CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-767/S011
20-398/S022
20-210/S032

APPROVAL LETTER

NDA 20-210/S-032
NDA 20-398/S-022
NDA 20-767/S-011

MAR - 6

Janssen Research Foundation
Attention: Cynthia Chianese
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Chianese:

Please refer to your supplemental new drug applications dated January 24, 2000, received January 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Propulsid (cisapride) Tablets, Suspension, and Propulsid Quicksolv Rapidly-Disintegrating Tablets, respectively.

These "Changes Being Effected" supplemental new drug applications provide for revision of the cisapride labeling as follows:

1. Package Insert: Multiple revisions to the Boxed Warning, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the package insert to better characterize the risks associated with cisapride's use, in response to the Division's December 7, 1999 and January 10, 2000 letters. These revisions include the addition of language recommending a 12-lead ECG and assessment of serum electrolytes and creatinine prior to initiating therapy with cisapride.

2. Medication Guide: Multiple revisions to the Medication Guide to harmonize it with the package insert.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted January 24, 2000, patient package insert submitted January 24, 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we

request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

At the next printing of the package insert, please revise the Boxed Warning and ADVERSE REACTIONS section, Ongoing Postmarketing Surveillance subsection as follows (new text is indicated by a double underline):

- The first paragraph, third sentence should be revised to read, "In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors for ventricular arrhythmias.

The Agency may be notified of this change in the next annual report.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 3-3-00 /S/ 3/6/00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-767/S011
20-398/S022
20-210/S032

FINAL PRINTED LABELING

APPROVED

JANSSEN
PHARMACEUTICA

PROPULSID®

(CISAPRIDE)
TABLETS/SUSPENSION

Rx only

Professional
Package Insert

FPO

7502617

Warning: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID®. From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors. These risk factors included the administration of other drugs which caused QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors; in the remaining cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse event frequency cannot be made. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions.**)

Numerous drug classes and agents increase the risk of developing serious cardiac arrhythmias. PROPULSID® is contraindicated in patients taking certain ***macrolide antibiotics*** (such as clarithromycin, erythromycin, and troleandomycin), certain ***antifungals*** (such as fluconazole, itraconazole, and ketoconazole), ***protease inhibitors*** (such as indinavir and ritonavir), ***phenothiazines*** (such as prochlorperazine and promethazine), ***Class IA and Class III antiarrhythmics*** (such as quinidine, procainamide, and sotalol); ***tricyclic antidepressants*** (such as amitriptyline); certain ***antidepressants*** (such as nefazodone and maprotiline); certain ***antipsychotic medications*** (such as sertindole), as well as ***other agents*** (such as bepridil, sparfloxacin, and grapefruit juice). (See **PRECAUTIONS: Drug Interactions.**) **The preceding list is not comprehensive.**

QT prolongation, torsades de pointes (sometimes with syncope), cardiac arrest and sudden death have been reported in patients taking PROPULSID® without the above-mentioned contraindicated drugs. Most patients had disorders that may have predisposed them to arrhythmias with PROPULSID®. These include history of prolonged electrocardiographic QT intervals or known family history of congenital long QT syndrome; history of ventricular arrhythmias, ischemic or valvular heart disease; other structural heart defects; cardiomyopathy; congestive heart failure; clinically significant bradycardia; sinus node dysfunction; second or third degree atrioventricular block; respiratory failure; or conditions that result in electrolyte disorders (hypokalemia, hypocalcemia, and hypomagnesemia), such as severe dehydration, vomiting, or malnutrition; eating disorders; renal failure; or the administration of potassium-wasting diuretics or insulin in acute settings. PROPULSID® is contraindicated in patients with these conditions.

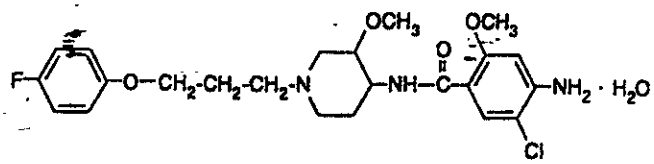
A 12-lead ECG should be performed prior to administration of PROPULSID®. Treatment with PROPULSID® should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID® and whenever conditions develop that may affect electrolyte balance or renal function. (See **DOSAGE AND ADMINISTRATION.**)

If syncope, rapid or irregular heartbeat develop, patients should immediately stop taking PROPULSID® and seek the attention of a physician.

Recommended doses of PROPULSID® should not be exceeded.

DESCRIPTION

PROPULSID® (cisapride) Tablets and Suspension contain cisapride as the monohydrate, which is an oral gastrointestinal agent chemically designated as (±)-cis-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate. Its empirical formula is $C_{23}H_{29}ClFN_3O_4 \cdot H_2O$. The molecular weight is 483.97 and the structural formula is:



Cisapride as the monohydrate is a white to slightly beige odorless powder. It is practically insoluble in water, sparingly soluble in methanol, and soluble in acetone. Each 1.04 mg of cisapride as the monohydrate is equivalent to one mg of cisapride.

PROPULSID® is available for oral use in tablets containing cisapride as the monohydrate equivalent to 10 mg or 20 mg of cisapride and as a suspension containing the equivalent of 1 mg/mL of cisapride. The inactive ingredients in the tablets are colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone, and starch (corn). The 20 mg tablets also contain FD&C Blue No. 2 aluminum lake. The inactive ingredients in the suspension are hydroxypropyl methylcellulose, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 20, propylparaben, sodium chloride, sorbitol, and water. The 1 mg/mL suspension also contains artificial cherry cream flavor and FD&C Red No. 40.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme. PROPULSID® (cisapride) is extensively metabolized; unchanged drug accounts for less than 10% of urinary and fecal recovery following oral administration. Norcisapride, formed by N-dealkylation, is the principal metabolite in plasma, feces and urine. PROPULSID® is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hours after dosing. The absolute bioavailability of PROPULSID® is 35-40%. When gastric acidity was reduced by high dose histamine H_2 receptor blocker and sodium bicarbonate in fasting subjects, there was a decrease in the rate, and to a lesser degree the extent, of PROPULSID® tablet absorption. (This has not been established for the suspension.) PROPULSID® binds to an extent of 97.5-98% to plasma proteins, mainly to albumin. The volume of distribution of PROPULSID® is about 180 L, indicating extensive tissue distribution.

The plasma clearance of PROPULSID® is about 100 mL/min. The mean terminal half-life reported for PROPULSID® ranges from 6 to 12 hours; longer half-lives, up to 20 hours, have been reported following intravenous (IV) administration.

There was no unusual drug accumulation due to time-dependent or non-linear changes in pharmacokinetics. After cessation of the repeated dosing, the elimination half-lives (8 to 10 hr) were in the same order as after single dosing. The degree of accumulation of PROPULSID® and/or its metabolites may be somewhat higher in patients with hepatic or renal impairment and in elderly patients compared to young healthy volunteers, but the differences are not consistent. Dose adjustments are recommended in patients with hepatic impairment. (See **DOSAGE AND ADMINISTRATION.**)

The pharmacokinetics of cisapride in pediatric patients are not well characterized. Therefore, it is unknown if the dose-response relationship in the adult population can be extrapolated to the pediatric population. (See **PRECAUTIONS: Pediatric Use.**)

Pharmacodynamics

The onset of pharmacological action of cisapride is approximately 30 to 60 minutes after oral administration.

Cisapride promotes gastric motility. The mechanism of action of cisapride is thought to be primarily enhancement of release of acetylcholine at the myenteric plexus. Cisapride does not induce muscarinic or nicotinic receptor stimulation, nor does it inhibit acetylcholinesterase activity. It is less potent than metoclopramide in dopamine receptor-blocking effects in rats. It does not increase or decrease basal or pentagastrin-induced gastric acid secretion.

In vitro studies have shown that cisapride is a serotonin-4 (5-HT_4) receptor agonist.

Electrophysiological studies in *in vivo* anesthetized guinea pig and rabbit models and *in vitro* isolated rabbit Purkinje fibers and ventricular papillary muscle and isolated rabbit ventricular myocyte models, have shown that cisapride prolonged cardiac repolarization without slowing conduction by selectively blocking the rapid component of the delayed rectifying K^+ current (I_{Kr}) which leads to a lengthening of the action potential (QT Syndrome).

