.

D. The effect of approval upon compliance with current emission requirements at the production site

The proposed action is not expected to have impact on compliance with the current waste legislation or to violate the current permit.

00-00037

6.2.3. Solid Waste

A. List of substances to be emitted:

The sludge obtained by the waste water treatment and the filter cake generated after filtration account for the majority of the solid waste that will be incinerated. Process solvents will either be recuperated or incinerated depending on their composition.

B. The controls exercised

No waste treatment is done at the site. Waste is temporarily stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator. A manifest system is used.

Recuperation takes place at third-party facilities; however, some solvent recuperation will be done at the distillation unit at Janssen-Beerse.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Waste treatment is done in compliance with the Flemish regional waste legislation. Since no treatment takes place at the site no special permit for treatment is required. However monthly and yearly reports to the authorities are required. Monthly report in Appendix 5.

D. The effect of approval upon compliance with current emission requirements at the production site

The synthesis of the drug substance cisapride at the production site in Janssen Pharmaceutica, Geel, will have no impact on compliance with current waste legislation.

00-00038

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

6.3.

The site at _____ has facilities both for chemical and pharmaceutical production. Only a part of the synthesis of cisapride is conducted at this site, starting from Janssen Intermediate T1341. Also, manufacturing of the drug product (10 mg and 20 mg tablets) will take place at the _____ site.

6.3.1. Waste water.

A. List of substances to be emitted:

Drug substance

All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.

The water layer originated from the synthesis process is lead to the waste water treatment plant. The aqueous layers with high B.O.D./ C.O.D. content from "drug substance" production have a B.O.D. (Biological Oxygen Demand) range of 2500-4000 mg/l and a C.O.D. (Chemical Oxygen Demand) range of 5000-9000 mg/l.

Drug product

The manufacturing of the cisapride tablets occurs in stainless steel containers. It consists of sieving and mixing the ingredients, spraying a solution in a fluidized-bed granulator, drying and sieving the granules. The pressing to tablets occurs in a rotary tablet press. The manufacturing process is summarized in more detail in Confidential Appendix B.

Following product removal, the process containers are cleaned and rinsed with water. Aqueous layers from "drug product" production have a low B.O.D./ C.O.D. content. The B.O.D. range lies between 300-400 mg/l and the C.O.D. range between 400-500 mg/l.

Detailed information on the introduction of substances into the environment is available in Confidential Appendix C.

B. The controls exercised

Description of the Waste Water Treatment System

The combined process waste waters from _____ come into two aerated tanks with a capacity of 30,000 gallons each. Effluent from the equalization tanks is pumped to the pH adjustment tanks. After the pH adjustment tanks, the separation of solids (already flocculated and coagulated by the addition of polymers) takes place. The underflow from the clarifier is pumped to the sludge digester. The effluent from the primary clarifier is transferred to an equalization tank with a 167,000 gallons capacity and then to the bioreactor for the secondary biological treatment.

Powdered activated carbon is added at the entrance of the bioreactor to improve the B.O.D. and C.O.D. removal efficiency. After biological treatment, the water flows to the secondary clarifiers to separate the sludge from the water effluent. The water effluent is pumped to a holding tank. The aerobic digester tank is designed to further stabilize the biological solids prior to dewatering and disposal.

00-00039

The two stages biological waste water treatment system has a capacity from 900 kg. B.O.D./day.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

The effluent from the WWTP is discharged in compliance with the requirements set forth in the "Industrial waste water discharge permit", issued by dated February 12, 1990.

The permit is available in Appendix 6.

Major requirements :

*** Bulk discharge into the**

Treatment Plant.

- | | |
|--------------------|---|
| - Flow rate | The permittee shall not discharge more than 5 tank-trucks (40,000 gallons) per day. |
| - pH | 6.5 - 9.0 |
| - B.O.D. | 175 mg/l |
| - C.O.D. | 300 mg/l |
| - Suspended Solids | 125 mg/l |

*** Discharge into the**

WWTP

- | | |
|-------------|------------|
| - Flow rate | 60,000 LPD |
| - pH | 6.5-9.0 |
| - B.O.D. | 250 mg/l |
| - C.O.D. | 425 mg/l |

D. The effect of approval upon compliance with current emission requirements at the production site

The proposed action is not expected to adversely affect the waste water treatment plant efficiency and is not expected to have impact on compliance with current waste legislation or to violate the current permit.

