

Division Draft #4

PROPULSID™ (cisapride) Tablets

DESCRIPTION

PROPULSID™ (cisapride) Tablets contain cisapride as the monohydrate, which is an oral gastrointestinal prokinetic 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. Inactive ingredients 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.

CLINICAL PHARMACOLOGY

Pharmacokinetics

PROPULSID™ is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hr after dosing. The absolute bioavailability of PROPULSID™ is 35-40%. Experimentally reduced gastric acidity in fasting subjects caused a marked decrease in the rate and to a lesser degree the extent of PROPULSID™ absorption.

PROPULSID™ binds to an extent of 97.5-98% to plasma proteins, mainly to albumin. The

Replace with:

Experimentally, gastric acidity was reduced by high dose histamine H₂ receptor blocker ^{and} sodium bicarbonate in fasting subjects, ~~there was~~ caused a decrease in the rate,...

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 hr; longer half-lives, up to 20 hr, have been reported following intravenous (IV) administration. PROPULSID™ 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.

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

There is some evidence that the degree of

accumulation of PROPULSID™ 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 and do not require dosage adjustment.

Pharmacodynamics

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

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 effect in rats. It does not increase or decrease basal or pentagastrin-induced gastric acid secretion.

NDA 20-210 Draft Labeling
Page 5

Added due to review of Safety Update

In vitro studies have shown that cisapride is a serotonin-4 (5-HT₄) receptor agonist. This agonistic action may result in increased gastrointestinal motility and cardiac rate.

Esophagus: Single doses of cisapride (4 to 10 mg IV) increased the lower esophageal sphincter pressure (LESP) and lower esophageal peristalsis compared to placebo and/or metoclopramide. In patients with gastroesophageal reflux disease (GERD) and a LESP of <10 mm Hg, cisapride dose-dependently increased the strength of esophageal peristalsis and more than doubled LESP, raising it to normal values. The increase in LESP was partially reversed by atropine, suggesting that the effect is partly, but not exclusively, cholinergically-mediated. Twenty mg oral cisapride given once to healthy volunteers similarly increased LESP, starting 45 min after dosing, with a peak response at 75 min. The full duration of the effect was not monitored, and doses smaller than 20 mg were ineffective. Ten mg oral cisapride, administered 3 times daily for several days to patients with GERD, resulted in a significant increase in LESP, and an increased esophageal acid clearance.

Stomach: Cisapride (single 10 mg doses IV or

oral 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 was greatest when a dose of 10 mg was given both in the morning and at lunch, intermediate when 20 mg was given in the morning and least when only 10 mg was given in the morning. The increases in gastric emptying were proportional to the plasma levels measured following the different regimens.~~

Replace with:

...Acceleration of gastric emptying, measured over a four hour period following a radio-labeled test meal given at lunch time, was greatest when ~~preceded by~~ 10 mg ^{was both} cisapride given 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 cisapride can reduce the symptoms of nocturnal heartburn associated with gastroesophageal reflux disease. Two placebo-controlled studies, one 10 mg the other both 10 and 20 mg QID showed effects on nighttime heartburn although the 10 mg dose in the second study was only marginally effective. There was no consistent effect 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, neither 10 nor 20 mg taken 4 times was superior to placebo

In these multicenter trials, there was no significant effect of cisapride on LESP or 24-hour pH exposure.

Replace with:

Clinical trials have shown that cisapride can reduce the symptoms of nocturnal heartburn associated with gastroesophageal reflux disease. Two placebo-controlled studies, one ^{using a dose of} 10 mg, the other both 10 and 20 mg QID, showed effects on nighttime heartburn, although the 10 mg dose in the second study was only marginally effective. ^{There were no consistent} effects ~~not consistent~~ on daytime heartburn, or symptoms of regurgitation, ~~using a multiple endpoint analysis. There was no~~ consistent effect on histopathology of the esophagus. Use of antacids ^{only infrequently affected and} ~~was decreased~~ slightly decreased.

^{These clinical} ~~clinical trials not specifically~~ designed to determine therapeutic effects on LESP, despite showing ~~effectiveness in nocturnal~~ heartburn, did not show a significant effect on LESP, perhaps because the majority of these patients had normal LESP's at the beginning and end of the study period. In a clinical trial comparing 10 mg cisapride to placebo, pH probe ^{evaluation} ~~studies~~, in a relatively small number of patients, did not reveal a significant difference in pH.

INDICATIONS

PROPULSID™ (cisapride) is indicated for the symptomatic treatment of patients with nocturnal heartburn due to gastroesophageal reflux disease.