Esophagus: Twenty milligrams oral cisapride given once to healthy volunteers increased lower esophageal sphincter pressure (LESP), starting 45 minutes after dosing, with a peak response at 75 minutes. The full duration of the effect was not monitored, and doses smaller than 20 mg were ineffective. Ten milligrams oral cisapride, administered 3 times daily for several days to patients with gastroesophageal reflux disease (GERD), resulted in a significant increase in LESP, and an increased esophageal acid clearance.

Stomach: Cisapride (single 10 mg doses or 10 mg given orally 3 times daily up to six weeks) significantly accelerated gastric emptying of both liquids and solids. Acceleration of gastric emptying, measured over a four hour period following a radio-labeled test meal given at lunch time, was greatest when 10 mg cisapride was given both in the morning and again before the test meal, intermediate when 20 mg was given as a single administration in the morning and least when only 10 mg was given on the morning of the test meal. The increases in gastric emptying were proportional to the plasma levels of cisapride measured in these subjects over the same 4 hours that the gastric emptying test was conducted.

Clinical Trials

Clinical trials have shown that cisapride can reduce the severity of symptoms of nocturnal heartburn associated with gastroesophageal reflux disease. Two placebo-controlled studies, one using a dose of 10 mg q.i.d., the other both 10 and 20 mg q.i.d., showed effects on nighttime heartburn, although the 10 mg dose in the second study was only marginally effective. There were no consistent effects on daytime heartburn, symptoms of regurgitation, or histopathology of the esophagus. Use of antacids was only infrequently affected and slightly decreased. In a third controlled trial of similar design to the others, neither 10 mg nor 20 mg taken 4 times daily was superior to placebo. In these clinical trials cisapride did not show a significant effect on LESP.

In a clinical trial comparing 10 mg cisapride to placebo, pH probe evaluation, in a relatively small number of patients, did not reveal a significant difference in pH.

INDICATIONS AND USAGE

PROPULSID® (cisapride) is indicated for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. Because of the risk of serious, and sometimes fatal, ventricular arrhythmias (see **Boxed Warning**), PROPULSID® should generally be reserved for patients who do not respond adequately to lifestyle modifications (See **PRECAUTIONS: Information for Patients** and **Medication Guide**), antacids and gastric acid reducing agents.

CONTRAINDICATIONS

Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID® (cisapride) with other drugs that inhibit cytochrome P450 3A4 or that prolong the QT interval. Some of these events have been fatal. Concomitant oral or intravenous administration of these drugs with PROPULSID® is contraindicated. PROPULSID® is also contraindicated for patients with disorders that may predispose them to arrhythmias. (See Boxed Warning, WARNINGS, PRECAUTIONS and Drug Interactions.)

PROPULSID® should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

PROPULSID® is contraindicated in patients with known sensitivity or intolerance to the drug.

WARNINGS

PROPULSID® (cisapride) undergoes metabolism mainly by the hepatic cytochrome P450 3A4 isoenzyme. Drugs which inhibit this enzyme can lead to elevated cisapride blood levels. (See **PRECAUTIONS and Drug Interactions.**)

Numerous cases of serious cardiac arrhythmias, including ventricular arrhythmias and torsades de pointes associated with QT prolongation, have been reported in patients taking PROPULSID® alone or with the drugs listed above, or with disorders that may have predisposed them to arrhythmias. Some of these patients did not have cardiac disease; however, most had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. Some of these cases have been fatal. (See **Boxed Warning.**)

PRECAUTIONS

General: Potential benefits should be weighed against risks prior to administration of PROPULSID® (cisapride) to patients who have conditions that could predispose them to the development of serious arrhythmias, such as multiple organ failure, COPD, apnea and advanced cancer. (See **CONTRAINDICATIONS.**)

Information for Patients: Patients should be warned against concomitant use of promethazine (Phenergan®), bepridil (Vascor®), quinidine (such as Quinidex®, Cardioquin®, Quinaglute®), procainamide (Procanbid®), sotalol (Betapace®), erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin®, Pediazole®), clarithromycin (Biaxin®), troleandomycin (TAO®), sparfloxacin (Zagam®), amitriptyline (Elavil®), maprotiline (Ludiomil®), nefazodone (Serzone®), fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), prochlorperazine (Compazine®), sertindole, indinavir (Crixivan®), ritonavir (Norvir®) and warfarin (Coumadin®). (See **Drug Interactions.**) **The preceding list is not comprehensive.**

Recommended doses should not be exceeded.

Patients should be advised to stop PROPULSID® and seek medical attention if they faint or become faint, dizzy, experience an irregular heartbeat or pulse, or any other unusual symptoms while using PROPULSID®.

Patients should be questioned about concomitant medication use. Patients taking PROPULSID® should also be advised to inform their physician when new medications are prescribed.

Patients should be advised to refrain from consuming grapefruit juice for the duration of their PROPULSID® therapy.

Although PROPULSID® does not affect psychomotor function nor does it induce sedation or drowsiness when used alone, patients should be advised that the sedative effects of benzodiazepines and of alcohol may be enhanced by PROPULSID®.

Patients should be advised that generally the following lifestyle changes should be tried before using any drug for nighttime heartburn, including PROPULSID®: avoiding alcohol, quitting/decreasing cigarette smoking, elevating the head of the bed, avoiding large meals/meals just before bedtime, losing weight, avoiding fatty foods, chocolate, caffeine, or citrus.

Patients should be given the Medication Guide for additional information.

Drug Interactions: Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme. In some cases where serious ventricular arrhythmias, QT prolongation, and torsades de pointes have occurred when PROPULSID® was taken in conjunction with one of the cytochrome P450 3A4 inhibitors, elevated blood cisapride levels were noted at the time of the QT prolongation.

Antibiotics: *In vitro* and/or *in vivo* data show that **clarithromycin, erythromycin** and **troleandomycin** markedly inhibit the metabolism of PROPULSID®, which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG.

Anticholinergics: Concurrent administration of certain anticholinergic compounds, such as belladonna alkaloids and dicyclomine, would be expected to compromise the beneficial effects of PROPULSID®.

Anticoagulants (oral): In patients receiving oral anticoagulants, the coagulation times were increased in some cases. It is advisable to check coagulation time within the first few days after the start and discontinuation of PROPULSID® therapy, with an appropriate adjustment of the anticoagulant dose, if necessary.

Antidepressants: *In vitro* data indicate that **nefazodone** inhibits the metabolism of PROPULSID®, which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG.

Antifungals: *In vitro* and/or *in vivo* data indicate that **fluconazole, itraconazole** and **oral ketoconazole** markedly inhibit the metabolism of PROPULSID®, which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG. Human pharmacokinetic data indicate that oral ketoconazole markedly inhibits the metabolism of cisapride, resulting in a mean eight-fold increase in AUC of cisapride. A study in 14 normal male and female volunteers suggests that coadministration of PROPULSID® and ketoconazole can result in prolongation of the QT interval on the ECG.

Diuretics: Drugs such as furosemide and the thiazides are associated with depletion of electrolytes which may result in PROPULSID®-induced cardiac arrhythmias. Serum electrolytes should be assessed in diuretic-treated patients before initiating PROPULSID® therapy and periodically thereafter. PROPULSID®-treated patients to whom diuretic therapy is added should undergo careful electrolyte monitoring after diuretic initiation.

H_2 receptor antagonists: **Cimetidine** coadministration leads to an increased peak plasma concentration and AUC of PROPULSID®; there is no effect on PROPULSID® absorption when it is coadministered with **ranitidine**. The gastrointestinal absorption of cimetidine and ranitidine is accelerated when they are coadministered with PROPULSID®.

Protease Inhibitors: *In vitro* data indicate that **indinavir** and **ritonavir** markedly inhibit the metabolism of PROPULSID® which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG.

Other: Co-administration of grapefruit juice with cisapride increases the bioavailability of cisapride by an average of 50%. Patients on PROPULSID® should refrain from consuming grapefruit juice for the duration of their PROPULSID® therapy.

PROPULSID® should not be used concomitantly with other drugs known to prolong the QT interval: certain antiarrhythmics, including those of Class IA (such as quinidine and procainamide) and Class III (such as sotalol); tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as sertindole); bepridil, and sparfloxacin. **The preceding lists are not comprehensive.**

The acceleration of gastric emptying by PROPULSID® could affect the rate of absorption of other drugs. Patients receiving narrow therapeutic ratio drugs or other drugs that require careful titration should be followed closely; if plasma levels are being monitored, they should be reassessed.