00-00040

6.3.2 Air Emissions.

A. List of substances to be emitted:

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

Drug substance

Emissions from "drug substance" production are discharged to the atmosphere through a two stage scrubber system. In addition all reactors are equipped with their own cooler condensing system. The emissions contain organic - Volatile Organic Compound (VOC) - and inorganic emissions.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO₂ is absorbed with NaOH.

Description of the VOC Abatement Emission Control system.

In the near future the V. O. C. from the "drug substance" production will be controlled with a two stage activated carbon adsorption system (similar to the system which is planned at Geel; see Item 6.2.2.). The basic engineering is completed and the installation of the system is planned for 1993.

Drug product

The manufacturing process for the finished product operation consists of weighing, processing by automatic sieving and mixing and formulating in the tablet form. Dust emissions from the "drug product" production are controlled with a high efficiency, dust filtration system. Emissions are negligible.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Air emissions are in compliance with the requirements set forth in the "Air emission permit", dated January 31, 1990. The permit is obtained from the Environmental Quality Board.

The permit and the major requirements are available in Appendix 6.

D. The effect of approval upon compliance with current emission requirements at the production site

The proposed action is not expected to have impact on compliance with the current waste legislation or to violate the current permit.

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6.3.3. Solid Waste

A. List of substances to be emitted:

The sludge obtained by the waste water treatment will be disposed of by landfilling. The filter cake generated after filtration (drug substance), the off spec formulations and some packaging materials (drug product) account for the majority of the solid waste that will be incinerated.

Packaging materials and process solvents will either be recuperated or incinerated depending on their composition.

B. The controls exercised

No hazardous waste treatment is done at the site. Waste is temporarily stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator.

A RCRA part B permit was obtained on August 11, 1986.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Hazardous and solid waste treatment, storage and disposal is done in compliance with the requirements set forth in the RCRA permit #PRD-980536049, available in Appendix 6.

D. The effect of approval upon compliance with current emission requirements at the production site

The synthesis of the drug substance cisapride and manufacturing of the 10 mg and 20 mg tablets at production site will have no impact on compliance with current waste legislation.

00-00042

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

E. Estimate of the Concentrations of Substances Expected to Enter the Environment as a Result of Use and/or Disposal of Products Affected by the Action.

1. Maximum Expected Emitted Concentration (MEEC) of Cisapride in Wastewater from Use of Drug Product

The maximum expected emitted concentration (MEEC) of cisapride in wastewater from use of the drug product has been estimated based upon the mathematical formula provided in the PMA interim guidance document[6]. The corresponding calculation is provided in Appendix D.

The MEEC is based on certain assumptions, including dosing an estimate of the number of patients that would be prescribed the drug during the fifth year of marketing at the maximum therapeutic dose. In addition, although cisapride is the administered drug, one metabolite, produced by oxidative N-dealkylation of cisapride, is predominantly excreted (see Appendix H). This is not taken into account in the calculation in Appendix D. However, since the primary metabolite is a cleavage product, and hence of lower molecular weight than cisapride, the calculated MEEC represents a worst-case upper limit.

2. Expected Environmental Concentration (EEC) of Cisapride in the Aquatic Environment from Use of Drug Product

The expected environmental concentration (EEC) of cisapride in the aquatic environment from use of the drug product has been estimated by correcting the MEEC by appropriate factors based upon processes that would be expected to remove and/or dilute cisapride present in wastewater. The corresponding calculation is provided in Appendix D. Based upon information provided in Item 7, sorption of the drug onto sludge/sediment at the wastewater treatment facility and dilution of the effluent wastewater by the receiving surface waters are the anticipated primary removal/dilution processes. Taken together, these factors would be expected to reduce the MEEC of cisapride by at least several orders of magnitude.

3. Expected Emissions from Disposal

No substances are expected to enter the environment from disposal because solid waste from manufacturing, packaging, labeling, quality control testing, and distribution (i.e. waste resulting from rejected, returned or outdated substance/product) is disposed of by incineration or landfilling.

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7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The purpose of this section is to present information relevant to the fate and transport of cisapride. Assessment of the fate/transport scenario of cisapride requires an evaluation of processes affecting its structural transformations and its partitioning between the environmental media (air, soil and water). These processes include hydrolysis, photolysis, oxidation, volatilization, sorption, bioaccumulation and biodegradation.

