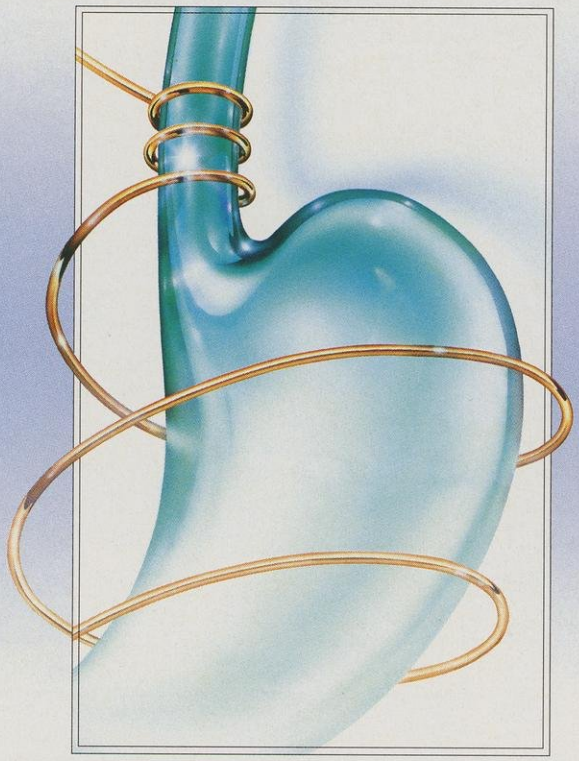
Propulsid advertisement.

[s.l.]: [s.n.], 1992

NOW AVAILABLE IN 10MG AND NEW 20MG TABLETS

TARGET THE UNDERLYING PHYSIOLOGIC DEFECTS ASSOCIATED WITH NOCTURNAL HEARTBURN IN GERD PATIENTS...



PROPULSID®
cisapride
10MG & 20MG TABLETS

TRIPLE MECHANISM OF ACTION... PROPULSID ADDRESSES UPPER GI DYNAMICS*

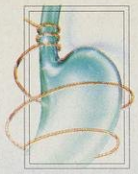
1. Increases lower esophageal sphincter tone[1]

2. Improves esophageal peristalsis[2]

3. Promotes gastric emptying[3]

*These effects were shown in pharmacology trials. U.S. clinical trials did not, nor were they designed to, document these effects in GERD patients with nocturnal heartburn.

Please see brief summary of prescribing information on following page.

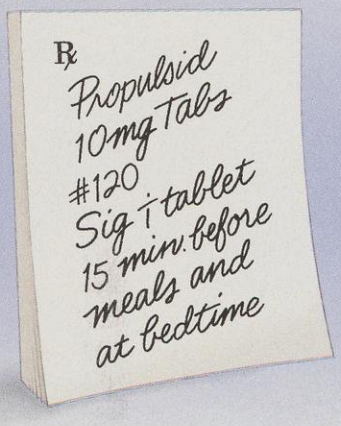


PROPULSID®

cisapride

10MG & 20MG TABLETS

SIMPLE DOSING SCHEDULE...



Dosage may be increased to 20 mg, given 15 minutes before meals and at bedtime, if needed.

For additional medical information, call 1-800-JANSSEN (9AM-5PM Eastern Time).

- **Highly effective in nocturnal heartburn in GERD patients**
- **More than 8 years of clinical experience worldwide; over 30 million patient treatments**
- **Well tolerated—In U.S. clinical trials, the following adverse events were most commonly reported:**

	PROPULSID	PLACEBO
Headache	19.3%	17.1%
Diarrhea	14.2%	10.3%
Abdominal Pain	10.2%	7.7%
Nausea	7.6%	7.6%
Rhinitis	7.3%	5.7%
Constipation	6.7%	3.4%

Before prescribing, please consult complete prescribing information in Janssen Pharmaceutica's literature or package insert. The following is a brief summary.

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 compromise the beneficial effects of PROPULSID®.

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.

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.

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, and a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg was not tumorigenic.

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*.

Cisapride was found to have no effect on fertility and reproductive performance of male rats at oral doses of 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 (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 (F_0) rats.

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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

The U.S. clinical trial population included 1728 patients (comprised of 506 with gastroesophageal reflux disorders, and the remainder with other motility disorders). Of the adverse events that occurred at a frequency of >1% in the GERD trials, only the incidence of nausea and vomiting differed significantly between PROPULSID® and placebo. The following adverse experiences were reported in more than 1% of the 1728 patients treated with PROPULSID® (PROPULSID® vs Placebo):

Nervous System: headache (19.3%, 17.1%). ***Gastrointestinal***: diarrhea (14.2%, 10.3%), abdominal pain (10.2%, 7.7%), nausea (7.6%, 7.7%), 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*** : 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 foreign marketing experience, there have been rare reports of seizures and extrapyramidal effects, 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.