Carcinogenesis, mutagenesis, impairment of fertility: In a twenty-five month oral carcinogenicity study in rats, cisapride at daily doses up to 80 mg/kg was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this dose represents 50 times the maximum recommended human dose (1.6 mg/kg/day) on a mg/kg basis and 7 times the maximum recommended human dose (54.4 mg/m^2) on a body surface area basis. In a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg was not tumorigenic. This dose represents 50 times the maximum recommended human dose on a mg/kg basis and about 4 times the maximum recommended human dose on a body surface area basis.

Cisapride was not mutagenic in the *in vitro* Ames test, human lymphocyte chromosomal aberration test, mouse lymphoma cell forward mutation test, and rat hepatocyte UDS test and *in vivo* rat micronucleus test, male and female mouse dominant lethal mutations tests, and sex linked recessive lethal test in male *Drosophila melanogaster.*

Fertility and reproductive performance studies were conducted in male and female rats. Cisapride was found to have no effect on fertility and reproductive performance of male rats at oral doses up to 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m^2 basis). In the female rats, cisapride at oral doses of 40 mg/kg/day and higher prolonged the breeding interval required for impregnation. Similar effects were also observed at maturity in the female offspring (F_1) of the female rats (F_0) treated with oral doses of cisapride at 10 mg/kg/day or higher. Cisapride at an oral dose of 160 mg/kg/day also exerted contragestational/pregnancy disrupting effects in female rats (F_0).

Pregnancy: Teratogenic effects: Pregnancy category C: Oral teratology studies have been conducted in rats (doses up to 160 mg/kg/day) and rabbits (doses up to 40 mg/kg/day). There was no evidence of a teratogenic potential of cisapride in rats or rabbits. Cisapride was embryotoxic and fetotoxic in rats at a dose of 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m^2 basis) and in rabbits at a dose of 20 mg/kg/day (approximately 12 times the maximum recommended human dose on a mg/kg basis) or higher. It also produced reduced birth weights of pups in rats at 40 and 160 mg/kg/day and adversely affected the pup survival. There are no adequate and well-controlled studies in pregnant women. Cisapride should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the mother and the fetus.

Nursing Mothers: Cisapride is excreted in human milk at concentrations approximately one twentieth of those observed in plasma. Caution should be exercised when PROPULSID® is administered to a nursing woman, and particular care must be taken if the nursing infant or the mother is taking a drug that might alter PROPULSID®'s metabolism in the infant. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions.**)

Pediatric Use: Safety and effectiveness in pediatric patients under the age of 16 years have not been established for any indication. Although causality has not been established, serious adverse events, including death, have been reported in infants and children treated with PROPULSID®. Several pediatric deaths were due to cardiovascular events (third degree heart

block and ventricular tachycardia). Pediatric deaths have been associated with seizures and there has been at least one case of "sudden unexplained death" in a 3-month-old infant. Other unlabeled potentially serious events which have been reported in pediatric patients include: antinuclear antibody (ANA) positive, anemia, hemolytic anemia, methemoglobinemia, hyperglycemia, hypoglycemia with acidosis, unexplained apneic episodes, confusion, impaired concentration, depression, apathy, visual changes accompanied by amnesia, and severe photosensitivity reaction. (See **OVERDOSAGE.**)

Geriatric Use: Steady-state plasma levels are generally higher in older than in younger patients, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

The rate of common adverse experiences in patients greater than 65 years of age in clinical trials was similar to that in younger adults.

ADVERSE REACTIONS

In the U.S. clinical trial population of 1728 patients (comprising 506 with gastroesophageal reflux disorders, and the remainder with other disorders) the following adverse experiences were reported in more than 1% of patients treated with PROPULSID® (cisapride) and at least as often on PROPULSID® as on placebo.

System/Adverse Event	PROPULSID® N=1042	Placebo N=686
Central & Peripheral Nervous Systems		
Headache	19.3%	17.1%
Gastrointestinal		
Diarrhea	14.2	10.3
Abdominal pain	10.2	7.7
Nausea	7.6	7.6
Constipation	6.7	3.4
Flatulence	3.5	3.1
Dyspepsia	2.7	1.0
Respiratory System		
Rhinitis	7.3	5.7
Sinusitis	3.6	3.5
Coughing	1.5	1.2
Resistance Mechanism		
Viral infection	3.6	3.2
Upper respiratory tract infection	3.1	2.8
Body as a Whole		
Pain	3.4	2.3
Fever	2.2	1.5
Urinary System		
Urinary tract infection	2.4	1.9
Micturition frequency	1.2	0.6
Psychiatric		
Insomnia	1.9	1.3
Anxiety	1.4	1.0
Nervousness	1.4	0.7
Skin & Appendages		
Rash	1.6	1.6
Pruritus	1.2	1.0
Musculoskeletal System		
Arthralgia	1.4	1.2
Vision		
Abnormal vision	1.4	0.3
Reproductive, Female		
Vaginitis	1.2	0.9

The following adverse events also reported in more than 1% of PROPULSID® patients were more frequently reported on placebo: dizziness, vomiting, pharyngitis, chest pain, fatigue, back pain, depression, dehydration and myalgia.

Diarrhea, abdominal pain, constipation, flatulence and rhinitis all occurred more frequently in patients using 20 mg of PROPULSID® than in patients using 10 mg.

Additional adverse experiences reported to occur in 1% or less of patients in the U.S. clinical studies are: dry mouth, somnolence, palpitation, migraine, tremor and edema.

In other U.S. and international trials and in postmarketing experience, there have been rare reports of seizures and extrapyramidal effects. Also reported have been tachycardia, elevated liver enzymes, hepatitis, thrombocytopenia, leukopenia, aplastic anemia, pancytopenia and granulocytopenia. The relationship of PROPULSID® to the event was not clear in these cases.

Cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation, in some cases resulting in death, have been reported. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions.**)

Ongoing Postmarketing Surveillance: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID®. From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors. These risk factors included the administration of other drugs which caused QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors; in the remaining cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse event frequency cannot be made. (See **Boxed Warning, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions.**) PROPULSID®-induced serious ventricular arrhythmias and death may not correlate with the degree of drug-induced prolongation of the QT interval detected by 12-lead ECG.

In addition to the cardiovascular adverse events, the following events have been identified during post-approval use of PROPULSID® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion in this insert due to a combination of their seriousness, frequency of reporting, or potential causal connection to PROPULSID®: allergic reactions, including bronchospasm, urticaria, and angioedema; possible exacerbation of asthma; psychiatric events,

including confusion, depression, suicide attempt, and hallucinations; extrapyramidal effects including akathisia, Parkinson-like symptoms, dyskinetic and dystonic reactions; gynecomastia, female breast enlargement, urinary incontinence, hyperprolactinemia and galactorrhea.

The following events were specifically reported in the pediatric population: antinuclear antibody (ANA) positive, anemia, hemolytic anemia, methemoglobinemia, hyperglycemia, hypoglycemia with acidosis, unexplained apneic episodes, confusion, impaired concentration, depression, apathy, visual changes accompanied by amnesia, and severe photosensitivity reaction.

There have been rare cases of sinus tachycardia reported. Rechallenge precipitated the tachycardia again in some of those patients.

OVERDOSAGE

With overdose, rare cases of QT prolongation and ventricular arrhythmia have been reported.

A one-month-old male infant received 2 mg/kg of cisapride four times per day for 5 days. The patient developed third degree heart block and subsequently died of right ventricular perforation caused by pacemaker wire insertion.

In instances of overdose, patients should be evaluated for possible QT prolongation and ventricular arrhythmias, including torsades de pointes. Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

Reports of overdosage with PROPULSID® (cisapride) also include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency.

Single oral doses of cisapride at 4000 mg/kg, 160 mg/kg, 1280 mg/kg and 640 mg/kg were lethal in adult rats, neonatal rats, mice, and dogs, respectively. Symptoms of acute toxicity were ptosis, tremors, convulsions, dyspnea, loss of righting reflex, catalepsy, catatonia, hypotonia and diarrhea.

DOSAGE AND ADMINISTRATION

5 mL (1 teaspoon) suspension = 5 mg.