As mentioned in Item 6.e, cisapride is metabolized in man predominantly by an oxidative N-dealkylation process to produce primarily one metabolite (see Confidential Appendix H). Accordingly, both cisapride and its major metabolite may enter the environment through use. For the purposes of the fate studies, cisapride has been chosen as the study molecule. A rationale for this choice is provided in Confidential Appendix G.

A summary of the environmental fate and transport of cisapride is provided in Table 7A. A concluding statement regarding the probable fate of cisapride in the environment is provided in Item 7.4.

7.1. AIR

Atmospheric processes are not relevant to the environmental fate of cisapride, because it is released only to sewage treatment facilities where volatilization of drug substance to the atmosphere could not be an operative process. Cisapride is not a volatile substance, as indicated by its low vapor pressure, which was calculated to be 7.57×10^{-16} Pa [3, 4, 5] according to the method developed by Mackay *et. al.*

7.2. SOIL

7.2.1. Soil Sorption/Desorption

In the soil sorption/desorption studies, three different soils were used, all of which showed that cisapride is adsorbed strongly to soil with minor degrees of desorption. The octanol-water partition coefficient (log P of about 2-4 in aqueous media between pH 5-9) corroborates the results of sorption to lipophilic material.

Since sewage sludge/sediment is ordinarily disposed of by incineration or landfilling (which constitute final disposal), other soil environmental processes which may deplete cisapride need not be considered.

00-00045

7.3. WATER

Aquatic processes are not considered to be very significant to the environmental fate of cisapride in the water of the sewage treatment facility or the surface water that potentially receives the effluent, since the cisapride present in waste water will be strongly sorbed to the waste sludge/sediment. Thus, there will be little or no tendency for cisapride to be released to the effluent water. Nevertheless, to the small extent that cisapride may be released to the aquatic environment, the possible fate of cisapride due to various aquatic environmental processes is considered in this section.

7.3.1 Hydrolysis

The hydrolysis of cisapride was examined following the FDA handbook PB 87-175345, test 3.09. The preliminary test was conducted at 50 °C in buffer solutions at pH 5, 7 and 9. A small amount (<10%) of decomposition was observed after 5 days at each pH. Thus, cisapride can be considered fairly hydrolytically stable.

7.3.2 Photolysis

Cisapride exhibits a moderately intense absorption maximum at about 308 nm (log e about 4 at 308 nm) which extends to about 320 nm. The sum of wavelength distributions of atmospheric sunlight less than 320 nm accounts for only about 2% of total atmospheric sunlight [7]. Furthermore, since only negligible amounts of cisapride would be expected to become desorbed from the sediment and transported upward to the shallow depths of the surface water (where exposure to sunlight would be maximized), photochemical processes are not considered to be environmentally significant.

7.3.3 Oxidation

Hydroxyl (and alkylperoxy) radicals, generated in surface water from the photolysis of naturally occurring substances that absorb terrestrial sunlight [8], have been observed to oxidize many organic chemicals [9]. However, as a model, thermally induced oxidative decomposition of cisapride drug substance using hydrogen peroxide (a potential source of hydroxyl and peroxy radicals) results in the formation of only a small amount of oxidation products (see Confidential Appendix E). Nevertheless, since other oxidative pathways may be available, it is conceivable that oxidative processes could contribute to the degradation of small amounts of cisapride that may be released to the effluent water.

7.3.4. Sorption

As discussed in Item 7.2.1, the octanol-water partition coefficient indicates that cisapride will mainly become sorbed to lipophilic material in sewage sludge or sediment.

7.3.5. Volatilization

The octanol-water partition coefficient indicates that cisapride will be strongly sorbed to sludge/sediment and so will only be available in very low concentrations at the water surface. This factor, taken together with its low vapor pressure, ensures that volatilization will not be a significant process in the aquatic media.

00-00046

7.3.6. Biodegradation

The biodegradability of Cisapride was investigated according to the FDA Handbook: PB 87-175345, test 3.11. A composite inoculum, consisting of secondary effluent from a domestic waste water treatment plant and soil extract, was used. The inoculum was specifically adapted to the test and reference substance before the start of the biodegradation test. Cisapride cannot be regarded as biodegradable under the used test conditions. However, the CO₂ evolution test is a simple screening test for ready biodegradability. This negative result does not necessarily mean that the chemical will not be biodegraded under relevant environmental conditions.