CONTRAINDICATIONS

PROPULSID™ (cisapride) 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.

PRECAUTIONS

Information for Patients: Although PROPULSID™ (cisapride) 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 accelerated by PROPULSID™.

Drug Interactions: Concurrent administration of anticholinergic compounds ^{would be expected to} ~~may~~ compromise the beneficial effects of PROPULSID™. ^{9/}The acceleration of gastric emptying by PROPULSID™ ^{could} ~~may~~ affect the rate of absorption of other drugs.)

^{Patients receiving} ~~For~~ narrow therapeutic ratio drugs or other drugs that require careful titration, ~~it should be appreciated that PROPULSID may alter absorption when given concomitantly.~~ ^{Followed} Patients on such drugs should be ^{monitored} closely; ^{if} plasma levels, ^{are being} ~~if~~ monitored, ^{they} ~~should~~ be reassessed.

In patients receiving anticoagulants, the coagulation times ^{were} ~~did~~ increase in some cases. It is advisable to check coagulation time one week after the start and discontinuation of PROPULSID™ therapy, with an appropriate adjustment of the anticoagulant dose, if necessary.

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™.

Carcinogenesis, mutagenesis, impairment of fertility: In a twenty-five month oral carcinogenicity study in rats, cisapride at daily doses up to 80 mg/kg, ~~(172 mg/m²)~~, was not tumorigenic.

Replace with:

~~(670.8 mg/m²)~~

For a 50 kg person (1.3 m² body surface area), this dose represents 50 times the recommended maximum clinical dose (1.6 mg/kg/day) on a mg/kg basis and 8 times the clinical dose (59.2 mg/m²) on a body surface area basis.

Replace with:

For a 50 kg person of average height (1.46 m² body surface area), this dose represents 50 times the recommended maximum clinical dose (1.6 mg/kg/day) on a mg/kg basis and ⁷~~11.8~~ times the clinical dose (54.4 mg/m²) on a body surface area basis.

In a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg, ~~(240 mg/m²)~~ was not tumorigenic. This dose represents 50 times the recommended maximum clinical dose

Replace with:

~~(665.8 mg/m²)~~

on a mg/kg basis and ~~5.6~~^{about 4} times the recommended maximum clinical dose on a body surface area basis.

Replace with:
5.6 times

Cisapride was not mutagenic in 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. 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 (F₁) of the female rats (F₀) treated with oral doses of

(100 times the maximum recommended human dose, on a mg/kg basis and 10 times the human dose on a mg/m² basis)

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 (F₀).

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 and in rabbits at a dose of 20 mg/kg/day 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 justifies the potential risk to the fetus.

Nursing Mothers: Cisapride is excreted in

*uncompounded
max/min*
(100 times the human dose on a mg/kg basis and 14 times the human dose on a mg/m² basis)

human milk at concentrations approximately one twentieth of those observed in plasma. Caution should be exercised when PROPULSID™ is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

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 adverse experiences in patients greater than 65 years of age was similar to that in younger adults.

Firm has responded to our requests for the following (SEE PAGE 17):

1. to refer to the total data base,
2. to identify causes of discontinuation, and
3. show adverse reactions for 10 vs 20 mg or state that there is no difference.

ADVERSE REACTIONS

In the U.S. clinical trial population of 506 patients with gastroesophageal reflux disorders the following adverse experiences were reported to occur in more than 1% of patients treated with PROPULSID™ (cisapride).

	PROPULSID™ n=315	Placebo n=191
Headache	20.0%	20.4%
Diarrhea	14.9	12.0
Abdominal pain	7.9	3.7
Constipation	7.3	3.7
Nausea	6.3	1.6
Vomiting	4.8	1.0
Pain	3.8	2.6
Flatulence	2.9	1.6
Dizziness	2.5	1.6
Chest pain	1.9	1.6
Malaise	1.9	0.0
Arthralgia	1.3	1.6
Myalgia	1.3	1.6
Dysuria	1.3	0.0

Fever

1.3

1.0

Additional adverse experiences reported to occur in 1% or less of patients in U.S. GERD studies are: Abnormal vision, anxiety, insomnia, dry mouth, somnolence, palpitation, rash, edema and pruritus.

In other U.S. and international trials and in foreign marketing experience, there have been reports of seizures and abnormal movements, tachycardia, elevated liver enzymes, and hepatitis. The relationship of PROPULSID[®] to the event was not clear in these cases.