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

OVERDOSAGE

Reports of overdosage 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, 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. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

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). PROPULSID® is also provided as blue tablets, debossed "Janssen" and PROPULSID/20, containing the equivalent of 20 mg cisapride in bottles of 100(NDC 50458-440-10).

Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture. The 20 mg tablets should also be protected from light.

October 1993 7502603

U.S. Patent No. 4,962,115

References
1. Ceccatelli P, et al. *Gut.* 1988;29:631-635.
2. Baldi F, et al. *Progr Med.* 1987;43(suppl 1):29-34.
3. Jian R, et al. *Gut.* 1985;26:352-358.

innovators in GI therapy

JANSSEN PHARMACEUTICA RESEARCH FOUNDATION

Titusville, NJ 08560-0200

JPI-PR-014-R-1 April 1994 Printed in U.S.A.

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N E W

PROPULSID®

cisapride 10MG TABLETS

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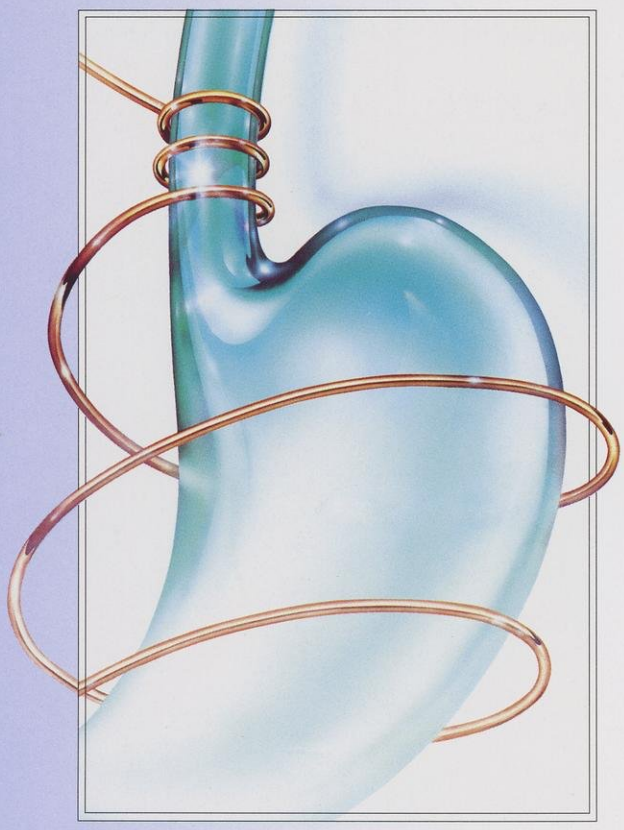


TRIPLE MECHANISM OF ACTION...

ONE

Increases lower esophageal sphincter tone[1]**—to re-establish esophageal barrier**

TWO

Improves esophageal peristalsis[2]**—to assist in clearance of acidic materials**

THREE

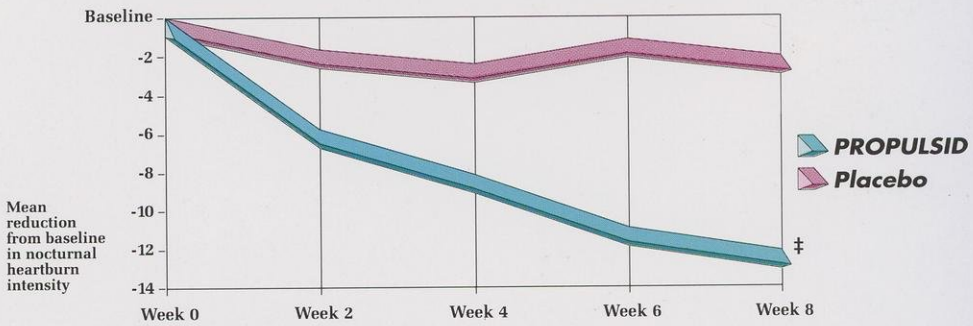
Promotes gastric emptying[3]**—to reduce back pressure on the lower esophageal sphincter**

*These effects were shown in pharmacology trials; U.S. clinical trials did not document these effects in GERD patients with nocturnal heartburn.

Please see brief summary of prescribing information on last page.

SIGNIFICANTLY IMPROVES NOCTURNAL HEARTBURN...†

...ONE OF THE MOST SEVERE SYMPTOMS IN GERD PATIENTS



†Patient assessments of moderate-to-severe symptoms in a U.S. clinical trial (N=147).