7.3.7 Bioconcentration

The bioconcentration factor (BCF) has been defined as the concentration of a chemical in an organism divided by the concentration of the chemical in water. The bioconcentration factor for fish can be calculated from the following equation: [10]

$$\log \text{BCF} = 0.79 \log K_{ow} - 0.40 \quad (r^2 = 0.926; n = 122)$$

where: K_{ow} = octanol-water partition coefficient

r^2 = the coefficient of determination (proportionate reduction in error)

n = the number of chemicals from which the regression was developed

Using the octanol-water partition coefficient ($\log K_{ow} = 2.86$) determined for cisapride in water, the $\log \text{BCF}$ calculated by this method is 1.86. This value indicates that the tendency for bioconcentration of cisapride in aquatic life is negligible [11].

7.4 Probable Fate of Cisapride in Environmental Systems

Based upon the fate studies provided in Confidential Appendix E, waste cisapride will partition predominantly to the sludge in the wastewater treatment facilities. The predominant pathway for its destruction is by sorption onto waste sludge/sediment, which is then disposed of by incineration or landfill. Other processes, such as biodegradation, may also contribute to depletion of cisapride. The processes that may affect the environmental fate of cisapride are summarized in Table 7A.

The maximum expected emitted concentration (MEEC) of cisapride in the waste water from the use of drug product has been estimated (see Confidential Appendix D). As discussed in Item 6.e, this calculation does not take into account other factors such as the favorable partitioning of cisapride to the waste sludge (which might be expected to reduce the MEEC by two to four orders of magnitude) and dilution of the effluent from the waste water to the receiving body of surface water (which may vary by a factor of about 10^{-7} for fast-flowing rivers to essentially no dilution for settling ponds or intermittently dry drainage channels [12,13]). Taking these factors into consideration, it can be concluded that the actual concentration of cisapride which is emitted to the aquatic environment will be at least several orders of magnitude less than the MEEC.

TABLE 7A. SUMMARY OF ENVIRONMENTAL FATE AND TRANSPORT OF CISAPRIDE

ENVIRONMENTAL PROCESS	SUMMARY STATEMENT
Hydrolysis	Cisapride can be considered fairly hydrolytically stable, based upon direct measurements between pH 5-9
Photolysis	Photolysis is not considered significant since only negligible amounts of cisapride will become exposed to low-wavelength sunlight
Oxidation	Oxidation of cisapride by hydroxyl radicals may occur slowly in aqueous media as modeled using hydrogen peroxide (a potential source of hydroxyl radicals)
Sorption	Cisapride will be strongly sorbed to sewage sludge and sediment based upon octanol-water partition data and soil sorption/desorption studies
Volatilization	Volatilization is an unlikely transport process for cisapride because of its extremely low estimated vapor pressure and its propensity to be sorbed to sludge/sediment
Biodegradation	Biodegradation of cisapride can not be excluded under actual environmental conditions (although it does not occur with a simple CO ₂ evolution test)
Bioconcentration	Cisapride is not considered to have a tendency for bioconcentration

00-00048

8. EFFECT OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The purpose of this section is to predict the effect of cisapride at the ecosystem level in each of the environmental media (air, soil and water) based upon (to the extent applicable) quantitative comparison between the introduction/fate scenario of cisapride (Items 6-7) and toxicity data for relevant organisms/species in each environmental compartment.

Toxicity data are summarized in 8.1-8.5 below and are further described in Confidential Appendix F. The environmental effects are summarized in 8.6 and Table 8A.

8.1. Algal Assay

The effect of Cisapride on the growth of two species, being the unicellular green alga *Selenastrum capricornutum* and the unicellular blue green alga *Microcystis aeruginosa* was investigated following the FDA Handbook test 4.01: Algal Assay.

The effect on the growth of *Selenastrum capricornutum*:

The exposure period was 9 days because the plateau-phase was reached. Test concentrations were 10, 32, 100, 320 and 1000 mg/L. Cisapride exerts a delay in the growth of the alga *Selenastrum capricornutum* at concentrations higher than 320 mg/L at first. Later on, the growth is stimulated in those concentration, but eventually it does not exert an inhibitory nor a stimulatory effect on the maximum standing crop of the alga.