ADVERSE REACTIONS

In the U.S. clinical trial population of 1728 patients (comprising 506 with gastroesophageal reflux disorders, and the remainder with other motility disorders) the following adverse experiences were reported in more than 1% of patients treated with PROPULSID® (cisapride). The percent of patients who discontinued treatment is displayed in parenthesis.

System/Adverse Event	PROPULSID® N=1042	Placebo N=686
<u>Central & Peripheral Nervous Systems</u>		
Headache	19.3% (1.1%)	17.1% (0.4%)
Dizziness	5.1 (0.2)	5.1 (0.1)
<u>Gastrointestinal</u>		
Diarrhea	14.2 (0.7)	10.3 (0.1)
Abdominal pain	10.2 (1.2)	7.7 (0.9)
Nausea	7.6 (1.0)	7.6 (0.3)
Vomiting	6.7 (0.6)	7.6 (0.1)
Constipation	6.7 (0.1)	3.4 (0.0)
Flatulence	3.5 (0.4)	3.1 (0.4)
Dyspepsia	2.7 (0.1)	1.0 (0.0)
<u>Respiratory System</u>		
Rhinitis	7.3 (0.1)	5.7 (0.1)
Sinusitis	3.6 (0.0)	3.5 (0.0)
Pharyngitis	2.1 (0.0)	2.0 (0.1)
Coughing	1.5 (0.2)	1.2 (0.0)
<u>Resistance Mechanism</u>		
Viral infection	3.6 (0.2)	3.2 (0.0)
Upper respiratory tract infection	3.1 (0.0)	2.8 (0.0)
Infection	1.2 (0.0)	1.3 (0.0)
<u>Body as a Whole</u>		
Pain	3.4 (0.0)	2.3 (0.0)
Chest pain	2.2 (0.1)	2.3 (0.0)
Fever	2.2 (0.1)	1.5 (0.0)
Injury	1.0 (0.0)	0.6 (0.0)
Fatigue	1.8 (0.1)	3.6 (0.0)
Back pain	1.7 (0.0)	2.9 (0.0)
<u>Urinary System</u>		
Urinary tract infection	2.4 (0.0)	1.9 (0.0)
Micturition frequency	1.2 (0.1)	0.6 (0.0)
<u>Psychiatric</u>		
Insomnia	1.9 (0.3)	1.3 (0.4)
Anxiety	1.4 (0.1)	1.0 (0.1)
Nervousness	1.4 (0.2)	0.7 (0.0)
Depression	1.2 (0.0)	0.6 (0.1)
<u>Skin & Appendages</u>		
Rash	1.6 (0.0)	1.6 (0.3)
Pruritus	1.2 (0.1)	1.0 (0.0)
<u>Metabolic & Nutritional</u>		
Dehydration	1.5 (0.0)	1.0 (0.0)
<u>Musculoskeletal System</u>		
Arthralgia	1.4 (0.1)	1.2 (0.0)
Myalgia	1.0 (0.0)	1.3 (0.0)
<u>Vision</u>		
Abnormal vision	1.4 (0.2)	0.3 (0.0)
<u>Reproductive, Female</u>		
Vaginitis	1.2 (0.0)	0.9 (0.0)

and at least as often as PROPULSID as on placebo

omit completely - too non-specific

omit completely - too non-specific

The following adverse events were also reported in more than 1% of propulsid patients were more frequently reported on placebo: dizziness, vomiting, pharyngitis, chest pain, fatigue, back pain, dehydration, fatigue

Also add (as a result of Safety Update Review) leukopenia, aplastic anemia, pancytopenia, granulocytopenia

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.

Add

In other U.S. and international trials and in foreign marketing experience, there have been rare reports of seizures and extrapyramidal effects, tachycardia, elevated liver enzymes, hepatitis, and thrombocytopenia. The relationship of PROPULSID® to the event was not clear in these cases.

NDA 20-210 Draft Labeling
Page 17 18

Added due to review of Safety Update

There have been rare cases of ^{stated} tachycardia reported. Rechallenge precipitated relapse in some of those patients.

OVERDOSAGE

Reports of overdose with PROIULSID™ (cisapride) include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency. Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

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

Adults: Initiate therapy with 10 mg of
PROPULSID™ (cisapride) 4 times daily at least
15 minutes before meals and at bedtime. It

~~is likely that the dosage will need to be
increased to 20 mg, given as above, to obtain
a satisfactory effect.~~

Replace with:

~~The dosage can be increased to 20
mg, given as above, if needed to
obtain a satisfactory effect.~~

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.