A 12-lead ECG should be performed prior to administration of PROPULSID® (cisapride). Treatment with PROPULSID® should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID® and whenever conditions develop that may affect electrolyte balance or renal function.

Adults: Initiate therapy with one 10 mg tablet of PROPULSID® or 10 mL of the suspension 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

Caution must be exercised in elderly patients since there is a significant proportion who have conditions or use other drugs which contraindicate the use of PROPULSID®. A 12-lead ECG and serum electrolyte measurement should be performed prior to treatment with PROPULSID®. In elderly patients, steady-state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

It is recommended that the daily dose be halved in patients with hepatic insufficiency.

The minimum effective dose of PROPULSID® should be used. Recommended doses should not be exceeded. PROPULSID® should be discontinued if relief of nocturnal heartburn does not occur.

HOW SUPPLIED

PROPULSID® (cisapride) Tablets are provided as scored white tablets debossed "Janssen" and P/10 containing the equivalent of 10 mg of cisapride in blister packages of 100 (NDC 50458-430-01) and in unit of use bottles of 120 (NDC 50458-430-12). PROPULSID® is also provided as blue tablets, debossed "Janssen" and P/20, containing the equivalent of 20 mg cisapride in blister packages of 100 (NDC 50458-440-01) and in unit of use bottles of 60 (NDC 50458-440-06).

PROPULSID® Suspension is provided as a bright pink homogeneous suspension containing the equivalent of 1 mg/mL of cisapride in 16 oz. unit of use bottles containing 450 mL (NDC 50458-450-45).

Unit of use bottles should be dispensed as an intact unit. The Medication Guide should be dispensed with the product.

Store at 15°-25°C (59°-77°F). Protect the tablets from moisture. The 20 mg tablets should also be protected from light.

Phenergan is a registered trademark of Wyeth-Ayerst Laboratories
Vascor is a registered trademark of Ortho-McNeil Pharmaceutical
Quinidex is a registered trademark of A. H. Robins Co., Inc.
Cardioquin is a registered trademark of Purdue Frederick
Quinaglute and Betapace are registered trademarks of Berlex Laboratories
Procanbid is a registered trademark of Monarch Pharmaceuticals
E.E.S., Biaxin and Norvir are registered trademarks of Abbott Laboratories
E-Mycin is a registered trademark of Knoll Laboratories
Ilotycin is a registered trademark of Dista Products Company
Pediazole is a registered trademark of Ross Products Division
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JANSSEN
PHARMACEUTICA
Titusville, NJ 08560

7502617
U.S. Patent No. 4,962,115
Revised May 1999, January 2000

7515202

MEDICATION GUIDE
IMPORTANT: READ COMPLETELY BEFORE USE. Do not take PROPULSID® if you have a medical condition or take a drug listed in this Medication Guide in the section "Who Should Not Take PROPULSID®?"

APPROVED

MEDICATION GUIDE

Brand Name: PROPULSID® (pro-pul-sid)
Generic Name: cisapride
Available as: Tablets and Suspension (liquid form)

What is the Most Important Information I Should Know About PROPULSID®(cisapride)?

PROPULSID® may cause serious irregular heartbeats that **may cause death.** Taking PROPULSID® together with certain other medicines or if you have certain medical conditions increases the chance that you will have irregular heartbeats. PROPULSID® should **never** be taken with these other medicines or if you have these conditions. A list of these medicines and these medical conditions is in the section **"Who Should Not Take PROPULSID®?". If you faint or feel faint, become dizzy or have irregular heartbeats while using PROPULSID®, stop taking PROPULSID® and get medical help right away.**

What is PROPULSID® (cisapride)?

PROPULSID® is a medicine approved only to treat the symptoms of nighttime heartburn in adults. Nocturnal, or nighttime, heartburn is a common symptom of a medical condition called gastroesophageal reflux disease (GERD). It occurs when stomach contents wash back, or "reflux," into the esophagus (a muscular tube that carries food from the mouth to the stomach). Reflux is very common at nighttime because stomach contents can easily wash backwards when you are lying down. Usually, physicians recommend that patients with nighttime heartburn make simple lifestyle changes and use antacids or acid-reducing agents to relieve their symptoms. (See the section **"What Else Can I Do for Nighttime Heartburn?"** for more details.) These other lifestyle changes and medicines should be tried first because of the risk of serious, and sometimes fatal, irregular heartbeats associated with the use of PROPULSID®.

Who Should Not Take PROPULSID® (cisapride)?

Some patients who have taken certain medicines together with PROPULSID® have experienced serious problems such as fainting, dizziness and irregular heartbeats. These problems can cause death. Medications that should never be taken with PROPULSID® include:

Type of Drug	Examples of Generic Names (Brand Name)
Anti-allergy:	promethazine (Phenergan®)
Anti-angina: (for heart pain)	bepridil (Vascor®)
Antiarrhythmics: (for irregular heart rhythm)	quinidine (such as Quinidex®, Cardioquin®, Quinaglute®) procainamide (Procanbid®) sotalol (Betapace®)
Antibiotics:	erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin®, Pediazole®) clarithromycin (Biaxin®), troleandomycin (TAO®) sparfloxacin (Zagam®)
Antidepressants:	amitriptyline (Elavil®) maprotiline (Ludiomil®) nefazodone (Serzone®)
Antifungals:	fluconazole (Diflucan®) itraconazole (Sporanox®) oral ketoconazole (Nizoral®)
Anti-nausea:	prochlorperazine (Compazine®) promethazine (Phenergan®)
Antipsychotics:	sertindole prochlorperazine (Compazine®)
Protease Inhibitors:	indinavir (Crixivan®) ritonavir (Norvir®)

- This is not a complete list of medications that you should not take. Therefore, tell your doctor about all other prescriptions and nonprescription drugs you are taking, including herbal supplements. **While taking PROPULSID®, do not start a new medicine without first consulting your doctor or pharmacist.**

Also, you should not take PROPULSID® if you have any of these conditions:

- **a history of irregular heartbeats**
- **an abnormal electrocardiogram (ECG or EKG)**
- **heart disease**
- **kidney disease**
- **lung disease**
- **low blood levels of potassium, calcium or magnesium**
- **an eating disorder (such as bulimia and anorexia)**
- **your body has suddenly lost a lot of water**
- **persistent vomiting**

- Tell your doctor if you have any type of medical condition, especially a heart condition or kidney or lung disease. Be sure your doctor knows about both your personal and family medical history before you take PROPULSID®.
- If you have not tried other medicines to relieve your nighttime heartburn, tell your doctor before using PROPULSID®.
- **The safety and effectiveness of PROPULSID® in children younger than 16 years have not been demonstrated for any use.** Serious adverse events, including death, have been reported in infants and children while being treated with PROPULSID®, although there is no clear evidence that PROPULSID® caused them.

How Should I Take PROPULSID® (cisapride)?

- Take PROPULSID® exactly as your doctor prescribes it.
- Never take more than the recommended dose of PROPULSID®. Always take your medicine for as long as the doctor has prescribed it, even if you are beginning to feel better right away.
- If you forget to take a dose, do not take the missed dose. Take the next dose at the regularly scheduled time. **Never take more than your prescribed dose at any one time to make up for the missed dose.**
- PROPULSID® does not work for everyone. If you do not get relief of your nighttime heartburn, talk to your doctor about whether to stop using PROPULSID®.

What Should I Avoid While Taking PROPULSID® (cisapride)?

- **Never** take PROPULSID® with the medications listed in the above section **"Who Should Not Take PROPULSID® (cisapride)?"**
- Do not take prescription or non-prescription medicines while taking PROPULSID® without checking first with your doctor.
- Do not drink grapefruit juice at any time while you are on PROPULSID® therapy. Drinking grapefruit juice while you are on PROPULSID® therapy may cause the same kinds of serious irregular heartbeats as taking PROPULSID® with the wrong medicines.
- Tell your doctor if you are pregnant or nursing. Your doctor will talk to you about whether you should take PROPULSID® while pregnant or nursing, based on the benefits and risks.

What are the Possible Side Effects of PROPULSID® (cisapride)?

- PROPULSID® may cause serious irregular heartbeats that **may cause death.**

Stop taking PROPULSID® and call your doctor right away if you:

- **faint or feel faint**
- **become dizzy**
- **have irregular heartbeats or pulse**
- **develop any unusual symptoms**

These may be signs of a serious side effect.