Symptom reduction was significantly better than placebo (‡end point analysis $p<.05$)

WELL TOLERATED

More than 8 years of clinical experience; over 30 million patient treatments

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NEW PROPULSID® cisapride 10MG TABLETS

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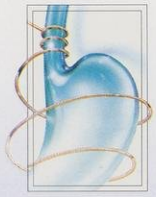

NEW
PROPULSID®
cisapride 10MG TABLETS

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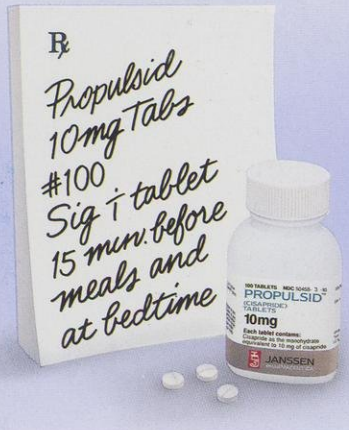

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Pediatric Use: Safety and effectiveness in children have not been established.

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Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture.

July 1993
U.S. Patent No. 4,962,115

References
1. Ceccatelli P, et al. *Gut*. 1988;29:631-635. 2. Baldi F, et al. *Progr Med*. 1987;43 (suppl 1): 29-34. 3. Jian R, et al. *Gut*. 1985;26:352-358.

innovators in GI therapy
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Titusville, NJ 08560-0200

JPI-PR-005 October 1993 Printed in U.S.A.

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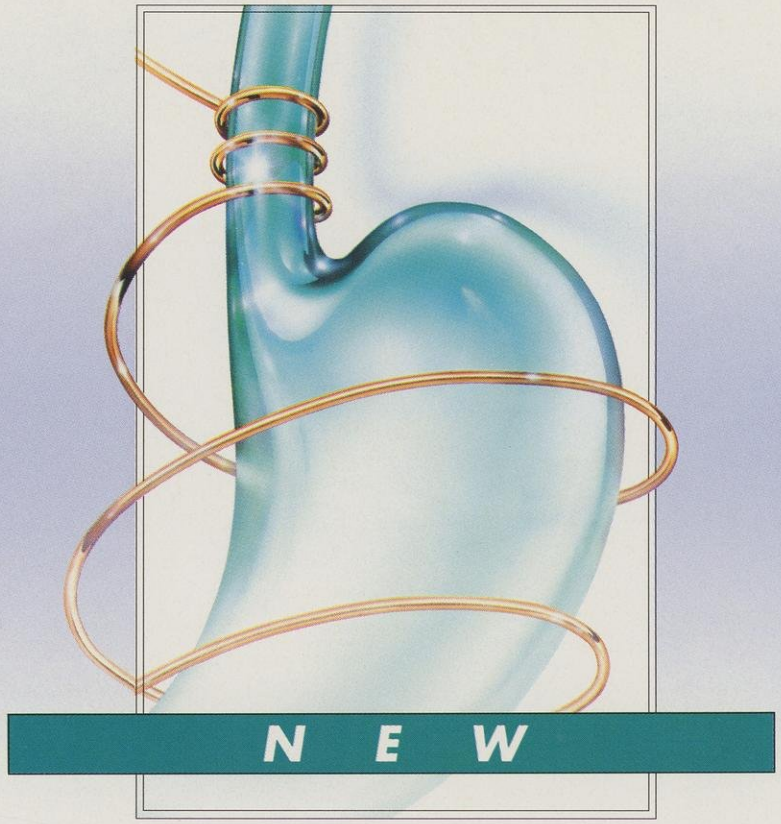

PROPULSID®

cisapride 10MG TABLETS

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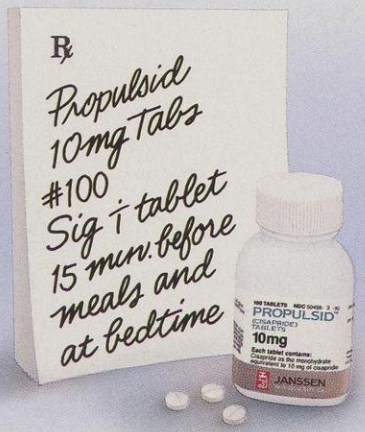

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The U.S. clinical trial population included 1728 patients (comprised of 506 with gastroesophageal reflux disorders, and the remainder with other motility disorders). Of the adverse events that occurred at a frequency of >1% in the GERD trials, only the incidence of nausea and vomiting differed significantly between PROPULSID® and placebo. The following adverse experiences were reported in more than 1% of the 1728 patients treated with PROPULSID®(PROPULSID®vs Placebo):

Nervous System: headache (19.3%, 17.1%). ***Gastrointestinal***: diarrhea (14.2%, 10.3%), abdominal pain (10.2%, 7.7%), nausea (7.6%, 7.7%), 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*** : 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 foreign marketing experience, there have been rare reports of seizures and extrapyramidal effects, 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.

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

OVERDOSAGE
Reports of overdosage 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, 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. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

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 bottles of 100 (NDC 50458-430-10).

Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture.

July 1993
U.S. Patent No. 4,962,115

References
1. Ceccatelli P, et al. *Gut.* 1988;29:631-635. 2. Baldi F, et al. *Progr Med.* 1987;43 (suppl 1): 29-34. 3. Jian R, et al. *Gut.* 1985;26:352-358.

innovators in GI therapy
JANSSEN PHARMACEUTICA RESEARCH FOUNDATION
Titusville, NJ 08560-0200

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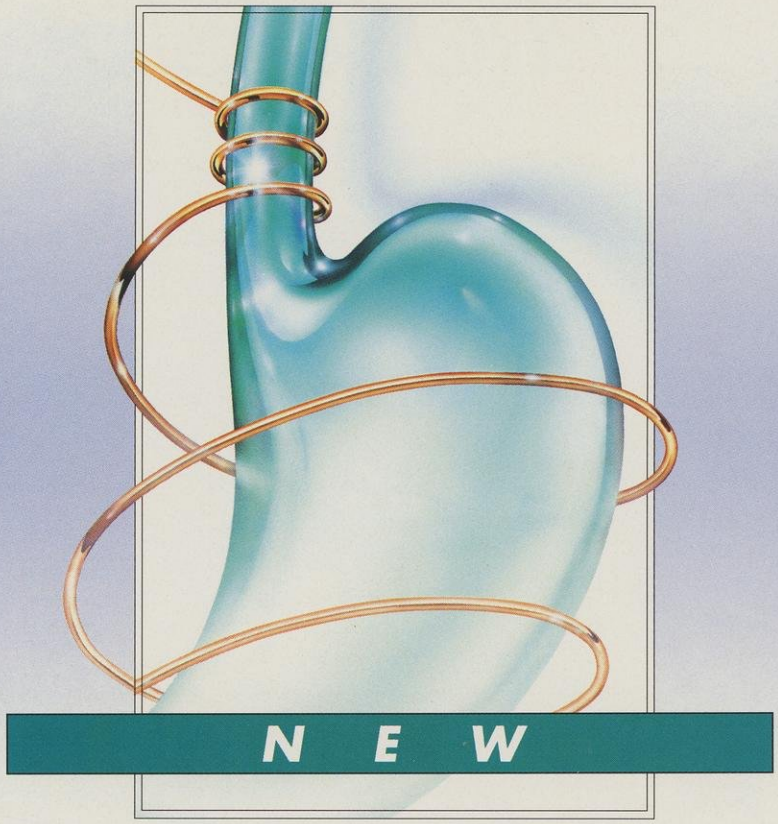
NOW...TARGET THE UNDERLYING PHYSIOLOGIC DEFECTS ASSOCIATED WITH NOCTURNAL HEARTBURN IN GERD PATIENTS...



PROPULSID®

cisapride 10MG TABLETS

TRIPLE MECHANISM OF ACTION... PROPULSID ADDRESSES UPPER GI DYNAMICS*

1. Increases lower esophageal sphincter tone[1]

2. Improves esophageal peristalsis[2]

3. Promotes gastric emptying[3]

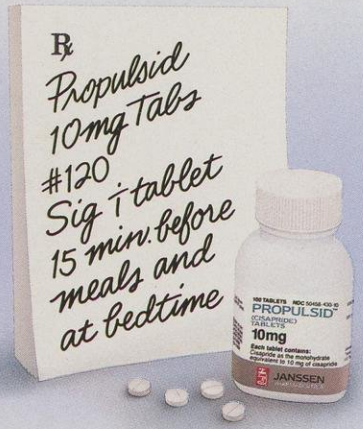
*These effects were shown in pharmacology trials; U.S. clinical trials did not document these effects in GERD patients with nocturnal heartburn.

Please see brief summary of prescribing information on following page.

NOW...TARGET THE UNDERLYING PHYSIOLOGIC DEFECTS ASSOCIATED WITH NOCTURNAL HEARTBURN...

NEW
PROPULSID®
cisapride 10MG TABLETS

SIMPLE DOSING SCHEDULE...



- **Highly effective in nocturnal heartburn in GERD patients**
- **Well tolerated**
- **More than 8 years of clinical experience worldwide; over 30 million patient treatments**

For additional medical information, call 1-800-JANSSEN (9AM-5PM Eastern Time).

Dosage may be increased to 20 mg, given 15 minutes before meals and at bedtime, if needed.

Before prescribing, please consult complete prescribing information in Janssen Pharmaceutica's literature or package insert. The following is a brief summary.

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 compromise the beneficial effects of PROPULSID®.

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.

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.

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, and a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg was not tumorigenic.

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*.

Cisapride was found to have no effect on fertility and reproductive performance of male rats at oral doses of 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 (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 (F_0) rats.

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 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.

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August 1993
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