HOW SUPPLIED

PROPULSID™ (cisapride) is 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 bottles of 100 (NDC
50458-430-10), 250 (NDC 50458-430-25), and
500 (NDC 50458-430-50). PROPULSID™ is also
provided as blue

*In most patients the
dosage will need to
be increased to
20mg, given as
above, to obtain a
satisfactory result.*

tablets, debossed "Janssen" and PROPULSID/20,
containing the equivalent of 20 mg cisapride
in blister packages of 100 (NDC 50458-440-01)
and in bottles of 100 (NDC 50458-440-10), 120
(NDC 50458-440-12), 250 (NDC 50458-440-25),
and 500 (NDC 50458-440-50). Store at
controlled room temperature, 15°-30°C (59°-
80°F). Protect from moisture.

Add:

The 20 mg tablets should also be
protected from light

JANSSEN PHARMACEUTICA INC.

Piscataway, New Jersey 08855
Titusville, 08560

Date: ~~August 1991~~
~~June 1991~~ 1993
4,962,115

Patent:

Division Draft 3

PROPULSID™ (cisapride) Tablets

DESCRIPTION

PROPULSID™ (cisapride) Tablets contain cisapride as the monohydrate, which is an oral gastrointestinal prokinetic agent chemically designated as (\pm)-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. Inactive ingredients 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.

CLINICAL PHARMACOLOGY

Pharmacokinetics

PROPULSID™ is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hr after dosing. The absolute bioavailability of PROPULSID™ is 35-40%.

Revised based on Alpha NDA

Experimentally reduced gastric acidity in fasting subjects caused a marked decrease in the rate and to a lesser degree the extent of PROPULSID™ absorption. 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 hr; longer half-lives, up to 20 hr, have been reported following intravenous (IV) administration. PROPULSID™ 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.

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

There is some evidence that the degree of accumulation of PROPULSID™ 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 and do not require dosage adjustment.

Pharmacodynamics

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

The mechanism of action of cisapride is ^{thought to be primarily} ~~primarily due to the~~ 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 effect in rats. It does not increase or decrease basal or pentagastrin-induced gastric acid secretion.

Esophagus: Single doses of cisapride (4 to 10 mg IV) increased the lower esophageal sphincter pressure (LESP) and lower esophageal peristalsis compared to placebo and/or metoclopramide. In patients with gastroesophageal reflux disease (GERD) and a LESP of <10 mm Hg, cisapride dose-dependently increased the strength of esophageal peristalsis and more than doubled LESP, raising it to normal values. The increase in LESP was partially reversed by atropine, suggesting that the effect is partly, but not exclusively, cholinergically-mediated. Twenty mg oral cisapride given once to healthy volunteers similarly increased LESP, starting 45 min after dosing, with a peak response at 75 min. The full duration of the effect was not monitored, and doses smaller than 20 mg were ineffective. Ten mg oral cisapride, administered 3 times daily for several days to patients with GERD, resulted in a significant increase in LESP, and an increased esophageal acid clearance.

Stomach: Cisapride (single 10 mg doses IV or oral 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 was greatest when a dose of 10 mg was given both in the morning and at lunch, intermediate when 20 mg was given in the morning and least when only 10 mg was given in the morning. The increases in gastric emptying were proportional to the plasma levels measured ^{when?} following the different regimens. ~~It was determined that once a threshold plasma concentration of 50 to 70~~

~~ng/mL of cisapride was reached, there was a predictable relationship between plasma concentrations of cisapride and gastric emptying.~~

Clinical trials have shown cisapride can reduce the symptoms of nocturnal heartburn associated with gastroesophageal reflux disease. ~~Results of three large randomized parallel comparisons of 10/20 mg QID with placebo were not uniform, but showed fairly consistent effects on nighttime heartburn, with no consistent effect on daytime heartburn, or symptoms of regurgitation, or histopathology of the esophagus. Use of antacids was only infrequently selected. In two studies comparing both 10 and 20 mg taken 4 times daily to placebo, 10 mg was superior to both treatments in one study while 20 mg was superior in the other.~~ *Two placebo-controlled studies, one of 10 mg and the other of both 10 and 20 mg, were only marginally effective.*

In these multicenter trials, there was no significant effect of cisapride on LESP or 24-hour pH exposure.

INDICATIONS

PROPULSID™ (cisapride) is indicated for the symptomatic treatment of patients with nocturnal heartburn due to gastroesophageal reflux disease.

CONTRAINDICATIONS

PROPULSID™ (cisapride) 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.

PRECAUTIONS

Information for Patients: Although PROPULSID™ (cisapride) 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 accelerated by PROPULSID™.