- PROPULSID®'s, most common side effects are headache, diarrhea, stomach pain, nausea, constipation and a runny nose. Other side effects have been reported less often. Be sure to ask your doctor or pharmacist about the side effects of any medicine that you are taking, including PROPULSID®.
- PROPULSID® may cause you to become more drowsy than normal if you drink alcohol or take medicines called benzodiazepines (used to reduce anxiety).

What Else Can I do for Nighttime Heartburn?

- Stop smoking or reduce the number of cigarettes you smoke.
- Elevate the head of your bed when you sleep.
- Avoid eating large meals or eating just before bedtime.
- Do not lie down right after eating.
- If you are overweight or your doctor recommends it, try to lose weight.
- Avoid fatty foods and foods containing chocolate, caffeine or citrus.
- Avoid alcoholic drinks.

All of these lifestyle changes will help to restore your body to a more normal way of functioning.

General Information

This leaflet provides a summary of information about PROPULSID®. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you need to report problems associated with the use of PROPULSID®, contact your doctor. If you have additional questions or concerns, or want more information about PROPULSID®, contact your doctor or pharmacist. You can also call the Janssen One-to-One™ Customer Action Center toll-free at 1-800-526-7736 for more information. Your pharmacist also has a longer leaflet about PROPULSID® that is written for health professionals that you can ask to read. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Elavil is a registered trademark of Zeneca Pharmaceuticals

Ludiomil is a registered trademark of Novartis Pharmaceuticals Corporation

Serzone is a registered trademark of Bristol-Myers Squibb Co.

Compazine is a registered trademark of SmithKline Beecham Pharmaceuticals

Crixivan is a registered trademark of Merck & Co., Inc.

7515202
U.S. Patent No. 4,962,115
May 1999, January 2000

JANSSEN
PHARMACEUTICA
Titusville, NJ 08560

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-767/S011
20-398/S022
20-210/S032

ADMINISTRATIVE DOCUMENTS

20-767

Section

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Numbers and Names of Drugs:

MAR - 6 2000

NDA 20-210/S-030
NDA 20-210/S-032; Propulsid (cisapride) Tablets

NDA 20-398/S-020
NDA 20-398/S-022; Propulsid (cisapride) Suspension

NDA 20-767/S-009
NDA 20-767/S-011; Propulsid Quicksolv (cisapride) Rapidly-Disintegrating Tablets

Sponsor: Janssen Research Foundation

Material Reviewed

Submission Date(s): January 24, 2000, final printed labeling (FPL; package insert and medication guide)

Receipt Date(s): January 27, 2000

Background and Summary Description: Propulsid (cisapride), available as tablets, suspension, and rapidly-disintegrating tablets, is approved for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. The approved dose is 10 mg QID, with escalation to 20 mg QID for non-responders. All three formulations share a package insert and a patient medication guide.

NDA 20-210/S-030;
NDA 20-398/S-020; and
NDA 20-767/S-009:

These supplements were submitted as "Special Supplement(s)- Changes Being Effected" on June 1, 1999. They provide for revision of the labeling as follows:

1. Package Insert:

   a. Addition of "clinically significant bradycardia" and "known family history of long QT syndrome" to the CONTRAINDICATIONS section and boxed warning,

   b. Revision of the PRECAUTIONS section to include addition of a statement that

coadministration of grapefruit juice with cisapride increases the bioavailability of cisapride and concomitant use should be avoided, and

c. Addition of specific EPS symptoms (akathisia, Parkinson-like symptoms, dyskinetic and dystonic reactions) in the ADVERSE REACTIONS section, Postmarketing Reports subsection.

2. Medication Guide:

a. Multiple revisions to the sections entitled "WHAT IS PROPULSID (cisapride)?"; "WHO SHOULD NOT TAKE PROPULSID (cisapride)?"; HOW SHOULD I TAKE PROPULSID (cisapride)?"; and "WHAT SHOULD I AVOID WHILE TAKING PROPULSID (cisapride)?" in response to the Division's February 12, 1999 letter, and

b. Addition of a statement not to take Propulsid with grapefruit juice.

The sponsor issued a "Dear Doctor" letter, dated June 1, 1999, in conjunction with these supplements.

The supplements were approvable on November 29, 1999, pending revised FPL. The applicant responded to the approvable letter with a January 24, 2000 submission.

NDA 20-210/S-032;
NDA 20-398/S- — and
NDA 20-767/S-011:

In letters dated December 7, 1999 and January 10, 2000 and teleconferences held January 11 and 12, 2000, the Division requested that the applicant further revise the cisapride labeling to better characterize the risks associated with the compound's use. In addition, the Division asked the sponsor to include language indicating that a 12-lead ECG, serum creatinine and serum electrolytes should be obtained prior to initiating cisapride therapy.

In response to the Division's requests, these supplements were submitted as "Special Supplement(s)-Changes Being Effected" on January 24, 2000. In conjunction with these supplements, the sponsor also issued a "Dear Doctor" letter.

Note: This review applies to all six supplements, given that the FPL submitted January 24, 2000 for NDAs 20-210/S-030; 20-398/S-020; and 20-767/S-009 is identical to the FPL submitted as NDAs 20-210/S-032; 20-398/S — and 20-767/S-011 on the same date.

Review

Throughout this review, new text is represented by a double underline, and deleted text is represented by a strikethrough.

Package Insert:

The currently approved insert (**coded 7502615, Revised June 1998, September 1998; Acknowledged and Retained February 12, 1999**) was compared to the submitted insert (**coded 7502617, Revised May 1999, January 2000**). In addition to minor editorial and formatting changes that do not affect the meaning of any information being conveyed, the following changes have been made.

1. Boxed Warning:

   a. The first paragraph has been revised as follows:

   "Warning: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID®.

   From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors. These risk factors included the administration of other drugs which caused QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors; in the remaining cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse event frequency cannot be made. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and

Drug Interactions.)"

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is acceptable. According to Dr. Victor Raczkowski, Deputy Director, Office of Drug Evaluation III, the applicant should be asked to further revise the third sentence to read, "In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors for ventricular arrhythmias." This revision can be made at the next printing of the package insert and the Agency notified in the subsequent annual report.

b. The second paragraph now reads

"Numerous drug classes and agents increase the risk of developing serious cardiac arrhythmias. PROPULSID® is contraindicated in patients taking certain ***macrolide antibiotics*** (such as clarithromycin, erythromycin, and troleandomycin), certain ***antifungals*** (such as fluconazole, itraconazole, and ketoconazole), ***protease inhibitors*** (such as indinavir and ritonavir), ***phenothiazines*** (such as prochlorperazine and promethazine), ***Class IA and Class III antiarrhythmics*** (such as quinidine, procainamide, and sotalol); ***tricyclic antidepressants*** (such as amitriptyline); certain ***antidepressants*** (such as nefazodone and maprotiline); certain ***antipsychotic medications*** (such as sertindole), as well as ***other agents*** (such as bepridil, sparfloxacin, and grapefruit juice). (See **PRECAUTIONS: Drug Interactions.**) **The preceding list is not comprehensive."**

This revision was requested by the Division in the January 10, 2000 letter and further modified in the January 12, 2000 teleconference, therefore, it is acceptable.

c. The third paragraph reads,

"QT prolongation, torsades de pointes (sometimes with syncope), cardiac arrest and sudden death have been reported in patients taking PROPULSID without the above-mentioned contraindicated drugs. Most patients had disorders that may have predisposed them to arrhythmias with cisapride. These include history of prolonged electrocardiographic QT intervals or known family history of congenital long QT syndrome; history of ventricular arrhythmias, ischemic or valvular heart disease; other structural heart defects; cardiomyopathy; congestive heart failure; clinically significant bradycardia; sinus node dysfunction; second or third degree atrioventricular block; respiratory failure; or conditions that result in electrolyte disorders (hypokalemia, hypocalcemia, and hypomagnesemia), such as severe dehydration, vomiting, or malnutrition; eating disorders; renal failure; or the administration of potassium-wasting

diuretics or insulin in acute settings. PROPULSID® is contraindicated in patients with these conditions.