The effect on the growth of *Microcystis aeruginosa*:

The exposure period was 13 days because the plateau-phase was reached. Test concentrations were 10, 32, 100, 320 and 1000 mg/L. Cisapride exerts a slight stimulation in the growth of the alga *Microcystis aeruginosa* at concentrations higher than 100 mg/L at first. Later on, the growth is slightly inhibited in those concentration so eventually the maximum standing crop of the alga is not affected.

8.2. Toxicity Towards Microbial Organisms

To determine if cisapride would affect the development of environmentally important bacteria, fungi or blue-green alga, the Microbial Growth Inhibition test was performed according to the FDA Handbook test 4.02: Microbial Growth Inhibition. Representative species of 5 different groups, being free-living nitrogen fixing bacteria, blue-green alga, soil bacteria, ascomycetes and moulds, were tested for their sensitivity to cisapride. The growth of none of these organisms seemed to be inhibited by concentrations of cisapride up to 100 ppm; thus, the actual concentrations of cisapride in the sewage system or surface water will not affect the development of these environmentally important microorganisms.

8.3. Daphnia Acute Toxicity

The acute toxicity of Cisapride in the water-flea *Daphnia magna* was investigated following the FDA Handbook: PB 87-175345, test 4.08: Nominal test substance concentrations were 100, 180, 320, 560 and 1000 mg/L cisapride. The exposure period was 48 hours and the number of immobile daphnids was recorded daily. The EC₅₀ - 48 h value of Cisapride in the water-flea *Daphnia magna* was determined to be >1000 mg cisapride per litre.

00-00049

8.4. Freshwater Fish Acute Toxicity

The acute toxicity of Cisapride in the Bluegill sunfish *Lepomis macrochirus* was investigated following the FDA Handbook: PB 87-175345"; 4.11: Freshwater Fish Acute Toxicity. Nominal test substance concentrations were 100, 180, 320, 560 and 1000 mg/L cisapride. The exposure period was 96 hours. The behaviour and the mortality of the Bluegill sunfish were recorded daily. The LC₅₀ - 96 h value of cisapride in the Bluegill sunfish was determined to be >1000 mg cisapride per litre.

8.5 Toxicity In Mammalian Species

The toxicological effects of cisapride on several mammals (mouse, rat, dog) have been determined (original NDA, Non-clinical Pharmacology and Toxicology section) and are discussed further in Appendix F. From these data, acute LD₅₀ values for mouse, rat and dog oral administration are all >2500 mg/kg .

8.6 Conclusions

In accordance with 21 CFR 25.15 (b)(6), the criterion concentration of cisapride (for cisapride to be defined as toxic in the environment) would be 1% of the concentration resulting in 50% lethality. For the test organisms described in 8.3-8.4, the criterion concentration would be >10 mg/L (>10 ppm) cisapride. This value is at least several orders of magnitude greater than the estimated concentration of cisapride in sewage treatment facilities (discussed in Item 6) . Similar statements may be made regarding the animal toxicity studies described in 8.5. The toxicity criterion concentration/emission concentration ratio may be expected to increase by at least several more orders of magnitude in surface waters (due to sludge/water partitioning and dilution effects discussed in Item 7). Therefore, the concentrations required to observe toxicological effects are exceedingly high relative to the emitted concentrations due to use. The results summarized in 8.1-8.2 demonstrate that cisapride does not affect the development of alga nor of environmentally important microorganisms that would be found in sewage sludge or aquatic ecosystems. Since cisapride does not effectively volatilize to the atmospheric compartment (as discussed in Item 7), airborne effects of cisapride are not environmentally relevant.

Therefore, the overall conclusion is that emission of cisapride from use of the drug will not result in environmentally adverse effects.

TABLE 8A. SUMMARY OF ENVIRONMENTAL EFFECTS OF CISAPRIDE

STUDY/REF.	RESULTS/CONCLUSIONS
Algal Assay (EA Handbk, 4.01)	No effect on growth observed at up to 1000 mg/L cisapride after 9 days in the green alga and after 13 days in the blue-green alga; therefore cisapride is considered to have no effect on algal growth.
Microbial Toxicity (EA Handbk, 4.02)	No growth inhibition observed at up to 100 ppm cisapride; therefore cisapride is considered nontoxic towards sewage and surface water microorganisms
Daphnia Acute Toxicity (EA Handbk, 4.08)	The EC50 48 hr value is >1000 mg cisapride per litre ; therefore cisapride is considered non-immobilizing towards related water organisms
Bluegill Acute Toxicity (EA Handbk, 4.11)	The LC50 96 hr value is >1000 mg cisapride per litre ; therefore cisapride is considered nontoxic towards related fresh-water fish
Mouse/Rat/ Dog Acute Toxicity (Appendix F)	The LD50 14 day value is >2500 mg/kg for all species when administered orally; therefore cisapride is considered nontoxic towards related mammalian life