Drug Interactions: Concurrent administration of anticholinergic compounds may compromise the beneficial effects of PROPULSID™. The acceleration of gastric emptying by PROPULSID™ may affect the rate of absorption of other drugs.

For narrow therapeutic ratio drugs or other drugs that require careful titration, it should be appreciated that PROPULSID™ may alter absorption when given concomitantly. Patients on such drugs should be monitored closely; plasma levels, if monitored, should be reassessed.

In patients receiving anticoagulants, the coagulation times did increase in some cases. It is advisable to check coagulation time one week after the start and discontinuation of PROPULSID™ therapy, with an appropriate adjustment of the anticoagulant dose, if necessary.

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

Carcinogenesis, mutagenesis, impairment of fertility: In a twenty-five month oral carcinogenicity study in rats, cisapride at daily doses up to 80 mg/kg (472 mg/m²) was not tumorigenic. For a 50-kg person (1.5 m² body surface area), this dose represents 50 times the recommended maximum clinical dose (1.6 mg/kg/day) on a mg/kg basis and 8 times the clinical dose (59.2 mg/m²) on a body surface area basis. In a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg (240 mg/m²) was not tumorigenic. This dose represents 50 times the recommended maximum clinical dose on a mg/kg basis and 4 times the recommended maximum clinical dose on a body surface

area basis.

Cisapride was not mutagenic in 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. 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 (F₁) of the female rats (F₀) 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 (F₀).

Was there maternal toxicity + what were the fetal toxic doses?

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 and in rabbits at a dose of 20 mg/kg/day 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 justifies the potential risk to 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.

Pediatric Use: Safety and effectiveness in children have not been established.

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 adverse experiences in patients greater than 65 years of age was similar to that in younger adults.

ADVERSE REACTIONS

Refer to total data base.
Identify causes
of discontinuation

In the U.S. clinical trial population of 506 patients with gastroesophageal reflux disorders the following adverse experiences were reported to occur in more than 1% of patients treated with PROPULSID™ (cisapride).

	PROPULSID™ n=315	Placebo n=191
Headache	20.0%	20.4%
Diarrhea	14.9	12.0
Abdominal pain	7.9	3.7
Constipation	7.3	3.7
Nausea	6.3	1.6
Voaiting	4.8	1.0
Pain	3.8	2.6
Flatulence	2.9	1.6
Dizziness	2.5	1.6
Chest pain	1.9	1.6
Malaise	1.9	0.0
Arthralgia	1.3	1.6
Myalgia	1.3	1.6
Dysuria	1.3	0.0
Fever	1.3	1.0

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Additional adverse experiences reported to occur in 1% or less of patients in U.S. GERD studies are: Abnormal vision, anxiety, insomnia, dry mouth, somnolence, palpitation, rash, edema and pruritis.

In other U.S. and international trials and in foreign marketing experience, there have been reports of seizures ^($\frac{1}{100}$ %) and abnormal movements, tachycardia, elevated liver enzymes, and hepatitis. The relationship of PROPULSID™ to the event was not clear in these cases.

OVERDOSAGE

Reports of overdose with PROPULSID™ (cisapride) include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency. Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

Single oral doses of cisapride at 4000 mg/kg, 1600 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.

DOSE AND ADMINISTRATION

Adults: Initiate therapy with 10 mg of PROPULSID™ (cisapride) 4 times daily at least 15 minutes before meals and at bedtime. *It is likely that will need to the dosage can be increased to 20 mg, given as above, to obtain a satisfactory effect.*

~~In patients with hepatic or renal insufficiency, the daily dose should be reduced to 10 mg twice daily during the first week.~~

~~Subsequently, this dose can be adjusted depending on the therapeutic effects or side effects.~~

~~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.~~

HOW SUPPLIED

PROPULSID™ (cisapride) is 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 bottles of 100 (NDC 50458-430-10), 250 (NDC 50458-430-25), and 500 (NDC 50458-430-50). PROPULSID™ is also provided as blue tablets, debossed "Janssen" and PROPULSID/20, containing the equivalent of 20 mg cisapride in blister packages of 100 (NDC

NDA 20-210
Draft Labeling, Page 13 14

50458-440-01) and in bottles of 100 (NDC 50458-440-10), 120 (NDC 50458-440-12), 250 (NDC 50458-440-25), and 500 (NDC 50458-440-50). Store at controlled room temperature, 15°-30°C (59°-80°F). Protect from moisture.

JANSSEN PHARMACEUTICA INC.

Piscataway, New Jersey 08855

Date: August 1991

Patent: 4,962,115