[redacted]

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is acceptable.

d. The fourth paragraph reads,

"A 12-lead ECG should be performed prior to administration of PROPULSID®. Treatment with PROPULSID® should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID® and whenever conditions develop that may affect electrolyte balance or renal function. (See **DOSAGE AND ADMINISTRATION.**)"

The Division requested this revision in the January 10, 2000 letter, therefore, it is acceptable.

e. The fifth and sixth paragraphs read,

"If syncope, rapid or irregular heartbeat develop, patients should immediately stop taking PROPULSID® and seek the attention of a physician.

Recommended doses of PROPULSID® should not be exceeded."

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is acceptable.

2. INDICATIONS AND USAGE section: The applicant has added a cross reference to the PRECAUTIONS section, Information for Patients subsection.

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is acceptable.

3. CONTRAINDICATIONS section:

This section reads,
"Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID (cisapride) with other drugs that inhibit cytochrome P450 3A4 or that prolong the QT interval. Some of these events have been fatal. Concomitant oral or intravenous administration of these [redacted] drugs with [redacted] PROPULSID [redacted] is contraindicated. PROPULSID is also contraindicated for patients with disorders that may predispose them to arrhythmias. (See Boxed Warning, WARNINGS, PRECAUTIONS and Drug Interactions.)"

PROPULSID should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

PROPULSID is contraindicated in patients with known sensitivity or intolerance to the drug."

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is acceptable.

4. WARNINGS section:

This section reads,

"PROPULSID (cisapride) undergoes metabolism mainly by the hepatic cytochrome P450 3A4 isoenzyme. Drugs which inhibit this enzyme can lead to elevated cisapride blood levels. (See **PRECAUTIONS** and **Drug Interactions**.)

Numerous cases of serious cardiac arrhythmias, including ventricular arrhythmias and torsades de pointes associated with QT prolongation, have been reported in patients taking PROPULSID alone or with the drugs listed above, or with disorders that may have predisposed them to arrhythmias. Some of these patients did not have cardiac disease; however, most had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. Some of these cases have been fatal. (See **Boxed Warning.)"**

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is

acceptable.

5. PRECAUTIONS section, Information for Patients subsection: This subsection reads,

"Patients should be warned against concomitant use of

promethazine (Phenergan®), bepridil (Vascor®), quinidine (such as Quinidex®, Cardioquin®, Quinaglute®), procainamide (Procanbid®), sotalol (Betapace®), erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin®, Pediazole®), clarithromycin (Biaxin®), troleandomycin (TAO®), sparfloxacin (Zagam®), amitriptyline (Elavil®), maprotiline (Ludiomil®), nefazodone (Serzone®), fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), prochlorperazine (Compazine®), sertindole, indinavir (Crixivan®), ritonavir (Norvir®) and warfarin (Coumadin®). (See **Drug Interactions.**) **The preceding list is not comprehensive.**

Recommended doses should not be exceeded.

Patients should be advised to stop PROPULSID and seek medical attention if they faint or become faint, dizzy, experience an irregular heartbeat or pulse, or any other unusual symptoms while using PROPULSID.

Patients should be questioned about concomitant medication use. Patients taking PROPULSID should also be advised to inform their physician when new medications are prescribed.

Patients should be advised to refrain from consuming grapefruit juice for the duration of their PROPULSID therapy.

Although PROPULSID does not affect psychomotor function nor does it induce sedation or drowsiness when used alone, patients should be advised that the sedative effects of benzodiazepines and of alcohol may be enhanced by PROPULSID.

Patients should be advised that generally the following lifestyle changes should be tried before using any drug for nighttime heartburn, including PROPULSID: avoiding alcohol, quitting/decreasing cigarette smoking, elevating the head of the bed, avoiding large meals/meals just before bedtime, losing weight, avoiding fatty foods, chocolate, caffeine, or citrus.

Patients should be given the Medication Guide for additional information.

These revisions were requested by the division in the January 10, 2000 letter, therefore, they

are acceptable.

6. PRECAUTIONS section, Drug Interactions subsection:

   a. A new "Diuretics" subsection has been added. It reads, "drugs such as furosemide and the thiazides are associated with depletion of electrolytes which may result in PROPULSID®-induced cardiac arrhythmias. Serum electrolytes should be assessed in diuretic-treated patients before initiating PROPULSID® therapy and periodically thereafter. PROPULSID®-treated patients to whom diuretic therapy is added should undergo careful electrolyte monitoring after diuretic initiation."

   b. A new "Other" subsection has been added. It reads, "Co-administration of grapefruit juice with PROPULSID® increases the bioavailability of cisapride by an average of 50%. Patients on PROPULSID® should refrain from consuming grapefruit juice for the duration of their PROPULSID® therapy."

   c. The next to the last paragraph now reads, " ——— PROPULSID should not be used concomitantly with other drugs known to prolong the QT interval: certain antiarrhythmics, including those of Class IA (such as quinidine and procainamide) and Class III (such as sotalol); tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as sertindole); ——— bepridil, and sparfloxacin ——— **The preceding lists ——— are not comprehensive.**

   These revisions were requested by the Division in the January 10, 2000 letter, and therefore, they are acceptable.

7. ADVERSE REACTIONS section:

   a. The Postmarketing Reports subsection has been renamed "Ongoing Postmarketing Surveillance."

   b. The Ongoing Postmarketing Surveillance subsection has been revised as follows:

   "Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de-pointes, and QT prolongation have been reported in patients taking PROPULSID®. From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors. These risk factors included the administration of other drugs which caused

QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors; in the remaining cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse event frequency cannot be made. (See Boxed Warning, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and Drug Interactions.) PROPULSID®-induced serious ventricular arrhythmias and death may not correlate with the degree of drug-induced prolongation of the QT interval detected by 12-lead ECG."

This revision was requested by the Division in the January 10, 2000 letter, therefore, it is acceptable. According to Dr. Victor Raczkowski, Deputy Director, Office of Drug Evaluation III, the applicant should be asked to further revise the third sentence to read, "In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors for ventricular arrhythmias." This revision can be made at the next printing of the package insert and the Agency notified in the subsequent annual report.

In addition to the cardiovascular adverse events, the following events have been identified during post-approval use of cisapride in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion in this insert due to a combination of their seriousness, frequency of reporting, or potential causal connection to cisapride: allergic reactions, including bronchospasm, urticaria, and angioedema; possible exacerbation of asthma; psychiatric events, including confusion, depression, suicide attempt, and hallucinations; extrapyramidal effects including akathisia, Parkinson-like symptoms, dyskinetic and dystonic reactions; gynecomastia, female breast enlargement, urinary incontinence, hyperprolactinemia and galactorrhea.

The following events were specifically reported in the pediatric population: antinuclear antibody (ANA) positive, anemia, hemolytic anemia, methemoglobinemia, hyperglycemia, hypoglycemia with acidosis, unexplained apneic episodes, confusion, impaired concentration, depression, apathy, visual changes accompanied by amnesia, and severe photosensitivity reaction.

There have been rare cases of sinus tachycardia reported. Rechallenge precipitated the tachycardia again in some of those patients."

These revisions were requested by the Division in the January 10, 2000 letter, therefore, they are acceptable.

8. DOSAGE AND ADMINISRATION section: This section now reads,

"5 mL (1 teaspoon) suspension = 5 mg.

A 12-lead ECG should be performed prior to administration of PROPULSID® (cisapride). Treatment with PROPULSID® should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID® and whenever conditions develop that may affect electrolyte balance or renal function."

Adults: Initiate therapy with one 10 mg tablet of PROPULSID ——— or 10 mL of the suspension 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

Caution must be exercised in elderly patients since there is a significant proportion who have conditions or use other drugs which contraindicate the use of PROPULSID. A 12-lead ECG and serum electrolyte measurement should be performed prior to treatment with PROPULSID. In elderly patients, steady –state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

It is recommended that the daily dose be halved in patients with hepatic insufficiency.

——— The minimum effective dose should be used. Recommended doses ——— should not be exceeded. PROPULSID should be discontinued if relief of nocturnal heartburn does not occur.

[redacted]

These revisions were requested by the division in the January 10, 2000 letter, therefore, they are acceptable.

Medication Guide:

APPEARS THIS WAY
ON ORIGINAL

The submitted medication guide **(coded 7515202; May 1999, January 2000)** was compared to the currently approved medication guide **(coded 7515202; September 1998, approved July 31, 1998, acknowledged and retained February 12, 1999)**. In addition to minor editorial and formatting changes which do not affect the meaning of the information being presented, the following revisions have been made.