00-00051

9. USE OF RESOURCES AND ENERGY

a. Natural Resources Required To Produce, Transport, Use and/or Dispose of Drug

The estimate of the energy requirement for the manufacture of cisapride for marketing in the US is less than 0.1 % of the total energy use for drug production.

Further information is provided in Confidential Appendix I.

b. Effects, If any, upon Endangered or Threatened Species and upon Property Listed In National Register of Historic Places:

Janssen Pharmaceutica will produce the drug substance and/or product only within the existing facilities in Belgium and . Hence, there will be no adverse effect on surrounding properties listed in the National Register of Historic Places. A letter of acknowledgement from the Historic Preservation Office in is provided in Appendix 7.

Based on the available information from Fate (Item 7) and Effect (Item 8), resource and energy use will not effect endangered or threatened species.

00-00052

10. MITIGATION MEASURES

The design and use of facilities, buildings, equipment, and procedures for manufacturing, packaging, distribution, and disposal of the drug substance and drug product meet current standards of operation (building and energy regulations), pharmaceutical production (Good Manufacturing Practices), environmental protection, and occupational exposure.

Occupational standards in Belgium are prescribed in the national "General Regulation for Labor Patronage" (Algemeen Reglement voor Arbeidsbescherming, ARAB). Most of the standards are the TLV's set by ACGIH. The Janssen facilities in Belgium comply with these standards, which are also included in our MSDS for chemical substances.

The controls exercised to mitigate potential adverse environmental impacts associated with operations have been described in Item 6. Internal and external inspections help assure that mitigation practices are maintained.

There is no potential adverse environmental impact from disposal of the drug product by consumers, which would require special disposal instructions in the package circular.

Other practices in place to mitigate potential adverse environmental impacts include:

- (a) Spill-control procedures, as required by Federal, State, and local regulation, or company policy, wherever there is potential for adverse effect.
- (b) Personnel hygiene and health, safety, and GMP training are monitored regularly.
- (c) Waste minimization is practiced, in accordance with regulations or when there is an opportunity for resource conservation. Examples include: recovering and redistillation of synthesis solvents; recycling cardboard, paper, glass and metals.

11. ALTERNATIVES TO THE PROPOSED ACTION

In accordance with Council on Environmental Quality (CEQ) regulations, the only alternative to the proposed action would be (a) No Action (Not Approved), i.e. the only alternative would be not effecting the proposed action to approve the marketing of PROPULSID® tablets. That would deprive persons with gastro-sophageal reflux disease of a demonstrably safe and effective drug.

Furthermore, significant environmental impacts have not been identified with the proposed action to produce and market PROPULSID® tablets. Manufacturing, packaging, labeling, quality-control testing and distribution of the product have not been associated with any known environmental impacts. Because of the strict environmental controls and mitigation practices exercised, there is low risk for adverse environmental impacts.

12. LIST OF PREPARERS.

- Steven Pikulin **Manager Technical Regulatory Affairs
Janssen US**

- Annemie Verluyten **Manager Environmental Assessments & Permits
Environmental Affairs.
Janssen Belgium**

- Leo Verveckken **Assistant-Manager Solid Dosage Forms
Pharmaceutical Production
Janssen Belgium**

- Roger Wils **Vice President
Environmental Affairs
Janssen Belgium**

Qualifications : Ref. to Appendix 8.

13. CERTIFICATIONS.

" The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm."

January 29, 1993



Roger Wills

Vice President Environmental Affairs.

00-00055

14. REFERENCES.

- [1] Spechler, S.J., et al. N. Engl. J. Med. 326(12), 786-792, 1992.
- [2] Mc Callum, R.W., Champion, M.C. "Gastrointestinal Motility Disorders: Diagnosis and Treatment." Williams & Wilkins, Baltimore, 135-162, 1990.
- [3] Meely, W. B. and Plau, G. E. (eds), "Estimation of the vapor pressure." Environmental Exposure from Chemicals. Boca Raton: CRC Press, Inc.
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- [7] Lide, D.R. (ed. in chief), Handbook of Chemistry and Physics. Boca Raton: CRC Press, Inc., 1992, 73rd ed.
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Copies of refs. [3], [4] and [5] follow this page.

00-00056

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls JUN 29 1993

NDA 20-210 CHEM. REVIEW #4 REVIEW DATE: 06/18/93

<u>SUBMISSION TYPE:</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
BC AMENDMENT	03/31/93	N/A	04/06/93
BC AMENDMENT	04/30/93	N/A	05/05/93

NAME & ADDRESS OF APPLICANT:

Janssen Research Foundation
1125 Titusville-Harbourton Road
Titusville, NJ 08560
(609) 730-3077

DRUG PRODUCT NAME

PROPRIETARY: Propulsid
NONPROPRIETARY/USAN: Cisapride Tablets
CODE NAME/#: R51619 (NDS)
THERAPEUTIC CLASS: 1-S

PHARMACOLOGICAL CATEGORY/INDICATION:

Peristaltic stimulant for the treatment of GERD

DOSAGE FORM: uncoated tablets

STRENGTHS: 10 & 20 mg tablets

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: see Chem Review #1

SUPPORTING DOCUMENTS: see Chem Review #1

RELATED DOCUMENTS: see Chem Review #1

CONSULTS:

Biopharm, completed 11/05/92
Environmental Assessment, await completed review of 03/31/93 amendment

REMARKS/COMMENTS:

The acceptable dissolution spec is Q- [redacted] for product release and stability.

Based on the submitted stability data and acceptable dissolution spec, the acceptable expiration dates are 36M for 10 mg tablets in bottles, 18M for 10 mg tablets in blisters, 24M for 20 mg tablets in bottles, and [redacted]

CONCLUSIONS & RECOMMENDATIONS:

The NDA is APPROVABLE pending submission of further chemistry information. A draft AE letter is item 27 of this review. The CSO should communicate the information in this letter to the firm by telephone and request that they respond with hard copy as soon as possible so that the review can be completed and the NDA approved.

 / S / 6/29/93
Mike Adams
Review Chemist, HFD-180

 / S / 6/29/93
for John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
NDA 20-210
HFD-180/Division File
HFD-180/MAdams
HFD-181/KJohnson
R/D Initial: JGibbs/6-21-93 Filename: WP:
MA/dob DRAFT 6/24/93/F/T 6-29-93

APPEARS THIS WAY
ON ORIGINAL

07/19/93

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA 20-210 CHEM. REVIEW #6 REVIEW DATE: 07/19/93

<u>SUBMISSION TYPE:</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AC AMENDMENT	07/14/93	07/15/93	07/19/93

NAME & ADDRESS OF APPLICANT:
Janssen Research Foundation
1125 Titusville-Harbourton Road
Titusville, NJ 08560
(609) 730-3077

DRUG PRODUCT NAME
PROPRIETARY: Propulsid
NONPROPRIETARY/USAN: Cisapride Tablets
CODE NAME/#: R51619 (NDS)
THERAPEUTIC CLASS: 1

PHARMACOLOGICAL CATEGORY/INDICATION:
Peristaltic stimulant for the treatment of GERD

DOSAGE FORM: uncoated tablets

STRENGTHS: 10 & 20 mg tablets

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: see Chem Review #1

SUPPORTING DOCUMENTS: see Chem Review #1

RELATED DOCUMENTS: see Chem Review #1

CONSULTS:

Biopharm, completed 11/05/92
Environmental Assessment, completed 07/15/93
Follow/Up EIR for cGMP clearance made 06/17/93 has received no response; inquiry has been made.

REMARKS/COMMENTS: none

CONCLUSIONS & RECOMMENDATIONS:

The NDA is APPROVABLE pending final cGMP clearance.
The proposed test methods should be submitted for FDA validation.

 / S / 07/21/93
Mike Adams
Review Chemist, HFD-180

 / S / 7/21/93
John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
NDA 20,210
HFD-180/Division File
HFD-180/MAdams
HFD-181/KJohnson
R/D Initial: JGibbs/7-20-93
MA/dob DRAFT 7-20-93/F/T7-21-93
Filename:

APPEARS THIS WAY
ON ORIGINAL