1. Header/Overall:

   a. The [redacted] have been deleted from the header.

      This is an acceptable editorial revision.

   b. New text has been added, which reads "**MEDICATION GUIDE IMPORTANT: READ COMPLETELY BEFORE USE. Do not take PROPULSID® if you have a medical condition or take a drug listed in this Medication Guide in the section "Who Should Not Take PROPULSID®?"**"

   c. Section titles have been changed from all capital letters to initial capitals only.

   d. The [redacted] as well as the [redacted] have been deleted.

      These revisions were requested by the Division in the December 7, 1999 letter, therefore, they are acceptable.

2. What is the Most Important Information I Should Know About PROPULSID (cisapride)?

   This section has been revised as follows:

[redacted]

PROPULSID® may cause serious irregular heartbeats that **may cause death.** Taking PROPULSID® together with certain other medicines or if you have certain medical conditions increases the chance that you will have irregular heartbeats. PROPULSID® should **never** be taken with these other medicines or if you have these conditions. A list of these medicines and these medical conditions is in the section **"Who Should Not Take PROPULSID®?". If you faint or feel faint, become dizzy or have irregular heartbeats while using PROPULSID®, stop taking**

PROPULSID® and get medical help right away."

This revision was requested by the Division in the December 7, 1999 letter, therefore, it is acceptable.

3. What is PROPULSID (cisapride)?

This section has been revised as follows:

PROPULSID® is a medicine approved only to treat the symptoms of nighttime heartburn in adults. Nocturnal, or nighttime, heartburn is a common symptom of a medical condition called gastroesophageal reflux disease (GERD). It occurs when stomach contents wash back, or "reflux," into the esophagus (a muscular tube that carries food from the mouth to the stomach). Reflux is very common at nighttime because stomach contents can easily wash backwards when you are lying down. Usually, physicians recommend that patients with nighttime heartburn make simple lifestyle changes and use antacids or acid-reducing agents to relieve their symptoms. (See the section **"What Else Can I Do for Nighttime Heartburn?"** for more details.) These other lifestyle changes and medicines should be tried first because of the risk of serious, and sometimes fatal, irregular heartbeats associated with the use of PROPULSID®."

This revision was requested by the Division in the December 7, 1999 letter, therefore, it is acceptable.

4. Who Should Not Take PROPULSID (cisapride)?

This section has been revised as follows:

"Some patients who have taken certain medicines together with PROPULSID® have experienced serious problems such as fainting, dizziness and irregular heartbeats. These problems can cause death. Medications that should never be taken with PROPULSID® include:

Type of Drug	Examples of Generic Name (Brand Name)
Anti-allergy:	**promethazine (Phenergan)**
Anti-angina: (for heart pain)	**bepridil (Vascor)**

Antiarrhythmics: (for irregular heart rhythm)	**quinidine (such as Quinidex, Cardioquin, Quinaglute)** **procainamide (Procanbid)** **sotalol (Betapace)**
Antibiotics:	**erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin®, Pediazole®)** **clarithromycin (Biaxin®), troleandomycin (TAO®)** **sparfloxacin (Zagam)**
Antidepressants:	**amitriptyline (Elavil)** **maprotiline (Ludiomil)** **nefazodone (Serzone®)**
Antifungals:	**fluconazole (Diflucan®)** **itraconazole (Sporanox®)** **oral ketoconazole (Nizoral®)**
Anti-nausea:	**prochlorperazine (Compazine)** **Promethazine (Phenergan)**
Antipsychotics:	**sertindole** **Prochlorperazine (Compazine)**
Protease Inhibitors:	**indinavir (Crixivan®)** **ritonavir (Norvir®)**

- This is not a complete list of medications that you should not take. Therefore, tell your doctor about all other prescription and nonprescription drugs you are taking, including herbal supplements. **While taking PROPULSID®, do not start a new medicine without first consulting your doctor or pharmacist.**

Also, you should not take PROPULSID® if you have any of these conditions:

- **a history of irregular heartbeats**
- **an abnormal electrocardiogram (ECG or EKG)**
- **heart disease**
- **kidney disease**
- **lung disease**
- **low blood levels of potassium, calcium or magnesium**
- **an eating disorder (such as bulimia and anorexia)**
- **your body has suddenly lost a lot of water**
- **persistent vomiting**

- **Tell your doctor if you have any type of medical condition, especially a heart condition or kidney or lung disease. Be sure your doctor knows about both your personal and family medical history before you take PROPULSID.**

- If you have not tried other [redacted] medicines to relieve your nighttime heartburn, tell your doctor before using PROPULSID®.

- **The safety and effectiveness of PROPULSID® in children younger than 16 years have not been demonstrated for any use.** Serious adverse events, including death, have been reported in infants and children while being treated with PROPULSID®, although there is no clear evidence that PROPULSID® caused them.

This revision was requested by the Division in the December 7, 1999 letter and further refined in a January 11, 2000 teleconference, therefore, it is acceptable.

5. How Should I Take PROPULSID (cisapride)?

This section has been revised as follows:

- [redacted] Take PROPULSID exactly as your doctor prescribes it.

- Never take more than the recommended dose of PROPULSID. Always take your [redacted] medicine for as long as the doctor has prescribed it, even if you are beginning to feel better right away.

- If you forget to take a dose, do not take the missed dose. Take the next dose at the regularly scheduled time. **Never take more than your prescribed dose at any one time to make up for the missed dose.**

- PROPULSID® does not work for everyone. If you do not get relief of your nighttime heartburn, talk to your doctor about whether to stop using PROPULSID®."

This revision was requested by the Division in the December 7, 1999 letter and further modified in a January 11, 2000 teleconference, therefore, it is acceptable.

6. What should I Avoid While Taking PROPULSID (cisapride)?

This section has been revised as follows:

- Never take PROPULSID® with the medications listed in the above section Who Should Not Take PROPULSID® (cisapride)?

- Do not take prescription or non-prescription medicines while taking PROPULSID without checking first with your doctor.

- Do not drink grapefruit juice at any time while you are on PROPULSID therapy. Drinking grapefruit juice while you are on PROPULSID therapy may cause the same kinds of serious irregular heartbeats as taking PROPULSID with the wrong medicines.

- Tell your doctor if you are pregnant or nursing. Your doctor will talk to you about whether you should take PROPULSID® while pregnant or nursing, based on the benefits and risks.

These revisions were requested by the Division in the December 7, 1999 letter and further modified in a January 11, 2000 teleconference, therefore, they are acceptable.

- **What are the Possible Side Effects of PROPULSID (cisapride)?**

This section has been revised as follows:

- PROPULSID® may cause serious irregular heartbeats that may cause death.

Stop taking PROPULSID and call your doctor right away if you

- **faint or feel faint**

- become dizzy
- have irregular heartbeats or pulse
- develop any unusual symptoms

These may be signs of a serious side effect.

- PROPULSID's most common side effects are headache, diarrhea, stomach pain, nausea, constipation and a runny nose. Other side effects have been reported less often. Be sure to ask your doctor or pharmacist about the side effects of any medicine that you are taking, including PROPULSID®.

- PROPULSID may cause you to become more drowsy than normal if you drink alcohol or take medicines called benzodiazepines (used to reduce anxiety)."

8. What Else Can I do for Nighttime Heartburn?

   The word has been replaced by the word "drinks."

   This revision was requested in the December 7, 1999 letter, therefore, it is acceptable.

9. General Information:

   This section has been revised to read, "This leaflet provides a summary of information about PROPULSID®. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you need to report problems associated with the use of PROPULSID, contact your doctor. If you have additional questions or concerns, , or want more information about PROPULSID®, contact your doctor or pharmacist. You can also call the Janssen One-to-One™ Customer Action Center toll-free at 1-800-526-7736 for more information. Your pharmacist also has a longer leaflet about PROPULSID® that is written for health professionals that you can ask to read. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others."

Conclusions

The submitted labeling is acceptable and can be approved. However, the applicant should be requested to make the following revisions at the next printing of the package insert:

Boxed Warning and ADVERSE REACTIONS section, Ongoing Postmarketing Surveillance subsection, first paragraph, third sentence:

This sentence should be revised to read, "In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors for ventricular arrhythmias.

The Agency may be notified of this revision in the next annual report.

/S/ 3/6/00
Regulatory Health Project Manager

/S/ 3-7-00

cc:
Original NDAs
HFD-180/Div. Files
HFD-180/MMcNeil
HFD-180/Talarico

draft: mm/February 18, 2000
r/d Initials: LTalarico 2/29/00
KJohnson 3/3/00
final: March 6, 2000

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

U.S. Food and Drug Administration

This is the retyped text of a letter from Janssen Pharmaceutica Research Foundation. Contact the company for a copy of any referenced enclosures.

IMPORTANT DRUG WARNING

January 24, 2000

Dear Doctor,

Janssen Pharmaceutica would like to inform you of important changes made in the PROPULSID (cisapride) labeling. We wish to draw your attention to the Boxed Warning, Drug Interactions and Dosage and Administration sections that contain the essential changes. Other sections of the labeling including Contraindications, Warnings, Precautions, and Adverse Reactions, have also been revised to reflect these changes. In addition, similar changes have been incorporated into the PROPULSID Patient Medication Guide. Highlights of the changes include the following:

- A 12-lead ECG should be obtained before PROPULSID is administered.
- PROPULSID should not be initiated if the QTc value exceeds 450 milliseconds.
- PROPULSID is contraindicated in patients with electrolyte disorders (hypokalemia, hypocalcemia and hypomagnesmia). Serum electrolytes should be assessed in diuretic-treated patients before initiating PROPULSID and periodically thereafter.

Revised information is highlighted in red:

BOXED WARNING

This section has been expanded and reorganized.

Warning: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID. From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID was used in patients with known risk factors. These risk factors included the administration of other drugs which caused QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes: or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors: in the remaining

cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse events frequency cannot be made (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and Drug Interactions.)**

Numerous drug classes and agents increase the risk of developing serious cardiac arrhythmias. **PROPULSID** is contraindicated in patients taking certain *macrolide antibiotics* (such as clarithromycin, erythromycin, and troleandomycin), certain *antifungals* (such as fluconazole, itraconazole, and ketoconazole), *protease inhibitors* (such as indinavir and ritonavir), *phenothiazines* (such as prochlorperazine and promethazine); *Class IA and Class III antiarrhythmics* (such as quinidine, procainamide, and sotalol); *tricylic antidepressants* (such as amitriptyline); certain *antidepressants* (such as nefazodone and maprotiline); certain *antipsycotic medications* (such as sertindole) as well as *other agents* (such as bepridil, sparfloxacin, and grapefruit juice). See PRECAUTIONS: Drug Interactions.) **The preceding list is not comprehensive.**

QT prolongation, torsades de pointes (sometimes with syncope), cardiac arrest and sudden death have been reported in patients taking PROPULSID without the above-mentioned contraindicated drugs. Most patients had disorders that may have predisposed them to arrhythmias with PROPULSID. These include history of prolonged electrocardiographic QT intervals or known family history of congenital long QT syndrome; history of ventricular arrhythmias, ischemic or vascular heart disease; other structural heart defects; cardiomyopathy; congestive heart failure: clinically significant bradycardias; sinus node dysfunction; second or third degree atrioventricular block; respiratory failure; or conditions that result in electrolyte disorders (hypokalemia, hypocalcemia, and hypomagnesemia), such as severe dehydration, vomiting, or malnutrition, eating disorders: renal failure; or the administration of potassium-wasting diuretics or insulin in acute settings. PROPULSID is contraindicated in patients with these conditions.

A 12-lead ECG should be performed prior to administration of PROPULSID. Treatment with PROPULSID should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID and whenever conditions develop that may affect electrolyte balance or renal function (**See DOSAGE AND ADMINISTRATION.**)

If syncope, rapid or irregular heartbeat develop, patients should immediately stop taking PROPULSID and seek the attention of a physician.

Recommended doses of PROPULSID should not be exceeded.

DRUG INTERACTIONS

This section has been revised as follows to include:

Diuretics: Drugs such as furosemide and the thiazides are associated with depletion of electrolytes which may result in PROPULSID -induced cardiac arrhythmias. Serum electrolytes should be assessed in diuretic-treated patients before initiating PROPULSID therapy and periodically thereafter. PROPULSID-treated patients to whom diuretic therapy is added should undergo careful electrolyte monitoring after diuretic initiation.

DOSAGE AND ADMINISTRATION

This section has been expanded to include:

Caution must be exercised in elderly patients since there is a significant proportion who have conditions or use other drugs which contraindicate the use of PROPULSID. A 12-lead ECG and serum electrolyte measurement should be performed prior to treatment with PROPULSID.

Janssen Pharmaceutica is committed to providing you with the most current product information available for the management of your patients receiving PROPULSID. You can further our understanding of adverse events by reporting all cases to Janssen at 1-800-JANSSEN (526-7736) or to the FDA MedWatch Program by phone 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail (using postage-paid form) MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or via www.fda.gov/medwatch.

Please refer to the enclosed revised package insert for full prescribing information, including Boxed Warning, and the medication guide. For additional medical information concerning PROPULSID, please call the Janssen One to One Customer Action Center at 1-800-JANSSEN (526-7736) from 8AM to 8PM Eastern Time, Monday through Friday.

Sincerely,

Jan Gheuens, MD
Vice President, Medical Affairs
Janssen Pharmaceutics

Janssen at Washington Crossing
1125 Trenton Harbouton Road
Post Office Box 200
Titusville, New Jersey 08500-0200

Return to Summary

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

20-767

NDA 20-210/S-032
NDA 20-398/S-022
NDA 20-767/S-011

CBE-0 SUPPLEMENT

FEB 29 2000

Janssen Research Foundation
Attention: Cynthia Chianese
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Chianese:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
20-210	S-032	Propulsid (cisapride) Tablets
20-398	S-022	Propulsid (cisapride) Suspension
20-767	S-011	Propulsid Quicksolv (cisapride) Rapidly-Disintegrating Tablets

Date of Supplements: January 24, 2000

Date of Receipt: January 27, 2000

These supplemental applications, submitted as "Supplement - Changes Being Effected" supplements, propose revision of the cisapride labeling as follows:

1. Package Insert: Multiple revisions to the Boxed Warning, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the package insert to better characterize the risks associated with cisapride's use, in response to the Division's December 7, 1999 and January 10, 2000 letters. These revisions include the addition of language recommending a 12-lead ECG and assessment of serum electrolytes and creatinine prior to initiating therapy with cisapride.

2. Medication Guide: Multiple revisions to the Medication Guide to make it consistent with the package insert.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on March 27, 2000 in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7510.

Sincerely,

/S/ 2/29/00

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-210, 20-398, 20-767
HFD-180/Div. Files
HFD-180/M.McNeil
DISTRICT OFFICE
Drafted by: mm/February 25, 2000
final: February 29, 2000
filename:

APPEARS THIS WAY
ON ORIGINAL

CBE-0 SUPPLEMENT ACKNOWLEDGEMENT (AC)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-767/S011
20-398/S022
20-210/S032

CORRESPONDENCE

JANSSEN • PHARMACEUTICA • • RESEARCH FOUNDATION •

NDA NO. 20-767 REF. NO. 011
NDA SUPPL FOR SE1 CBE 0

02/04/00
H-G-T

Sent via Federal Express

January 24, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation
Drug Products/HFD-180
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-210; PROPULSID® (cisapride) Tablets
NDA 20-398; PROPULSID® (cisapride) Suspension
NDA 20-767; PROPULSID® QUIKSOLV® (cisapride) Rapidly-Disintegrating Tablets
Special Supplement - Changes Being Effected

Dear Dr. Talarico:

In response to your December 7, 1999 and January 10, 2000 letters, we are submitting a Changes Being Effected supplement providing for changes to the Propulsid package insert and Medication Guide. This revised labeling reflects your January 10, 2000 version plus additional changes discussed via telephone on January 11 and 12, 2000.

This revised labeling is being implemented in production immediately and the attached Dear Doctor letter is being disseminated today. The Dear Doctor letter, including labeling and envelope, is also being submitted today on Form FDA 2253.

Twenty copies of final printed labeling are enclosed, with ten copies mounted. A word-processed copy of the version of the labeling is also provided in hard copy and on diskette.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Assistant Director, Regulatory Affairs

Enclosure
Desk copy (with disk): M. McNeil

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200